

Cow's milk allergy in infancy

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Cow's milk allergy affects approximately 2% of infants under 2 years of age. This review summarizes the recent advances in understanding its pathophysiology and immunological mechanisms. Apart from IgE-mediated atopic manifestations, T cell-mediated reactions have been demonstrated in infants with cow's milk allergy. The clinical spectrum ranges from immediate-type reactions, presenting with urticaria and angioedema to intermediate and late-onset reactions, including atopic dermatitis, infantile colic, gastro-oesophageal reflux, oesophagitis, infantile proctocolitis, food-associated enterocolitis and constipation. The exact mechanisms of these disorders are still poorly understood. Double-blind, placebo controlled food challenge, the definitive diagnostic test for cow's milk allergy, is increasingly being replaced by the measurement of food-specific antibodies, in combination with skin-prick or atopy patch testing. The treatment of cow's milk allergy relies on allergen avoidance and hypoallergenic formulae, or maternal elimination diets in breast-fed infants. *Curr Opin Allergy Clin Immunol* 2:217–225. © 2002 Lippincott Williams & Wilkins.

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Abbreviations

AAF	amino acid-based formula
AD	atopic dermatitis
APT	atopy patch testing
CMA	cow's milk allergy
DBPCFC	double-blind, placebo-controlled food challenge
GOR	gastro-oesophageal reflux
MFPI	multiple food protein intolerance of infancy
s-ECP	serum eosinophil cationic protein
SPT	skin-prick testing
TGF- β	transforming growth factor beta
TNF- α	tumour necrosis factor alpha
Th	T helper

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Introduction

Cow's milk allergy (CMA) is defined as an immunologically mediated adverse reaction to cow's milk proteins [1,2^{••}]. In industrialized nations, CMA affects approximately 2% of infants under 2 years of age, and is the most common food allergy in this age group [3–8]. Parents may overestimate milk as a cause of symptoms, but unrecognized reactions may also occur [9]. Cow's milk is often the first major food protein ingested by formula-fed infants, and may lead to early allergic sensitization. CMA can also occur in exclusively breast-fed infants [10[•]]. CMA in infancy and early childhood can be regarded as a model of food allergies, as a significant number of sensitized infants have other allergies [11]. It is uncertain to what extent the development of food allergies and atopy can be prevented by dietary allergen avoidance [12[•],13,14].

CMA presents with a broad range of clinical symptoms and syndromes [1,8]. The clinical spectrum extends from acute anaphylactic manifestations to diverse disorders, such as atopic dermatitis, food-associated wheeze, infantile colic, gastro-oesophageal reflux (GOR), oesophagitis, cow's milk enterocolitis, food-associated proctocolitis and constipation [8]. The mechanisms underlying the various clinical manifestations are poorly understood [15]. Whereas food allergies in older children are mainly caused by IgE hypersensitivity, in young children non-IgE-mediated mechanisms are increasingly being recognized [1].

Cow's milk protein chemistry

Bovine milk contains approximately 3.5% protein. Milk proteins are classified into caseins, whey proteins, fat globule membrane proteins, enzymes and other minor components. Casein precipitates from raw milk by acidification, and constitutes 80% of milk protein synthesized by the mammary secretory epithelium. Casein can be fractionated into α_{s1} -, α_{s2} -, β - and κ -casein, comprising 32, 10, 28 and 10% of total milk protein, respectively [16,17]. Caseins aggregate in micelles that also contain colloid calcium phosphate. Whey proteins, or milk serum proteins, remain soluble after acid precipitation and constitute 20% of total milk proteins. The major whey proteins are β -lactoglobulin, α -lactalbumin (synthesized by the mammary epithelium), and bovine serum albumin, which originates from blood. β -Lactoglobulin is acid-stable and is likely to remain intact after passage through the stomach, which may explain its role as an allergen in CMA.

Immunogenicity of cow's milk proteins

Casein is one of the major cow's milk allergens. Its most abundant form, α_{s1} -casein, is the basis for most cow's milk-based infant formulae. α_{s1} - and β -casein are both phosphoproteins with no secondary structure because of a lack of disulphide bonds [16]. These proteins are therefore considered strong candidates for linear epitopes. κ -Casein differs from the other casein fractions in that it has a tertiary structure, and is more likely to contain conformational epitopes [17,18•].

