Dietary approach to diagnosis and initial management of cow’s milk allergy (CMA) in infants

Clinical picture consistent with allergy to cow’s milk protein (CMP)

Presenting with gastrointestinal symptoms

- CMA highly likely
- Other causes for presenting symptoms improbable
  - Trial of CMP avoidance
  - Refer to Dietitian for weaning advice
  - Use EHF* as alternative

Symptoms not fully resolved
  - Trial of strict avoidance of CMP in all forms
  - Use Amino Acid formula as alternative
  - Referral to Allergy Clinic

No response
  - Diagnostic work up
  - Trial of avoidance & use of Amino Acid formula as appropriate

Presenting with acute allergic reactions or flare ups of atopic condition (e.g. eczema)

- CMA is likely
- Other causes for presenting symptoms improbable
  - Trial of CMP avoidance
  - Use EHF* as an alternative
  - Refer for Dietitian for weaning advice
  - Evaluation with allergy testing/challenge as appropriate

Severe
- Strict avoidance of CMP in all forms
- Use Amino Acid formula as an alternative
- Referral to Allergy Clinic
  - Evaluation with allergy testing

Not severe
- CMA is one possibility
- Other causes for presenting symptoms need to be excluded urgently
  - Trial of CMP avoidance
  - Use EHF* as an alternative
  - Refer for Dietitian for weaning advice
  - Evaluation with allergy testing/challenge as appropriate

Still reacting to EHF*
Notes:

1. Cow’s Milk Allergy (CMA) can result in a wide range of gastro-intestinal symptoms including vomiting, haematemesis, colic, failure to thrive, abdominal distension, diarrhoea and haematochezia (blood in the stools). Gastro-oesophageal reflux and constipation can also be associated with underlying CMA in a significant proportion of infants. A range of serious conditions can also result in similar symptoms. These include gastro-intestinal infections, urine infection, coeliac disease & malabsorptive states, cystic fibrosis, metabolic disorders, neurological disorders, inflammatory bowel disease, intussusception, and mal-rotation with persisting or intermittent volvulus. Thus making the correct diagnosis in this form of CMA may be the most important challenge in management and certain conditions may need to be excluded as early as possible. In CMA presenting with gastro-intestinal symptoms, “allergy tests” based on detection of IgEs may or may not be positive. Thus the diagnosis frequently rests on the clinical picture and response to avoidance measures. The extent of the diagnostic work up to exclude other possible conditions before the diagnosis of CMA is established will vary according to the nature of the presenting symptoms and the clarity of the link with the exposure to cow’s milk protein. Generally the following features should serve as “red flags”: Fever, tender or tense abdomen, circulatory changes, associated pallor, high inflammatory markers. Baby with recurrent vomiting, distress or diarrhoea associated with one of these features should be referred to hospital without delay.

2. In this type of presentation the diagnosis is usually not difficult to establish. There is a short interval between exposure and developing the reactions and the symptoms are of more acute nature. In infancy frequently the limited number of items included in the diet makes the diagnosis easier to establish. Allergy testing tends to be more helpful in this type of presentation.

3. The extent and acuteness of eczema flare ups linked to exposure to CMP vary; in some cases only repetitive intake results in gradual worsening of the eczema. In others, more acute type flare ups can happen after single exposure. “Allergy tests” based on detection of IgEs may or may not be helpful.

4. In cases where a highly modified form of cow’s milk protein is the suspected trigger (e.g. via maternal breast milk or in a highly cooked form such as in cakes and biscuits), it is more appropriate to use Neocate as an alternative formula feed.

5. In breast fed infants breast feeds can continue but CMP avoidance in maternal diet may be needed.

6. In breast fed infants breast feeds can continue but CMP avoidance in maternal diet will be necessary during the assessment phase.

7. Other dietary restrictions may need to be implemented on the baby’s and (if breast fed) mother’s diet. In some cases breast feeding may need to be interrupted temporarily or permanently.

8. Consultation with Paediatric Gastro-enterologist or Paediatric Surgeons may be needed.

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10. *: Neocate is the most widely used amino-acid formula in the UK, also available is Nutramigen AA.

