

**Current practice**

## Cow's milk allergy

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### Introduction

Milk and milk based products are the mainstay of the diet during infancy and early childhood. Cow's milk allergy (CMA) presents in the first year of life, and in general, prevalence is estimated to be 2-3%<sup>1,2</sup>. However, data on prevalence of cow's milk allergy is lacking in Sri Lanka. Adverse reactions to cow's milk could be immune or non-immune. CMA is defined as adverse reactions to one or more milk proteins (casein or whey beta lactoglobulin) caused through immunological mechanisms that occur reproducibly following intake of milk<sup>3</sup>. Lactose intolerance is a non-immune adverse reaction that should be distinguished from true allergy.

CMA is classified based on the underlying immune mechanism based on timing and organ system involved<sup>4</sup>. IgE mediated reactions are more common and occur within minutes or mostly within one hour after ingestion of even a small amount of milk. These reactions can vary from minor skin rash to life threatening anaphylaxis<sup>4</sup>. Delayed reactions are non-IgE mediated and generally onset is several hours to days following ingestion of a larger volume of milk<sup>3,4</sup>. Table I describes the diversity of presentations of CMA based on the immunological reaction.

**Table I: Manifestations of cow's milk allergy based on immune mechanisms**

| Manifestation             | IgE mediated              | Mixed  | Non-IgE mediated   |
|---------------------------|---------------------------|--|--|
| Systemic                  | Anaphylaxis               |  |  |
| Skin                      | Urticaria<br>Angio-oedema | Atopic dermatitis                              |  |
| Gastrointestinal symptoms | Immediate GI symptoms     | Eosinophilic oesophagitis /<br>Gastroenteritis | Allergic proctocolitis<br>Food protein induced<br>enterocolitis syndrome |
| Respiratory               | Bronchospasm              |  | Heiner syndrome  |

### Manifestations of IgE mediated immediate reactions

*Skin symptoms:* Acute urticaria and angioedema are the most common manifestations<sup>3,4</sup>. Rash often occurs within several minutes after ingestion, accompanied by an itch. However, CMA is rarely a cause of chronic urticaria<sup>5</sup>. Contact urticaria is also an IgE mediated manifestation caused by direct

contact of milk and symptoms are mild and are confined to the area of contact<sup>6</sup>.

*Gastrointestinal symptoms:* This includes vomiting, diarrhoea, bloody stools, abdominal pain and reflux disease<sup>3,4</sup>.

*Respiratory symptoms:* Chronic respiratory symptoms such as asthma are uncommon in food allergy<sup>3,4</sup>. However, acute upper respiratory tract symptoms (rhinitis, nasal congestion) and lower respiratory tract symptoms (wheezing, cough and stridor) are not uncommon and some manifestations are potentially life threatening<sup>3,4</sup>. Airway compromise due to laryngeal oedema, bronchospasm and airway collapse with mucus plugging is accountable for hypoxia during an immediate reaction<sup>3,4</sup>.

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*Cardiovascular symptoms:* Hypotension and shock are possible sequelae. However, they are rarely manifested in CMA<sup>3,4</sup>.

***Manifestations of Non IgE mediated, predominantly delayed onset reactions***

Non IgE mediated reactions range from minor reflux disease to life threatening gastrointestinal fluid loss in food protein induced enterocolitis (FPIES)<sup>7</sup>.

*Gastrointestinal (GI) symptoms:* GI symptoms predominate in non IgE mediated, delayed onset reactions<sup>4</sup>. During infancy non specific symptoms such as vomiting, possetting, irritability (infantile colic), failure to thrive, diarrhoea, constipation and blood in stools are evident<sup>4</sup>. Therefore, diagnosis relies on careful history and examination, pattern of symptoms, failure to respond to standard management approaches and presence of other evidence of allergy e.g. eczema.

Gastro-oesophageal reflux is common in infants<sup>4</sup>. Non-allergic reflux is often effortless and pain free. However, in the presence of gastro-oesophageal reflux due to milk allergy, these infants are irritable, have screaming episodes associated with back arching and profuse vomiting<sup>4</sup>. They show little or no response to anti-reflux medication<sup>4</sup>.

Occasionally constipation is the only symptom of milk allergy<sup>4</sup>. History of milk allergy in the first year of life is associated with functional constipation in older children<sup>8</sup>. More often, it co-exists with other allergies e.g. eczema, allergic rhinitis and improvement is shown with elimination of cow's milk from the diet<sup>9</sup>. When compared to non allergic infant with constipation these infants will have severe distress and straining during defaecation and often passes softer stools. In these children it has been shown that they have higher internal sphincter tone<sup>10</sup>.

