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ABSTRACT

Cow's milk protein (CMP) is usually one of the first complementary foods to be introduced into the infant's diet and is commonly consumed throughout childhood as part of a balanced diet. CMP is capable of inducing a multitude of adverse reactions in children, which may involve organs like the skin, gastrointestinal (GI) tract or respiratory system. The diagnosis of CMP-induced adverse reactions requires an understanding of their classification and immunological basis as well as the strengths and limitations of diagnostic modalities. In addition to the well-recognised, immediate-onset IgE-mediated allergies, there is increasing evidence to support the role of CMP-induced allergy in a spectrum of delayed-onset disorders ranging from GI symptoms to chronic eczema. The mainstay of treatment is avoidance of CMP; this requires dietetic input to ensure that this does not lead to any nutritional compromise. This review is intended to highlight the broad spectrum of manifestations of CMP allergy and to offer an approach to the diagnosis and treatment thereof.

The use of cow's milk by humans began some 9000 years ago with the domestication of cattle. The method for making cheese from milk was known to the ancient Greeks and Romans. Substitutes for human milk existed long before the modern age of infant formulas but non-human mammalian milks were nutritionally inadequate and carried the risk of disease transmission such as bovine tuberculosis and brucellosis. However, as general sanitation measures improved during the latter part of the 19th century and as the differences in composition between human milk and cow's milk became better understood, the use of "humanised" animal milks became commonplace. Despite the many advances in the modification of cow's milk formulae, human breast milk remains unchallenged as the "gold standard" infant milk.[1]

It is thought that between 5% and 15% of infants show symptoms suggestive of an adverse reaction to cow's milk protein (CMP), while estimates of the prevalence of cow's milk protein allergy (CMPA) vary from 2% to 7.5%.[1] This review is intended to distinguish between non-allergic and allergic hypersensitivity reactions to cow's milk and highlight the broad spectrum of manifestations of CMPA and to offer a pragmatic approach to treatment; it is not a formal guideline, although many such guidelines have been produced both within Europe and internationally.[2a]

NOMENCLATURE

Before considering the spectrum of adverse reactions to cow's milk, it is worth clarifying commonly used nomenclature. Terms such as *food allergy*, *food intolerance* and *food hypersensitivity* are often used interchangeably, despite representing different conditions.

A recent classification with the World Allergy Organization (WAO) defines any adverse reaction to food as food hypersensitivity which can be divided into immune-mediated reactions (food allergy) and non-immune-mediated reactions (food intolerance). Food allergic reactions may be broadly divided into IgE-mediated (immediate-onset) reactions and non-IgE-mediated (delayed-onset) reactions[3] (table 1). Unfortunately, many patients and physicians still refer to delayed, non-IgE-mediated reactions to cow's milk as cow's milk intolerance, which erroneously implies a non-immune-mediated mechanism as well as allowing further confusion with lactose intolerance.

NON-IMMUNE-MEDIATED HYPERSENSITIVITY TO COW'S MILK

Lactose intolerance

Lactose is a disaccharide found in cow's milk and is digested in the small intestine by the brush border disaccharidase, lactase.[4] Three major types of lactose intolerance exist: congenital, primary (which includes congenital) and secondary. Congenital absence of intestinal lactase is extremely rare and is a lifelong disorder characterised by faltering growth and infantile diarrhoea from the first exposure to human milk, which contains lactose. This condition is isolated to small populations of Finns and Russians.[5] Conversely, primary lactose intolerance (hypolactasia) is common, and this genetically determined trait differs in frequency worldwide due to *cis*-acting polymorphism of regulation of lactase gene expression.[6 7] Secondary lactose intolerance refers to those patients that loose lactase enzyme expression in the brush border of intestinal villi secondary to inflammatory or structural damage called *enteropathy* (ie, viral gastroenteritis, giardiasis or coeliac disease). This is usually reversible and recovery is dependent on treatment or resolution of the underlying condition.[4]

Lactose intolerance is easily mistaken for non-IgE-mediated CMPA[8] due to symptom overlap. Symptoms arise due to the osmotic effects of lactose and fermentation thereof by intestinal bacteria. This may cause excessive flatus, explosive