11. Paediatric Dieticians at St. Peters Hospital.

Extensively Hydrolysed Formulae (EHF):

**FIRST LINE (lactose free):**
- Nutramigen lipil 1® (Mead Johnson) Birth – 6 months
- Nutramigen lipil 2® (Mead Johnson) 6 months – 1 year
- Similac Alimentum® (Abbott) 6 months – 1 year

**SECOND LINE** (contains lactose – do not use for infants with Eosinophilic Enteritis or who have watery acidic stools as they are likely to be experiencing lactose intolerance secondary to CMPA)
- Pepti 1® (Aptamil) Birth – 6 months
- Pepti 2® (Aptamil) 6 months – 1 year
- Althera® (Nestle) Birth – 1 year

These formulae can be tried if the infant is not tolerating the taste of Nutramigen® products and are able to tolerate lactose.

**THIRD LINE:**
Soya Formula (6 months – 1 year) only if first and second line are refused by the infant. Use with caution as high incidence of soya allergy in infants with CMPA.
- Infasoy®
- SMA Wysoy®

Amino acid formulae (AAF):

**First Line**
Neocate LCP® (SHS) Birth – 1 year (restricted use in line with Figure 1)
Nutramigen AA® (Mead Johnson) Birth – 1 year (restricted use in line with Figure 1)
Alfamino® (Nestle) Birth – 6 months (restricted use in line with Figure 1)

For infants above 1 year of age with just a diagnosis of CMPA and relying on formula as sole source of nutrition:
Neocate Advance® (to be prescribed in secondary care)

For infants above 1 year of age and unable to take any dairy free alternative milks due to multiple allergies but is able to manage some foods orally:
Neocate Active® 1 – 10 years (to be prescribed in secondary care)

Neocate Spoon® should only be prescribed in secondary care. It is a hypoallergenic supplement for use in the dietary management of CMPA, multiple food protein allergies and other conditions requiring an amino acid based food.
Executive summary

- Cow’s milk allergy may be defined as a reproducible adverse reaction of an immunological nature induced by cow’s milk protein. (A)
- Cow’s milk allergy can be classified into IgE mediated immediate-onset and non-IgE mediated delayed-onset types according to the timing of symptoms and organ involvement. (A)
- The prevalence of cow’s milk allergy is between 1.8% and 7.5% of infants during the first year of life. (B)
- Cow’s milk allergy commonly presents in infancy, with most affected children presenting with symptoms by 6 months of age. Onset is rare after 12 months. (B)
- Cow’s milk allergy has a favourable prognosis, as most children will outgrow their allergy by adulthood. (B)
- Cow’s milk allergy is more likely to persist in IgE mediated disease and where there is greater sensitivity (higher specific IgE levels), multiple food allergies and/or concomitant asthma and allergic rhinitis. (B)
- The clinical diagnosis in IgE mediated disease is made by a combination of typically presenting symptoms, e.g. urticaria and/or angio-oedema with vomiting and/or wheeze, soon after ingestion of cow’s milk, and evidence of sensitisation (presence of specific IgE). The spectrum of clinical severity ranges from skin symptoms only to life-threatening anaphylaxis. Clinical assessment should include a severity evaluation to ensure affected individuals are managed at the appropriate level. (B)
- The clinical diagnosis of non-IgE mediated disease is suspected by the development of delayed gastrointestinal or cutaneous symptoms that improve or resolve with exclusion and reappear with reintroduction of cow’s milk. As with IgE mediated disease, non-IgE mediated disease varies widely in clinical presentation from eczema exacerbations to life-threatening shock from gastrointestinal fluid loss secondary to inflammation (Food Protein Induced Enterocolitis Syndrome (FPIES)). (B)
- Gastrointestinal symptoms of non-IgE mediated cow’s milk allergy are variable and affect the entire gastrointestinal tract. There are some well recognised more easily identifiable conditions (e.g. eosinophilic proctitis) but symptoms are more commonly non-specific. Cow’s milk allergy should be considered in these circumstances where symptoms fail to respond to standard therapy or where other features of allergy are present. (B)
- Lactose intolerance can be confused with non-IgE mediated cow’s milk allergy as symptoms overlap. The terms are thus frequently mistakenly used interchangeably. Lactose intolerance should be considered where patients present only with typical gastrointestinal symptoms. (B)
- The reported levels of IgE required to support a diagnosis of IgE mediated cow’s milk allergy varies between studies and depends on the research population. A skin prick test (SPT) well size ≥5mm (≥2mm in younger infants) is strongly predictive of cow’s milk allergy. (C)
- A food challenge may be necessary to confirm the diagnosis either in IgE mediated disease where there is conflict between the history and diagnostic tests. (D)
- Food elimination and reintroduction is recommended for the assessment of non-IgE mediated cow’s milk allergy where there is diagnostic uncertainty. (C)
- The management of cow’s milk allergy comprises the avoidance of cow’s milk and cow’s milk products and dietary substitution with an allergenically and nutritionally suitable milk alternative. (D)
- The choice of cow’s milk substitute should take into account the age of the child, the severity of the allergy and the nutritional composition of the substitute. Nutritionally incomplete substitutes can lead to faltering growth and specific nutritional deficiencies. (D)
- As cow’s milk is the major source of calcium in infant diets, children on milk exclusion diets are at risk of a deficient calcium intake. A dietitian should assess calcium intake and dietary or pharmaceutical supplementation advised where appropriate. (D)
- Cow’s milk allergy will resolve in the majority of children. Individuals should be reassessed at 6-12 monthly intervals from 12 months of age to assess for suitability of reintroduction. (B)
- The reintroduction of cow’s milk may be graded according to the ‘milk ladder’ with less allergenic forms offered initially. More allergenic forms are then eaten sequentially as tolerated. Reintroduction can be performed at home or may need to be supervised in hospital. (D)
- Oral tolerance induction offers a novel treatment option to the small but clinically significant proportion of affected individuals whose cow’s milk allergy persists. (C)
- Cow’s milk allergy in adults more commonly arises in adulthood but may persist from childhood. This is frequently a severe form of allergy where up to 25% have experienced anaphylaxis. (C)