Several major and minor binding epitopes for IgE and IgG have recently been mapped on α_{s1} -, β - and κ -casein [18•,19•]. Some of the IgE binding regions on α_{s1} -, β - and κ -casein were recognized only by older children with CMA (4–18 years) but not by patients under 3 years of age [18•,19•]. More recently, Järvinen *et al.* [20•] also demonstrated IgE and IgG binding epitopes of the whey proteins α -lactalbumin and β -lactoglobulin. Some epitopes of β -lactoglobulin, but none of α -lactalbumin, were associated with the persistence of CMA. Several allergenic epitopes on casein and whey proteins may thus be predictive of the long-term persistence of CMA beyond childhood, and may become useful prognostic markers in the future. An increase in humoral antibodies (specific IgE, IgG4 and secretory IgA) after the introduction of cow's milk, and a subsequent decline in antibody titres towards the age of 3 years, may be key mechanisms involved in the development of immune tolerance. High levels of specific IgE antibodies to linear epitopes from α_{s1} - and β -casein have been found to be predictive for persistence of CMA [21].

In infants with CMA, non-IgE-mediated mechanisms play an important pathophysiological role [1]. Schade *et al.* [22] provided evidence of T cell activation in infants with CMA and atopic dermatitis (AD). All infants with AD had evidence of specific T helper (Th) cell reactivity to major cow's milk proteins. However, infants with CMA showed a Th2 predominant cytokine profile (high levels of IL-4, IL-5 and IL-13), whereas infants without CMA had a Th1-skewed response (high level of IFN- γ , low IL-4, IL-5 and IL-13). That study inferred that antigen-specific Th2 cells may mediate the skin manifestations of children with AD and CMA.

Several heterogeneous T cell recognition sites for β -lactoglobulin have been identified in a study of Japanese children with CMA [23]. Elsayed *et al.* [24] studied the IgE and T cell recognition of α_{s1} -casein, its five purified cyanogen bromide cleavage fragments and 13 synthetic overlapping peptides. Sera from 18 Australian children with CMA, and peripheral blood mononuclear cells and T cells from five Norwegian adults with CMA were studied. After allergen stimulation of the peripheral blood mononuclear cells, T helper cell profiles (CD4

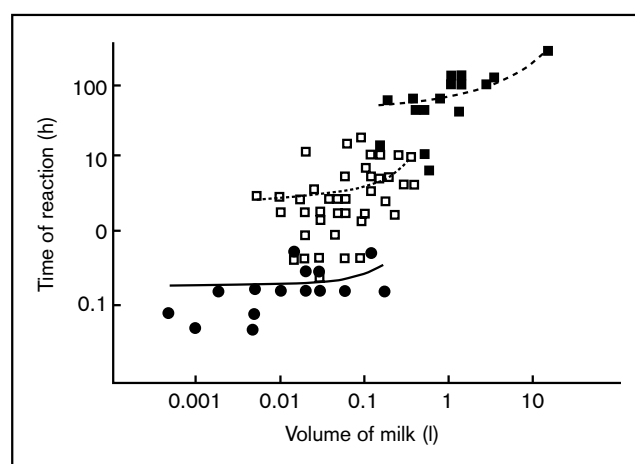
Th1, Th2, and Th0 cells) were characterized based on the cell culture filtrate content of cytosine. The Th2 subpopulation was the most prevalent. α_{s1} -Casein-specific T cells recognized most of the natural and synthetic peptides. Allergen-specific IgE and T cells recognized peptides of varying sizes along the entire chain of α_{s1} -casein, but peptides of less than six to eight amino acids were not recognized [24].

Timing of allergic reactions in relation to cow's milk intake

Clinical manifestations after challenge with cow's milk range from anaphylaxis and urticaria within minutes of challenge; distress, vomiting and diarrhoea within hours, to respiratory symptoms and atopic dermatitis flares after 24 h of ingesting cow's milk [25]. Three clinical patterns of allergic reactions to cow's milk have been identified (see Fig. 1).

