Cow's milk allergy in children

Cow's milk allergy is more common in children than in adults.

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The estimated prevalence of cow's milk allergy (CMA) varies between 2% and 7.5%, being higher in children than adults. Cow's milk allergy can develop in exclusively or partially breast-fed infants, when cow's milk protein (CMP) is introduced into the feeding regimen. The incidence of CMA is lower in exclusively breast-fed infants (0.5%) compared with formula-fed or mixed-fed infants, and clinical reactions in the breast-fed group are mostly mild to moderate. This might be related to lower levels of CMP in breast milk compared with cow's milk, immunomodulators in breast milk and differences in gut flora between breast-fed and formula-fed infants.

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Pathogenesis

CMA results from an immunological reaction (Fig. 1) to one or more milk proteins. This immunological basis distinguishes CMA from other adverse reactions to cow's milk protein such as lactose intolerance. CMA may be immunoglobulin E (IgE) or non-IgE-mediated and may be a manifestation of the atopic diatheses and multiple food allergy. Reactions to other foods (depending on the regional dietary intake) may occur in combination with CMA. Non-IgE-mediated disorders usually involve T cells (or eosinophils), present mainly with gastrointestinal symptoms and are less likely to develop multiple food allergy. IgE and non-IgE-mediated mechanisms may play a role in the pathogenesis of atopic dermatitis and the eosinophilic gastrointestinal disorders.

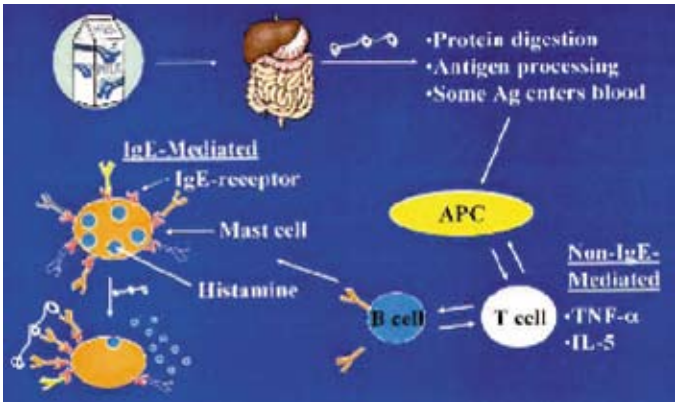

Fig. 1. Pathophysiology: immune mechanisms.

Clinical manifestations

The clinical manifestations of CMA depend to a great extent on the type of immunological reaction involved (Fig. 2).

IgE-mediated reactions

These occur <2 hours after ingestion. The most frequent manifestations are cutaneous (urticaria, angio-oedema, acute flare-up of atopic eczema) and gastrointestinal (vomiting, diarrhoea, colic). Atopic dermatitis is observed in approximately 10 - 15% of young children. It is primarily caused by dryness of the skin and is linked to hereditary factors. However, approximately one-third of patients with moderate to severe atopic dermatitis present with flares of eczema linked to a food allergy.[1] Cow's milk, hen's egg, and peanuts are the foods most frequently involved. Respiratory manifestations (asthma, allergic rhinitis) are infrequent, especially as isolated symptoms. There is a belief among the lay public that the consumption of milk and dairy products increases the production of mucus in the respiratory tract – there is no scientific confirmation of this. Anaphylaxis is the most severe manifestation.

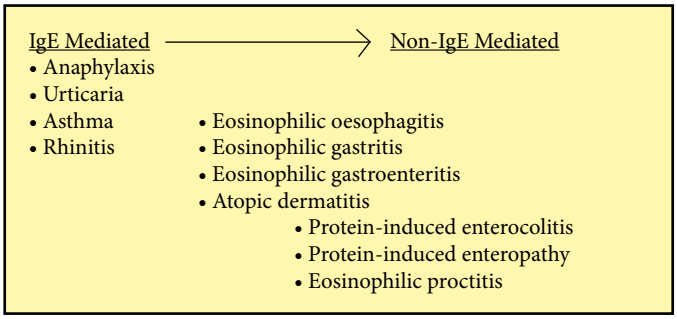

Fig. 2. Adverse reactions to cow's milk protein.