Grade of evidence/recommendations in parenthesis (see www.nice.org.uk)

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**bsaci** guideline for the diagnosis and management of cow’s milk allergy

### Definition and mechanism
CMA is defined as a reproducible adverse reaction to one or more milk proteins mediated by an immune mechanism.

An underlying immunological mechanism distinguishes CMA from other adverse reactions to milk, e.g. lactose intolerance.

CMA is classified as:
- **Immediate onset** (usually IgE mediated) typically with skin, respiratory, gastrointestinal and rarely cardiovascular symptoms.
- **Delayed onset** (non-IgE or combined IgE/non-IgE) with gastrointestinal symptoms and/or eczema.

### Prevalence, onset and evolution
CMA affects 2-3% of children, presenting typically at 3-6 months (rarely after 12 months).

Presentation can be delayed for weeks to months.

CMA has a favourable outcome, resolving in most children with 2/3 tolerant by school age. Predictors of persistence are:
1. Immediate onset symptoms vs delayed onset symptoms.
2. Reactivity to baked milk on first challenge or exposure.
3. Presence of other food allergies, especially egg allergy.
4. Concomitant asthma and/or allergic rhinitis.
5. Large SPT weal size or higher sIgE level at diagnosis.

### Clinical presentation and diagnostic evaluation
**Immediate onset** (within minutes to two hours)
- **Skin**: urticaria, pruritus and angioedema.
- **Gut**: abdominal pain, vomiting (repeated or profuse), diarrhoea.
- **Respiratory tract**: red/dry eyes, blocked/runny nose, sneezing, cough, wheeze, breathlessness.
- **Cardiovascular**: drowsiness, dizziness, pallor, collapse.

Wide range in severity from skin symptoms only, to life-threatening or fatal anaphylaxis. Presentation mild in the majority.

**Delayed onset** (frequently delayed - hours to days)
- **Gastrointestinal symptoms**: range of symptoms and severity.
- **Blood in stool** in otherwise well child.
- **Vomiting in inanimate child with back arching and screaming**.
- **Feed refusal** and aversion to lumps.
- **Dysphagia** (possible oesophageal eosinophilia, warrants biopsy).
- **Diarrhoea**: often protracted with propensity to faecal impaction.
- **Constipation**: straining with defaecation, but producing soft stools.
- **Unwell child**: delayed onset protracted vomiting and diarrhoea.