Patients with immediate reactions develop acute skin rashes with perioral erythema, facial angioedema or widespread urticaria, with or without signs of anaphylaxis. These infants have high levels of cow's milk-specific IgE antibodies. The intermediate group reacts within 1 to 24 h after ingestion, and presents predominantly with gastrointestinal symptoms, including vomiting and diarrhoea. They do not exhibit features of IgE sensitization. The late group, with symptoms occurring from 24 h up to 5 days after cow's milk challenge, presents with flares of atopic dermatitis or the development of cough and wheeze. This group shows variable degrees of IgE sensitization and has evidence of allergen-specific T cell proliferation [25–28]. Carroccio *et al.* [29] have recently described a group of children

Figure 1. Onset of allergic reactions in relation to ingested volume of cow's milk



● Immediate; □ intermediate; ■ late.
Reproduced with permission from Hill *et al.* [8].

presenting with very delayed reactions after challenge with cow's milk protein. In their cohort of 86 young children with CMA on a cow's milk-free diet, 10 patients relapsed 4–26 days after re-challenge. Symptoms included constipation, persistent wheeze or exacerbation of AD.

Diagnosis of cow's milk allergy

Double-blind placebo controlled food challenge (DBPCFC) is the definitive test for CMA [30–32]. DBPCFC, however, is resource consuming and not without risks. Several studies have therefore examined to what extent specific serum IgE antibody, skin-prick testing (SPT) or atopy patch testing (APT) can replace formal food challenges in the diagnosis of food allergies [33,34*,35–38,39*,40*,41–44,45*].

Cow's milk-specific serum IgE antibodies

IgE antibodies to cow's milk antigens have been shown to be a useful tool in the assessment of immediate-type CMA [33,34*,35,36]. Sampson and Ho [33] measured food-specific IgE antibodies in serum samples from 196 patients with atopic dermatitis, allergic rhinitis or asthma, and challenge-confirmed food allergies. In their study, food-specific IgE cut-off levels for cow's milk, egg, peanut and fish were determined that predicted the outcome of food challenges with more than 95% accuracy. These findings have recently been validated by the same authors in a prospective study of 100 consecutive children and adolescents with suspected food allergies [34*]. The previously found diagnostic cut-off levels for food-specific IgE antibodies were effective in predicting symptomatic allergy to cow's milk, egg, peanut and fish. The use of food-specific IgE testing may therefore significantly reduce the need for formal DBPCFC.

Other investigators have made similar observations. In a study of 170 infants under 12 months of age with suspected CMA [35], 44% had the diagnosis confirmed on subsequent challenge. A specific IgE greater than 2.5 KU(A)/l had a positive predictive value of 90% for immediate CMA. Saarinen *et al.* [36] found a much lower predictive value for specific IgE antibodies, even if used in conjunction with SPT or APT. These differences may be partly due to patient selection and different extract potencies.

Serum eosinophil cationic protein

Thirty-five children with CMA (mean age 16 months) were evaluated for serum eosinophil cationic protein (s-ECP) levels before and after cow's milk challenge [37]. Median s-ECP levels were higher in children who reacted on challenge, although the difference was not statistically significant. Saarinen *et al.* [36] found that levels of s-ECP greater than 25 µg/l were highly specific

for positive CMA challenges (specificity 98%), but lacked sensitivity. The clinical value of s-ECP as a diagnostic tool thus remains uncertain.