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Mixed IgE/non-IgE-mediated reactions

These are usually delayed (occur several hours or days after milk consumption). The eosinophilic gastrointestinal disorders (EGIDs) include eosinophilic oesophagitis, gastritis, gastroenteritis and colitis. In children, symptoms of eosinophilic oesophagitis are similar to gastro-oesophageal reflux and in adults, dysphagia and food impaction are common. Symptoms of EGIDs are usually chronic relapsing and the clinical presentation includes failure to thrive (due to chronic diarrhoea, refusal of food and/or vomiting); iron deficiency anaemia (due to occult or macroscopic blood loss); and hypoalbuminaemia or recurrent abdominal pain.

Non-IgE mediated reactions

These include food protein-induced (FPI) enterocolitis, enteropathy and proctolitis.[2] The clinical features of these disorders are listed in Table I. FPI disorders are typically cow's milk and soya protein induced[3] but may also occur with ingestion of solid foods including fish, chicken, turkey, corn and vegetables. FPI enteropathy usually presents with diarrhoea, mild to moderate steatorrhoea (80% of cases) and poor weight gain. Rectal bleeding is the usual presenting feature of FPI colitis. The infant is otherwise well and thriving.

Milk-induced enterocolitis is characterised by initial symptoms occurring during the first months of life as repeated vomiting episodes

Table I. Non-IgE-mediated paediatric gastrointestinal syndromes

	Enterocolitis	Enteropathy	Proctitis
Age of onset	Infant	Infant/toddler	Newborn
Duration	12 - 24 months	12 - 24 months	9 - 12 months
Characteristics	Failure to thrive Shock Lethargy Vomiting Diarrhoea	Malabsorption Villous atrophy Diarrhoea	Bloody stools No systemic symptoms

sometimes leading to dehydration.[3] A characteristic feature of this syndrome is a symptom-free interval of up to several hours between ingestion of milk, most often a cow's milk protein-based formula, and the first symptoms. Symptoms might be very severe and mimic sepsis. Milk-induced proctocolitis is mostly observed in young infants that are exclusively breast-fed.[4]

Skin-prick testing (with fresh milk or commercial reagents) and CAP-RAST (for determining specific IgE against cow's milk protein) are the currently available tests.

Diagnosis

Clinical evaluation

A comprehensive history (including a family history of atopy) and careful physical examination form the foundation for the diagnosis and management of CMA. Unfortunately, there is no one symptom that is pathognomonic for cow's milk allergy. The timing and pattern of symptoms aid the diagnosis. Symptoms of CMA occur often, but not always, within the first weeks after the introduction of cow's milk proteins. Many of the children with cow's milk allergy develop symptoms in at least two of the following organ systems: gastrointestinal (50 - 60%), skin (50 - 50%) and respiratory tract. Temporal relationship between feed ingestion and onset of symptoms should also be assessed (IgE-mediated reactions usually <2 hours; non-IgE-mediated occur several hours or days later).

Diagnostic tests

IgE-mediated CMA

Skin-prick testing (with fresh milk or commercial reagents) and ImmunoCAP-RAST (for determining specific IgE against cow's milk protein) are the currently available tests. In children older than 2 years a skin-prick test (SPT) reaction with a wheal diameter ≥8 mm (Table II)[5] or milk-specific IgE level ≥15.0 kU/l (Table III),[6] the likelihood is 95% that the child will have a positive milk challenge. The corresponding wheal size in children younger than 2 years is 6 mm diameter[5] and milk-specific IgE ≥5.0 ku/l.[7] A negative SPT or ImmunoCAP-RAST essentially excludes IgE-mediated disease. In patients with a strongly suggestive history of an IgE-mediated food allergic reaction, food challenges should be performed with physician supervision regardless of food-specific IgE value.