Table 1 Classification of food hypersensitivity reactions

IgE-mediated, immediate onset, reactions	
Gastrointestinal	Gastrointestinal anaphylaxis: symptoms include, vomiting, pain and/or diarrhoea
Cutaneous	Urticaria, angioedema, pruritus, morbilliform rashes and flushing
Respiratory	Acute rhinoconjunctivitis, wheezing, coughing and stridor
Generalised	Anaphylaxis
Mixed IgE and cell-mediated, immediate to delayed onset, reactions	
Gastrointestinal (GI)	Eosinophilic oesophagitis
Cutaneous	Atopic eczema
Cell mediated	
Gastrointestinal	Food protein-induced enterocolitis, food protein-induced proctocolitis and food protein-induced enteropathy syndrome—which may present with a clinical picture of "sepsis"
Respiratory	Food-induced pulmonary haemosiderosis (Heiner syndrome) (rare)—pulmonary haemosiderosis or bleeding in the lower respiratory tract
Mechanism uncertain	
GI dysmotility	Gastro-oesophageal reflux* Constipation* Infantile colic*

*These associations remain controversial.

diarrhoea, perianal excoriation, abdominal distension and pain. A diagnosis of lactose intolerance is made through the elimination and re-challenge of lactose, assessing stools for reducing sugars, hydrogen breath test (postlactose exposure) or, more rarely, by intestinal biopsy. Both the hydrogen breath test and tests for reducing sugars are helpful in older children but are frequently positive in babies <3 months. The mainstay of treatment of lactose intolerance is the total or partial dietary avoidance of lactose-containing foods (depending on the type of lactose intolerance) while achieving optimal nutritional intake.

IMMUNE-MEDIATED REACTIONS TO COW'S MILK

Cow's milk protein

Cow's milk constitutes of both casein and whey proteins. The coagulum (casein proteins) accounts for about 80% of the total protein content in cow's milk and the lactoserum (whey) for the rest. Casein consists of four protein fractions: α_{s1}- (32%), α_{s2}- (10%), β- (28%) and κ-casein (10%). The major whey globular proteins include α- and β-lactoglobulin, which contribute 5% and 10% of total milk protein, respectively.[9]

IgE-mediated CMP-induced reactions

IgE-mediated (immediate) food allergy affects between 3% and 6% of young children in the developed world, with CMPA and hen's egg allergy being the most common food allergies.[3 10–12] Food allergy is now considered a public health concern in the UK, as the condition is associated with significant morbidity and occasional mortality.[13]

Although genetic factors are important in the development of food allergy, the increased prevalence has occurred over a short period, a phenomenon that is unlikely to be due to germ-line genetic changes alone. As the exact mechanisms of sensitisation to milk are not clearly defined, the impact of environmental factors remains unclear. There is evidence to suggest that maternally ingested CMP reaches the fetus, albeit in extremely small amounts.[14] Although IgE is produced by the fetus from early gestation, there is little evidence to support the presence of detectable CMP-specific-IgE in cord blood. Two large birth cohort studies were unable to demonstrate measurable food-specific IgE in cord blood, even in those children who subsequently developed clinical or immunological food sensitisation.[15 16]

When the introduction of breast feeding is delayed or not possible post partum, it is common practice to offer a CMP-based formula to newborn infants. This early feed may represent the index "sensitising-event",[17] which can lead to B cell class switching and specific-IgE production with subsequent exposure to even minute amounts of bovine milk protein in human milk acting as a "booster sensitising dose" or even elicit allergic reactions in a significant proportion of breastfed CMPA neonates.[18 19] There are, however, two randomised studies that contradict this, suggesting that early CMP exposure is not a significant risk for the subsequent development of CMPA in both preterm and term infants.[20 21] Thus CMPA can present early in life, often before the ingestion of CMP, suggesting that ingestion is not the only route, or mechanism, for sensitisation. Indeed, when CMPA is already established, routes of exposure such as skin contact (eg, kiss contact) or inhalation of CMP-cooking vapours may induce allergic reactions.[22 23]