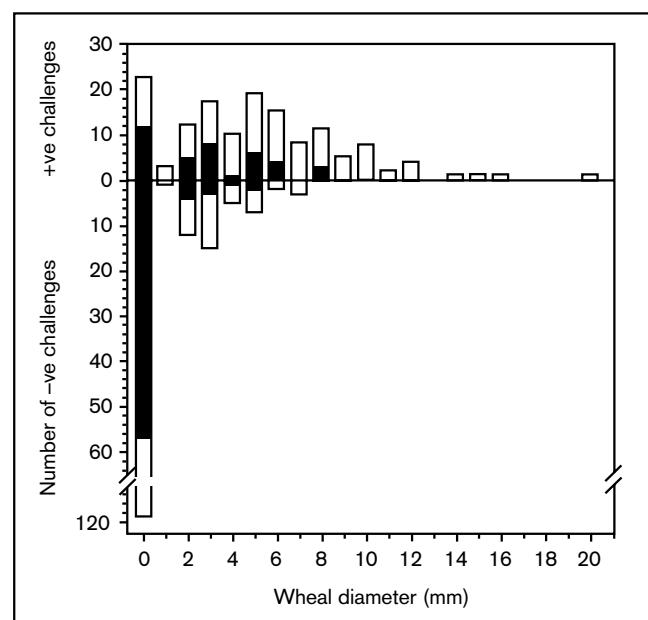
Skin-prick testing

SPT in the diagnosis of CMA is said to be unreliable in infancy. Sporik *et al.* [38] studied the 'diagnostic' wheal diameter to cow's milk, egg and peanut that was 100% predictive of a positive open food challenge. The cut-off wheal diameter was defined as the diameter above which all children presenting with suspected food allergy reacted (see Fig. 2). All children over 2 years with an SPT wheal diameter to cow's milk greater than 8 mm, and those under 2 years with an SPT greater than 6 mm, were challenge-positive. These 'diagnostic' cut-off wheal diameters were compared with food-specific IgE antibody levels in Australian children under 2 years of age [39*]. Compared with in-vitro antibody testing, the use of 'diagnostic' SPT tests reduced the need for food challenges by 23%. Further studies are needed to confirm these observations.

Atopy patch testing

Non-IgE-mediated hypersensitivity reactions to food are difficult to diagnose as they are not reliably detected by antibody or SPT [40*]. The APT is an epicutaneous test that was originally developed to diagnose sensitization to

Figure 2. Skin-prick test wheal diameter to cow's milk in relation to open challenge outcome in children with suspected cow's milk allergy



Open bars indicate positive food challenge, closed bars indicate negative challenge. Reproduced with permission from Sporik *et al.* [38].

aeroallergens [41]. Patch test skin reactions appear to be mediated by T cell responses [42]. Several studies have assessed the diagnostic accuracy of the APT in relation to SPT and serum IgE testing [43,44]. Majamaa *et al.* [43] found the APT to be more sensitive than SPT and IgE testing in detecting CMA in infancy. A study of 75 German children (age range 4 months to 12 years) [44] examined the diagnostic accuracy of the APT for cow's milk, egg, wheat and soybean. Findings were compared with formal DBPCFC and food-specific serum IgE antibodies. The APT was particularly useful in predicting late-phase clinical reactions (sensitivity 76%, specificity 95%). Roehr *et al.* [45•] reported that APT, in conjunction with positive food-specific IgE levels or positive SPT, reliably predicted positive food challenges, and argued that these tests may replace DBPCFC in the diagnosis of CMA. In summary, APT appears to be particularly useful in detecting non-IgE-mediated forms of food allergy, but it requires further prospective evaluation.

Cow's milk allergy in breast-fed infants

Breast-feeding is generally considered to be the most appropriate form of infant feeding as it may reduce the risk of the subsequent development of atopic disease [46,47]. However, a large study of 6209 infants [48] found that prolonged breast-feeding may increase the risk of IgE-sensitization. Allergic IgE sensitization can occur as early as during the fetal period [49,50]. Multiple food sensitization has been described in breast-fed infants [51]. There is increasing evidence that ingested cow's milk and other food antigens are secreted into human milk, and can potentially sensitize the breast-fed infant [10•,52–54]. By contrast, a recent Italian study [55] was unable to confirm the presence of bovine antigens in human milk, as assessed by gel electrophoresis, and argued that previous positive findings were caused by cross-reactivity with human milk proteins.