Table II. Skin-prick test reactions (wheal diameter) 100% predictive of positive milk challenge[5]

Cohort age	Wheal diameter
Children >2 yrs old	>8 mm
Children <2 yrs old	>6 mm

Table III. Recommended milk-specific IgE level (CAP-FEIA) 95% predictive of positive milk challenge

Cohort age	CAP-FEIA
Children >2 yrs old[6]	≥15 KUA/l
Children <2 yrs old[7]	≥5 KUA/l

Non-IgE-mediated CMA

There are no reliable tests for the diagnosis of non-IgE-mediated CMA. Initial diagnosis is based on a suggestive history and absence of positive SPT or ImmunoCAP-RAST. In these patients, the diagnosis primarily relies on a successful milk avoidance diet with clinical relapses after re-exposure to cow's milk proteins. In patients with atopic dermatitis in whom non-IgE-mediated cow's milk allergy is suspected, atopy patch testing (APT) may be a helpful diagnostic tool.[8]

Elimination-challenge testing

Food challenges remain the definitive procedure for the diagnosis of CMA. If the symptoms substantially improve or disappear after 2 - 4 weeks on an elimination diet, an open challenge with a formula based on whole cow's milk protein should be performed. Clinicians should be aware that the severity of a past reaction might not predict the severity of a challenge reaction, particularly after a period of dietary exclusion. Previous mild reactions may be followed by anaphylactic reactions in some infants with CMA. For this reason, open challenges should ideally be performed in a setting where resuscitation facilities are available. In a case of previous anaphylaxis, a challenge is contraindicated unless SPTs and/or specific IgE measurements show improvement. In these cases, the challenge should always be performed in a hospital setting.

- **Positive challenge: CMA confirmed.** If symptoms of CMA re-appear, the suspected diagnosis of CMA is confirmed and the infant should be maintained on an elimination diet using a milk substitute (discussed below) for at least 6 months. The challenge is then repeated. If it is possible to follow the infant with IgE-mediated allergy with SPTs and/or specific IgE determination, normalisation or improvement of these tests would help in choosing the time point of challenge. Supplementary feeding should be introduced carefully to avoid accidental intake of cow's milk protein.
- **Negative challenge: no CMA.** Children who do not develop symptoms on the cow's milk formula during challenge and up to 1 week after follow-up can resume their normal diet, although they should still be carefully monitored. Clinicians should advise parents to be attentive for delayed reactions, which may evolve over several days following the challenge.

Treatment of cow's milk allergy

Avoidance of cow's milk protein

Patients with cow's milk allergy must strictly avoid cow's milk and cow's milk protein-based products. Patients and their families must be instructed to read labels and identify milk-containing products. Particularly in young children, a well-balanced diet with sufficient intake of calcium and other essential nutrients must be ensured. The input of a paediatric dietician is most helpful in these patients. Mothers of breast-fed infants with CMA should continue breast-feeding but avoid causal foods.

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Alternative formulas (milk substitutes)

The recently published international guidelines[9,10] recommend extensively hydrolysed formulas (eHF) or amino-acid based formulas (AAF) as first-line alternatives for children with CMA.

In general, eHFs are nutritionally adequate but their main drawbacks are their bitter taste and expense (4 - 5 times the cost of standard formula – Table IV). Another potentially limiting factor is that most of the eHFs currently available in South Africa are not halaal or kosher.

Table IV. Relative cost of various formulas*

Modified cow's milk		
Lactogen	450 g	R35.50
Soya protein		
Isomil	450 g	R51.95
Infasoy	450 g	R56.00
Extensively hytrolysed		
Alimentum (casein)	450 g	R140.00
Nutramigen (casein)	400 g	R125.38
Alfare (whey)	400 g	R240.00
Pepticate (whey)	400 g	R199.95
Amino-acid		
Neocate	400 g	R499.91

*Retail prices, Dischem Pharmacy as at 1 January 2010.

The only AAF available in South Africa is Neocate® (SHS International, Rockville, USA). It is nutritionally adequate and well tolerated by children allergic to cow's milk and other foods. However, it is exorbitantly expensive (Table IV) and not widely available. Reimbursement for AAFs by health funders is also a potential problem – to date only a few medical aid societies have approved reimbursement for the use of AAF as a therapeutic formula and only for EGI disorders.

Soya formula is well tolerated in up to 85% of infants with IgE-mediated CMA but only in 50% of those with non-IgE-mediated CMA. However, soya is not recommended in infants below 6 months because of concerns about possible hormonal effects on the reproductive system (shown in animal studies) presumed to be due to phyto-oestrogens in the form of isoflavones (genistein, diadzen and their glycosides) present in soya protein. To date, no studies have evaluated safety of soya formula in humans – such studies are much needed.