IgE-mediated CMP-induced allergic reactions typically occur within minutes of exposure and range in severity from mild (eg, urticaria and/or angioedema) to severe and potentially life-threatening anaphylaxis (respiratory or cardiovascular compromise or collapse).[24] Reactions to accidental exposure are frequent in children with CMPA: the proportion of children with severe reactions is as high as 15%. Risk factors for severe reactions include very high levels of specific IgE to cow's milk and casein, and asthma.[25] Although rare, fatalities due to CMP-induced anaphylaxis have been reported.[26]

A prompt diagnosis of CMPA facilitates the strict avoidance of CMP-containing foods and the implementation of a personalised management plan. The diagnosis of CMPA is based on one or more of the following: a detailed clinical history (table 2), allergy testing (skin prick testing (SPT) and/or measurement of specific serum IgE) and if required, a supervised incremental oral challenge. An unequivocal history of allergic symptoms after milk exposure, coupled with evidence of sensitisation (on either skin prick test or specific IgE blood testing) makes a near-certain diagnosis. However, if the history is equivocal and allergy tests negative or if there is a positive test and an unconvincing history, then a supervised incremental oral milk challenge is required to resolve any diagnostic uncertainty. An "open" unblinded challenge is usually adequate for

Table 2 Allergic history

Questions should aim to establish the following:	Significance
What is the food allergen causing the index reaction?	Is the allergen typical for age? For example, allergies to cow's milk are common in young children but far less common in the second decade of life. In breastfed infants, it may not always be appreciated that CMP—transmitted via human milk—is responsible for the symptoms. Heat processing of the allergen is important. For example, a significant number of milk allergic children will tolerate heated milk—for example, baked milk, while still react to milk that is only heated to temperatures required for pasteurisation
What is the timing of the reaction postexposure?	IgE-mediated CMPA reactions usually occur within 20 min of exposure and always within 2 h thereof. Non-IgE-medicated CMP-induced immune reactions are typically more delayed in onset
Describe the allergic symptoms?	While symptoms are usually typical (as per table 1), CMP-induced reactions may not always be obvious—for example, the young infant who has a CMP-based formula "aversion". However, if symptoms are not typical of an immediate onset IgE-mediated reaction then a differential diagnosis must be considered. For example, a child who actively refuses CMP may do so for reasons other than allergy such as behavioural difficulties, oral tactile aversion or odour sensitivity; these children may falsely be labelled as being "allergic"
What is the route of allergen exposure?	A proportion of patients will react after skin contact or inhalation of CMP
What is the symptom severity?	A severe allergic reaction warrants a more stringent emergency management plan
Is there a history of CMP tolerance?	It is rare to have a history of ongoing tolerance to cow's milk before developing CMPA. Most infants with CMPA presents during infancy and usually after a single or only a few CMP exposures
Concomitant Disease, and in particular, Allergic Disease?	It should be determined if the patients diet is complete, are they at risk for nutritional compromise such as nutritional rickets? The majority of children with CMPA will have eczema. At least 25% of CMPA will go on to develop additional food allergies. Food-allergic infants are at risk for the development of asthma: asthma is a risk factor for more severe food-induced allergic reactions

CMP, cow's milk protein; CMPA, cow's milk protein allergy.

diagnosis whereas a double-blinded challenge is occasionally required, if the open challenge results in atypical or subjective features. Table 3 details aspects of milk challenges. The greater the SPT weal diameter or higher the specific IgE value to milk, the greater the probability that the child is clinically allergic. Higher test values do not, however, predict for a greater severity of future reactions. The need to perform food challenges is reduced by the use of age-dependent diagnostic decision points (table 4). These decision points may vary between centres and are influenced by variables such as age of the patient and concomitant allergic disease. Diagnostic decision points will therefore be most accurate when established for the community served by each specific allergy centre. European guidelines for the diagnosis of CMP allergy have been published.[2]