Immunological host factors may predispose to sensitization to food allergens through breast milk. Transforming growth factor beta (TGF- β) is considered to be an important immunoregulator in promoting the development of oral tolerance. During early infancy, breast milk is the main source of TGF- β . Kalliomäki *et al.* [56] found that TGF- β promotes specific IgA production in human colostrum. IgA antibodies in human milk have a protective effect on the sensitization to food allergens as they may prevent antigen entry at the intestinal surface of infants. In a study of 87 breast-fed infants, IgA concentrations in colostrum and human milk were significantly lower in mothers whose infants developed CMA in the first 12 months of life [57]. Other factors that may mediate the immune response to ingested food antigens include regulatory lymphokines such as tumour necrosis factor alpha (TNF- α) and IFN- γ . TNF- α is

produced by activated macrophages and T lymphocytes in human milk, and upregulates human leukocyte antigen class II expression. In a study of 43 breast-feeding mothers of infants with challenge-confirmed CMA [58], TNF- α production of milk leukocytes was significantly lower than in 16 healthy controls; IFN- γ production was similar in both groups. That study suggested that defective TNF- α production may be a factor impeding the development of oral tolerance to ingested food antigens in breast-fed infants.

Intolerance to extensively hydrolysed formula

Extensively hydrolysed formulae are commonly used in the treatment of infants with CMA. Over a 10-year period, the Melbourne Food Allergy Studies identified 60 infants who were allergic to cow's milk, hypoallergenic formulae (soy and extensively hydrolysed formulae), as well as several protein-containing foods, including egg, wheat, peanut and fish. This syndrome was called 'multiple food protein intolerance of infancy' (MFPI) [59]. Other centres have subsequently confirmed these observations [60–62]. It has been estimated that approximately 10% of infants with CMA are intolerant to extensively hydrolysed milk protein formula [63]. Infants with MFPI need to be distinguished from those with 'oligo-food hypersensitivity', who may be intolerant to common food proteins, including milk, but who tolerate soy or extensively hydrolysed milk formula. Children with oligo-food hypersensitivity do not encounter the complex nutritional problems of patients with MFPI.

The clinical manifestations of infants with MFPI include persistent crying and distress, vomiting/regurgitation, diarrhoea, failure to thrive or AD [59]. Symptoms usually develop during breast-feeding, and continue while ingesting extensively hydrolysed or soy formulae. A remission of symptoms can be achieved with amino acid-based formula (AAF) and a small number of hypoallergenic foods. Subsequent long-term follow-up until the age of 3 years demonstrated that most of these patients tolerated non-formula foods by the age of 2 years, and only three required long-term nutritional support with AAF at 3 years of age [64]. de Boissieu *et al.* [61] confirmed these findings, and described a subgroup of infants with hypersensitivity to cow's milk and extensively hydrolysed formula alone; in these infants disease remitted at an earlier age.

Recently recognized manifestations of cow's milk allergy

A significant proportion of infants with CMA present with features of IgE-sensitization, including anaphylaxis, urticaria and angioedema. As these syndromes are familiar, the authors will concentrate on aspects of the more recently recognized slowly evolving manifestations

of CMA, including AD, infantile colic, GOR, oesophagitis, cow's milk enterocolitis, food-associated proctocolitis and constipation [1,65].

Atopic dermatitis

AD is a chronic relapsing inflammatory skin disorder associated with increased serum IgE levels, allergen sensitization and a family history of allergic diseases [66,67]. The role of hypersensitivity to dietary antigens in the induction and maintenance of this chronic inflammatory response remains controversial. Hanifin [68] estimated that only 10% of children with AD have food allergies, whereas Sampson [69] reported that 74% of highly selected children with AD deteriorated on formal food challenge. In a study of 620 Australian children with a positive family history of food allergy [70], the association of high-level sensitization to foods and the presence of AD were prospectively evaluated. The frequency of IgE food allergy to cow's milk, egg and peanut was diagnosed by measuring SPT wheal diameters to extracts of these substances, using 'diagnostic' wheal diameters [38]. More infants with AD had positive SPT (≥ 6 mm wheal) to cow's milk, egg or peanut than those without AD. The calculated attributable risk for IgE-mediated food allergy as a cause of AD was 65% at 6 months, and 62% at 12 months. At 6 months, 83% of infants with severe AD had evidence of food sensitization, and 65% at 12 months. On the basis of these results, most infantile eczema is caused by an IgE-mediated adverse reaction to foods. A recent murine model of AD highlighted the potential importance of food-specific IgE antibodies [71]. The management of infantile AD should therefore incorporate appropriate strategies to diagnose and manage underlying food allergies.