Milk substitutes not recommended for treatment of CMA

Partially hydrolysed formulae (pHF) are contraindicated in the treatment of CMA (because of the high content of residual allergen – only 12 - 26% of cow's milk protein is hydrolysed in the currently available pHFs and there is a definite risk of allergic reactions to these products). Goat, sheep, buffalo and horse milk, unmodified soya and rice milk are also not recommended – these milks are not nutritionally adequate and may cross-react with proteins in cow's milk.

Specific oral tolerance induction

Avoidance may be difficult because accidental allergic reactions in children with CMA are common.[11] Specific oral tolerance induction (SOTI) or desensitisation is a promising therapy for IgE-mediated CMA. Randomised controlled trials have reported that about 35% of children become fully tolerant to cow's milk proteins after SOTI; 15 - 20% may not complete the procedure because of severe adverse reactions, but no fatal events have been documented. Follow-up data on children who become tolerant to cow's milk protein are inadequate and it is unclear where tolerance is transient or permanent.[12] Patients undergoing SOTI require careful monitoring. Various protocols have been described, some audacious and some prudent and the procedure is very time consuming. For these reasons, SOTI should be regarded for now as experimental therapy and must only be undertaken by practitioners who have been trained in this procedure.

Natural history

Earlier studies reported a good overall prognosis for CMA (i.e. developing tolerance to cow's milk protein), with most children outgrowing their allergy by 3 years of age. However, recent data suggest a less favourable prognosis. The prognosis appears to vary depending on whether the allergy is IgE-mediated or non-IgE-mediated, the titre of specific IgE at the time of diagnosis and the age of onset of CMA. A recent study involving 807 patients with IgE-meditated CMA reported rates of resolution as follows: 19% by age 4 years, 42% by age 8 years, 64% by age 12 years, and 79% by 16 years.[13] Children with IgE-mediated CMA are also at increased risk of developing other food allergies (up to 50%), allergy against inhalants (50 - 80%) as well as asthma and rhinoconjunctivitis in later childhood. Children of all ages with very high levels of specific IgE are likely to have persistent milk allergy. In contrast, non-IgE-mediated CMA generally resolves before the age of 1 year and these children are also less likely to develop multiple food allergy or allergy to inhalants. Onset of CMA in infancy has the most favourable prognosis.

Follow-up

Follow-up and re-evaluation of CMA are important. Follow-up assessment should include: adherence to diet, growth monitoring, control of co-existing disorders, reinforcement of key educational messages, e.g. reading food labels and preparedness for emergencies. Periodic re-challenges should be conducted to monitor tolerance (6 - 12-monthly). In cases of IgE-mediated CMA, milk-specific IgE levels should also be monitored periodically. Declining levels of specific IgE correlate well with development of tolerance.[14] A specific IgE level for cow's milk protein of 2 kU/l predicts a 50% chance of passing a challenge test.[15]

References available at www.cmej.org.za

In a nutshell

- Cow's milk allergy is one of the most frequent manifestations of food allergy and may present as an IgE- or non-IgE-mediated disease.
- Patients with IgE-mediated CMA and asthma are at risk of potentially severe allergic reactions.
- The diagnosis of CMA relies primarily on clinical evaluation (including oral challenge testing) supported by skin-prick testing and *in vitro* measurement of specific IgE.
- CMA can be adequately treated with dietary manipulation including avoidance of cow's milk protein products.
- Alternative formulas including eHF, AAF and soya formula may be used as milk substitutes. Selection of an alternative formula should be based on cost, availability, parental choice and religious factors.
- Soy is not recommended for infants below 6 months but may be considered in infants over 6 months of age with IgE-mediated CMA (85% of these infants will tolerate soya).
- Partially hydrolysed formulas are not recommended in the treatment of CMA.
- Specific oral tolerance induction (SOTI) is a promising new therapy for IgE-mediated CMA.
- All cases of CMA must be managed in collaboration with an experienced dietician who has expertise in food allergy. The dietician's role is to provide advice, recipes and education (reading food labels, checking for hidden ingredients, etc.) and to ensure nutritional adequacy. Severe cases of cow's milk allergy should be referred to a specialist with expertise in allergy.