Food protein induced enterocolitis (FPIES) is a life threatening condition with protracted vomiting, profuse watery diarrhoea which may be complicated by hypotension and acidosis within 1-3 hours of ingestion<sup>7</sup>. It is often misdiagnosed as sepsis and these children will have high white cell counts. However, absence of fever and negative cultures are clues to arrive at a diagnosis.

Allergic proctocolitis is typically manifested with frequent passage of stools with mucus mixed with streaks of blood in an otherwise healthy infant<sup>7</sup>. Symptoms subside with cessation of milk or milk products in the infant and maternal diet in an

exclusively breast fed infant<sup>7</sup>. This is essentially a non-IgE mediated reaction and these infants generally outgrow this condition by the end of first year<sup>7</sup>.

***Manifestations of mixed IgE and non IgE mediated reactions***

*GI symptoms:* Eosinophilic oesophagitis presents with abdominal pain, dysphagia, poor appetite, reflux and failure to thrive<sup>11</sup>. Both IgE mediated and non-IgE mediated mechanisms are responsible for eosinophilic infiltration of gastrointestinal tract<sup>11</sup>.

*Skin symptoms:* Cow's milk is responsible for exacerbations of eczema in some sensitized infants<sup>4</sup>. However, 40% of infants with moderate to severe eczema have food allergy<sup>12</sup>. Non eczematous (erythema, pruritus and urticaria) skin reactions in these children are immediate onset and IgE mediated<sup>4</sup>. Eczematous exacerbations are non-IgE mediated occurring after hours or days<sup>13</sup>. It is recommended that patients with eczema be treated with topical medications prior to considering a food allergy, since the majority of cases do not seem to be caused by it.

**Natural history of CMA**

Most reactions are triggered by cow's milk per se or cow's milk based foods. However a small percentage (0.4-0.5%) is through breast milk from maternal milk intake<sup>9</sup>. Symptoms usually develop within a week of cow's milk contact or could be delayed up to 36 weeks<sup>13</sup>. All are symptomatic before one year. Children with CMA should be monitored for development of tolerance, since most will outgrow their allergy in childhood, 80% of them developing tolerance by 5<sup>th</sup> birthday<sup>14</sup>. However, there is conflicting evidence and recent reports highlight that only 64% of children develop tolerance by 12 years of age<sup>15</sup>. Resolution of symptoms in non-IgE-mediated allergy is faster than IgE-mediated allergy<sup>14</sup>. Patients with high IgE content in the first 2 years of life are more likely to have persistence of allergy to adulthood<sup>14</sup>. Other predictors of persistence are presence of asthma or allergic rhinitis, immediate severe reactions at the onset and concomitant allergy to other foods<sup>15</sup>.

**Diagnosis of CMA**

Early and reliable diagnosis of CMA is important to avoid unnecessary dietary restrictions and to prevent life threatening events. Accuracy of diagnosis depends on a detailed history and proven underlying

immunological reaction. Oral food challenges and elimination and reintroduction are useful when a doubt exists. In history taking, timing of onset of symptoms and cow's milk ingestion, reproducibility and time when last symptoms occurred, should be recorded. Food diaries are useful for history taking.

#### *IgE mediated CMA*

Diagnosis of IgE mediated allergy is based on clinical history, examination and the presence of cow's milk specific IgE antibodies (skin prick testing or serum IgE)<sup>4</sup>. Skin prick testing (SPT) and serum IgE (sIgE) levels serve to detect the presence of tissue bound and circulating IgE antibodies, respectively. However, presence of IgE antibodies denotes sensitization and cannot differentiate sensitization from clinical allergy<sup>4</sup>. In the presence of a consistent history, reaction of larger than 3mm above the negative control in SPT or sIgE  $\geq$  0.35kU/L supports the diagnosis<sup>4</sup>. Higher wheal sizes and sIgE levels support greater likelihood of clinical allergy, although it does not correlate with severity of symptoms<sup>4</sup>. If the clinical diagnosis is doubtful, even higher SPT levels are considered irrelevant. Certain children would have higher sIgE levels without clinical allergy. However, in younger children with suggestive symptoms even lower SPT are predictive of allergy than in older children<sup>16</sup>. Further, sIgE and SPT are not helpful as screening tools since they have a poor predictive value<sup>4</sup>. When diagnostic uncertainty (e.g. positive test and unconvincing history or history is doubtful with negative IgE levels) exists, oral food challenges are helpful in confirming CMA<sup>4</sup>

#### *Non- IgE mediated allergy*

Cow's milk specific IgE levels or SPT are not helpful if the symptoms do not suggest an IgE-mediated reaction, such as delayed gastrointestinal reactions and some cases of atopic dermatitis. Atopic patch tests cannot be recommended for clinical diagnosis of non IgE mediated reactions since standardized techniques and reagents are not established yet<sup>17</sup>. A careful and detailed history is valuable in making a diagnosis when symptoms are only gastrointestinal. Elimination and re-introduction is the gold standard diagnostic test. Re-appearance of symptoms with reintroduction supports the diagnosis<sup>18</sup>. In FPIES, IgE-based allergy testing is commonly negative, and a presumptive diagnosis is made based on a typical presentation, resolution of symptoms on elimination diets, and exclusion of other causes. Biopsy supports the diagnosis of proctocolitis and resolution of symptoms with elimination.