Infantile colic and persistent distress

Persistent crying is a common paediatric problem that may affect up to 40% of young infants [72]. In the majority of cases, the distressed behaviour gradually improves by 3–4 months of age. In less than 5% of infants can the distressed behaviour be explained by an underlying medical aetiology [73]. However, in infants with unremitting distress persisting beyond the typical colic period, an underlying organic cause may be more likely [74].

The mechanisms leading to infantile colic are poorly understood, and the role of dietary factors in infantile colic has remained controversial [75]. Several studies have demonstrated a therapeutic benefit of extensively hydrolysed formula on crying in infants with colic [76,77]. An evaluation of such studies by meta-analysis demonstrated a modest treatment benefit of hypoallergenic formulae [78]. There is also anecdotal evidence that AAF may reduce crying in these infants [74,79].

Besides the effect of food allergies, interactive factors and behaviour patterning may also influence the clinical course of infantile colic [73].

Gastro-oesophageal reflux and oesophagitis

GOR is common in infancy and is considered to be pathological if it causes oesophagitis, failure to thrive or respiratory symptoms. The majority of infants will outgrow GOR by 12–18 months of age [80]. GOR has traditionally been considered to be a primary motility disorder. However, a secondary form caused by food protein allergies has been demonstrated [81]. In young children, both disorders are difficult to differentiate on the basis of clinical presentation [82]. CMA may cause delayed gastric emptying and gastric dysrhythmias and may induce reflex vomiting or exacerbate the symptoms of GOR [83•].

In a large study of 204 infants with histologically confirmed oesophagitis, more than 40% of patients had evidence of CMA and improved symptomatically on hydrolyzed formula [81]. Furthermore, infants with persistent distress and symptoms of GOR may respond to AAF [74]. It is generally assumed that oesophagitis is the direct result of peptic injury as a result of prolonged acid exposure to the oesophagus. However, non-acid peptic oesophagitis may be common in young infants. In a study of 125 infants with persistent distress and GOR symptoms, the relationship between pH monitoring findings and upper gastrointestinal histopathological findings was studied [84]. A total of 25% of infants had oesophagitis, but diagnostic agreement between the duration of oesophageal acid exposure on pH monitoring and the histological severity of oesophagitis was poor. These findings suggest that oesophagitis in young infants may not always be caused by acid-peptic injury, but may instead be part of an upper gastrointestinal inflammatory reaction associated with sensitization to food proteins, including cow's milk. The exact mechanisms require further investigation.

Other gastrointestinal manifestations

Apart from GOR, infants with CMA may present with a variety of gastrointestinal manifestations, including cow's milk-induced enterocolitis, allergic proctocolitis or constipation [1,65,86,87,92–94,98,99]. The mechanisms leading to the involvement of different parts of the gastrointestinal tract are still poorly understood [15].

Cow's milk-induced enterocolitis

CMA may present with vomiting, chronic diarrhoea, malabsorption and failure to thrive caused by widespread small intestinal damage [85,86]. On small bowel biopsy, a picture similar to coeliac disease may be found, with blunting of the villi and crypt elongation [87]. Intestinal permeability may be increased in patients with CMA

and may increase the risk of further antigenic sensitization [88]. Furthermore, protein loss from the bowel may be increased, as evidenced by the increased excretion of faecal α 1-antitrypsin [89•]. It appears that as a result of the availability of more appropriate cow's milk-based infant formulae and an earlier diagnosis of the condition, the prevalence of severe cow's milk enteropathy has declined. There is, however, recent evidence that cow's milk enteropathy may persist to school age [90•]. Some of these children may have only subtle clinical manifestations while ingesting small amounts of cow's milk protein [91].

Allergic proctocolitis

Infants with CMA may present with mild diarrhoea and rectal bleeding caused by allergic colitis [92]. Other systemic features are usually absent, and the infants appear generally well [93]. Allergic proctocolitis affects both breast- and formula-fed infants, and may present as early as on the first day of life [93–95]. An increase in intraepithelial lymphocytes (CD3+) can often be demonstrated in the colonic mucosa [96•]. This increase involves both T cell receptor α/β - and γ/δ -positive intraepithelial lymphocytes, consistent with an immunological response to intraluminal antigens. Infants usually respond within days to treatment with extensively hydrolyzed formula or AAF, or if breast-fed, to a maternal elimination diet [93,97]. Lake [93] found that in breast-fed infants, 65% responded to maternal cow's milk exclusion alone, whereas the remainder appeared to improve after the exclusion of egg, corn, soy or multiple foods. The prognosis is usually excellent, and most infants with allergic proctocolitis will develop tolerance to cow's milk protein by 12 months of age.