Wide range in severity from well child with bloody stools to unwell shocked child after profuse vomiting and diarrhoea (FPIES).

### Diagnostic evaluation
**Immediate onset** typical symptoms confirmed by SPT >3mm.
**Atypical or absent** symptoms need SPT >5mm.

**Delayed onset** GI symptoms milk exclusion and assess symptoms.
**Eczema**: milk exclusion 2-6wks, then reintroduction.

### Treatment
#### Dietary avoidance (avoidance advice)
- **How to read a label for a milk-free diet**
  - Look out on labels for any of the following ingredients:
    - Butter, butter fat, oil, acid, ester or milk.
    - Casesin, casein hydrolysate, sodium or calcium caseinate.
    - Cow’s milk (fresh, UHT, dried, powder, condensed).
    - Cheese, cottage cheese.
    - Cream, artificial cream.
    - Cards, ghee, custard.
    - Lactobumin, lactoglobulin, lactoferrtin, lactalbumin.
    - Milk solids (non-fat milk solids milk sugar or protein).
    - Animal milks (goat’s milk).
    - Sour cream or milk solids.
    - Whey, whey powder or syrup.
    - Sweetened, hydrolysed whey.
    - Yogurt, fromage frais.

- **Milk** is sometimes found hidden in the following:
  - Biscuits/baked goods.
  - Savoury snacks, soup, gravy.
  - Pastry, bater.

*In EU all pre-packaged must declare milk on allergy list if it is an ingredient.

#### Choice of substitute milks (replacing cow’s milk in diet)
**Suitable milk substitutes**
- Breast milk (suitable for most with CMA).
- Hypoallergenic formulas (first choice; AAF for severe CMA).
- Extensively hydrolysed formulas Amino-acid formulas
  - Aplamil Pepti 1, Altralac.
  - Nutramigen Lipil, Similac Almumem.
  - Nutramigen AA.
  - Pepti Junior, Peptomil.
  - Peptidea, MCT Peptidea.
- Soya based fortified drink (not recommended in infants <6mo).

**Unsuitable (U) or less desirable (L) milk substitutes**
- U - Heated or processed fresh cow’s milk.
- U - Other mammalian milks (e.g. goat’s, donkey’s, etc.).
- L - Alternative milk ‘beverages’ (e.g. almond, coconut, rice, soya) to be used under dietetic guidance in older children.

### Reintroduction (rate of resolution varies so timing and location (home or hospital) must be individually assessed)

**Guidance for reintroduction of cow’s milk**
1. Consider reintroduction from 12 months.
2. Review every 6-12 months (repeat SPT if IgE mediated).
3. Start with **baked milk** as less allergenic.
4. Home reintroduction may be attempted where:
   - Mild symptoms on noteworthy exposure.
   - No reaction in past 6 months.
   - Significant reduction in SPT (in IgE mediated).
5. Hospital reintroduction recommended in:
   - Any previous moderate to severe reaction (incl. FPIES).
   - Less severe reaction to trace exposure.
   - Regular asthma preventative treatment.
   - Multiple or complex allergies.
   - Parents unable to understand protocol.

Once tolerance is established, encourage greater exposure of less processed milk as in **Milk Ladder**.

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**bsaci** developed by the **bsaci standards of care committee**

Reviewed and updated (Nov 2014) – Dr Ashok Aralihond, Paediatric Consultant
| Author: | Dr Diab Haddad, Consultant Paediatrician (Specialist Interest in Paediatric Allergy and Respiratory Disease) |
| Ratified by: | Dr Peter Reynolds, on behalf of Children’s Services Clinical Governance Committee on: February 2011 |
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References:

1. NICE clinical guideline 116 February 2011 Food allergy in children and young people
2. Adopted from old guideline by Dr Diab Haddad
3. BSACI guideline for the diagnosis and management of cow’s milk allergy; Clinical & Experimental Allergy, 44, 642–672