#### *Mixed IgE and non IgE mediated reactions*

In most instances it is difficult to diagnose food allergy as the history is frequently confusing owing to the severity of the eczema. A careful history and elevated IgE levels (SPTs or sIgE assays) support the diagnosis. It is reported that 27.4% of children with eczema have elevated cow's milk specific IgE<sup>19</sup>. Diagnosis of eosinophilic oesophagitis is based on clinical presentation and biopsy after aggressive therapy with anti reflux medications, and the disappearance of eosinophils following an appropriate elimination diet<sup>20</sup>. Owing to the mixed reactions these children may have elevated IgE levels.

#### **Diagnostic pitfalls**

Heating, cooking and fermentation may influence the amount milk allergen in the processed food item<sup>21</sup>. Thus, tolerance to processed foods per se may not exclude allergy to milk in the form of liquid, powder or ice cream. Further, baby jars, cereals and rusks contain small amount of milk in addition to other ingredients such as wheat and soy. Therefore, CMA may be initially missed as a potential allergen or misdiagnosed as wheat and soy allergy.

#### **MANAGEMENT**

##### **Avoidance**

The mainstay of therapy of cow's milk allergy is complete avoidance<sup>4</sup>. Elimination of milk from the diet may lead to nutritional deficiencies, since milk is an important source of calcium, fat and protein in early childhood. Milk may be found in candy, custard, puddings, hotdogs, sausages, margarine and salad dressing and more. Certain food establishments keep shrimp in milk to avoid fishy odour. Due to shared utensils food can be contaminated with cow's milk. Certain bakery products are brushed with milk. Thus, it is difficult to avoid cow's milk since it is found in a variety of food items. Ideally, authorities should introduce legislation to list all the ingredients of food items making it easier for the consumers to identify food items that they should avoid.

Many children with CMA may tolerate processed food items (baked or extensively heated) and oral challenge test is useful in testing them for tolerability. Although they can be allowed continue to consume baked products, it is not known whether this will prevent, induce or delay the onset of tolerance to cow's milk. However, if they are reacting to intermediate forms of milk (e.g. pudding, yogurt), it

is advisable that they should avoid all forms of milk including processed items.

### **Substitutes**

If the infant is breast fed, mothers should be encouraged to continue breast feeding and milk substitutes are not necessary. However, since small amount of cow's milk protein beta lactoglobulin is excreted in mother's milk, if the infant is symptomatic while being breast fed, mother needs to avoid milk in her diet<sup>4</sup>. Soy infant formula is a valid option if breast feeding is not possible for any reason. However, due to high frequency of co-existence of cow's milk and soy allergy, some infants may require extensively hydrolysed cow's milk formulas. Occasionally amino acid formulas are indicated if an individual is highly sensitive and reacts to small amounts of residual milk proteins in an extensively hydrolysed formula. Most children with CMA are sensitive to goat and sheep milk due to cross reactivity and should not be recommended<sup>22</sup>. For older subjects who are on a milk free diet, calcium supplementation is recommended.

### **Oral immunotherapy**

There is growing evidence of the efficacy of oral immunotherapy with milk protein in the treatment of milk allergy<sup>23</sup>.

### **Milk reintroduction**

Appropriate timing of milk re-introduction should be assessed individually. Generally, resolution of non IgE mediated allergy is seen towards the end of the first year of life and earlier than resolution of IgE mediated symptoms. Development of tolerance correlates with reduction of serum IgE levels in IgE mediated CMA. Thus, timing of re-introduction can be determined by repeat measurements of IgE at 6-12 monthly intervals. Re-introduction should be carried out at hospital or at home depending on the severity of allergy the individual has experienced. Children who grow out of their CMA become tolerant to milk in baked form before intermediate milk products (yoghurt, puddings) and fresh milk since baking reduces protein allergenicity. Therefore, reintroduction of items with baked milk should be attempted first before less processed milk products. A fresh milk challenge is recommended in individuals who have achieved full tolerance of all baked milk products.

### **Summary**

CMA is manifested in a wide range clinical syndromes. Diagnosis of IgE mediated reactions is based on a convincing clinical history and measurement of cow's milk-specific IgE. Oral food challenge is useful for a definitive diagnosis in doubtful cases. However, diagnostic tests for non-IgE mediated manifestations are lacking. Avoidance of cow's milk is the mainstay of therapy, although there is growing evidence for new modalities of treatment such as oral and sublingual immunotherapy.

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