Constipation

Constipation may develop as a manifestation of CMA [98,99]. Iacono *et al.* [98] presented a series of 65 children under 6 years of age who presented with refractory constipation, often associated with anal fissures. Forty-four (68%) responded to treatment with soy milk and relapsed on subsequent challenge with cow's milk protein. Mucosal inflammation in the rectal biopsies was significantly associated with CMA. That study suggested that in a subgroup of infants and young children constipation may respond to cow's milk exclusion. The study has, however, been criticized for its methodology [100], and there remains controversy as to whether constipation is a clinical manifestation of CMA in young children.

Treatment and prognosis of cow's milk allergy

The diagnosis of CMA should be based on established diagnostic guidelines [2••] in order to avoid unnecessary dietary restrictions [101•]. The treatment of CMA

follows the general principles of allergen avoidance. Soy formula is often used as a cow's milk substitute. However, a significant proportion of infants with CMA may also be sensitized to soy protein [63,102]. Low-allergen solids (e.g. rice cereal, apple, pear, potato, pumpkin) are usually tolerated by 6 months of age, but the introduction of highly allergenic food items (e.g. egg, peanut and tree nuts) should be deferred until the second year of life. The value of partly and extensively hydrolyzed formulae in preventing and treating CMA is still controversial [12•,103,104]. It has been estimated that approximately 10% of infants with CMA may be intolerant of extensively hydrolyzed formulae [60–63,105]. In these infants, AAF has proved effective and safe [64,106•,107,108•].

In breast-fed infants, a maternal elimination diet is often effective, and may be of particular benefit in infants presenting with colic or AD [109]. An experienced dietitian should closely supervise the maternal diet, and dietary calcium supplementation may be required for the mother [97]. In infants on therapeutic elimination diets, growth parameters need to be closely monitored as energy and micronutrient intakes may be reduced compared with normal infants [110].

Approximately 85% of infants with CMA will develop tolerance to cow's milk protein by 3 years of age [5,6]. A 10-year study of 56 children with CMA showed a three- to fourfold increased risk of developing respiratory disease or AD, compared with 204 age-matched controls [111]. These conditions developed independently of the persistence of CMA. Although allergen avoidance appears to hasten the subsequent development of antigen tolerance, it remains unclear to what extent dietary manipulations alter the course of food allergies [12•,13]. Probiotic bacteria (*Lactobacillus* GG), if administered to mothers during pregnancy and postnatally to their infants for 6 months, have been shown to reduce the risk of subsequent atopic disease significantly [112•,113•]. This protective effect may be mediated by an increase in TGF- β concentrations in breast milk [113•].

Conclusion

Our understanding of the immunology and clinical presentations of CMA has improved over the past decades. Apart from the 'classic' IgE-mediated form of CMA, presenting with urticaria and angioedema, a spectrum of slowly evolving, non-IgE-mediated manifestations of CMA has been recognized. In infancy, manifestations of CMA may be mediated by antigen-specific activated T helper cells with a Th2-predominant profile. The exact mechanisms require further investigation. The definitive test for CMA remains the DBPCFC. However, the need for these resource-consuming

challenges can be reduced by the measurement of food-specific IgE antibodies, if used in conjunction with SPT. In the majority of cases, CMA remits spontaneously by 3 years of age. The persistence of CMA beyond early childhood has been linked to sensitization to several specific allergenic epitopes of casein and whey proteins. Hypoallergenic formulae (soy, extensively hydrolyzed or amino acid-based formulae) are the mainstay of treating infants with CMA. Elimination diets may compromise the energy and micronutrient intake, and growth parameters of infants with CMA need to be closely monitored. In breast-fed infants, maternal elimination diets have been shown to be effective. There is increasing evidence that probiotic bacteria may reduce the prevalence of food allergies and atopy in at-risk populations.

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