Recent advances in specific IgE testing allows for a more detailed diagnosis of an individual's CMPA. Advances include biotechnology that allows for the cloning, sequencing and expression of allergen components. For example, IgE testing can now be routinely performed to many of the CMP components such as α-lactalbumin, β-lactoglubulin, bovine serum albumin, casein and D-lactoferrin. Individual patients may react to one or more of these specific proteins, and each protein has specific characteristics. For example, casein is relatively heat stable and resistant to pepsin digestion. These characteristics may account for the variability in clinical reactivity and tolerance to milk and dairy products between patients and in the same patient over time. It is hoped that an increased understanding in the use of these novel IgE-component assays will enable the clinician to better predict for tolerance to cow's milk, heated cow's milk, or even different components of cow's milk—for example, whey proteins.[27]

The use of atopy patch testing (APT) has also been investigated for the diagnosis of both IgE and non-IgE CMP-induced immune reactions. Use of the APT is, however, subject to extreme variability as standardised tests do not exist for all foods. Variables include choice of allergen (and vehicle), test materials (eg, type and size of chamber) and technique (duration of application, time of reading and criteria used for the determination of a positive result). The role of the APT in routine allergy practice remains uncertain; in 2006, EAACI/GA2LEN released a position paper that reviewed the present status of the APT; however, in the UK, its use is restricted to research centres.[28–31]

IgE-mediated CMPA is generally a childhood allergy with at least 19% of children developing tolerance by 4 years of age, 42% by 8 years and 79% by 16 years.[24] Tolerance is initially acquired to extensively heated cow's milk—for example, baked foods, where the conformational epitopes are destroyed by heat. Indeed, about 70% of children with CMPA will tolerate extensively heated milk products; these children tend to outgrow their allergy earlier than those who react to extensively heated milk. Heated milk-reactive children have significantly larger skin prick test weals and higher milk-specific IgE and casein-specific IgE levels than the heated milk-tolerant children. Children who outgrow their milk allergy have milk-specific IgE antibodies primarily directed against conformational epitopes while those with persistent milk allergy have IgE antibodies directed against specific sequential epitopes. Children who have experienced only mild allergic reactions (ie, skin symptoms only) may also stand an increased chance of outgrowing their allergy. Although CMPA is a rare food allergy in adulthood reactions may be severe in nature.[32] This information may help better define likely prognosis and potential severity of reactions.

Non-IgE-mediated cow's milk-induced reactions

In addition to the well-recognised immediate-type IgE-mediated allergies, there is increasing evidence to support the role of CMP-induced immune-mediated reactions in a wide spectrum of other clinical disorders. Despite the lack of a clear role of IgE in the pathogenesis, these conditions are more common in atopic children, involve allergic inflammation and improve on CMP exclusion.[33] The major challenge to the diagnosis of non-IgE-mediated CMPA is the lack of a validated diagnostic

Table 3 Oral challenges to cow's milk

Rationale	Challenges are usually performed to elicit tolerance to an age-appropriate quantity of pasteurised cow's milk or formula—for example, 120–200 ml (age depending). There are, however, many other reasons as for undertaking a cow's milk challenge
Indications	Most allergy centres seek to achieve a 50% negative challenge outcome rate. The clinician needs to estimate this risk through considering one or more of the following variables: previous reaction severity, tolerance of extensively heated milk, concomitant asthma, age of the child and allergy test results (these may include one or more of specific IgE, IgE component tests, SPT to milk extract and fresh milk)
Setting	It is difficult to predict for the likely severity of future milk-induced allergic reactions. The majority of challenges can safely be performed in a Day Ward setting. If the challenge is considered "high risk", then a high care setting should be available with access to a PICU. Home challenges may safely be performed for non-IgE-mediated milk allergy outcomes, but only in the absence of evidence of an IgE-mediated milk allergy. If eczema is to be used as an outcome, then the patient may need to attend at set intervals for the standardised assessment thereof
Design	An "open" unblinded challenge is usually adequate for a certain diagnosis (particularly if the outcome is negative ie, tolerance). A double-blinded placebo-controlled food challenge (DBPCFC) is occasionally required to establish an unequivocal diagnosis of allergy. In order to minimise false positive results, research study designs need to make use of DBPCFC's. There are many possible variations to a challenge design; these include food used, number of incremental doses, intervals between doses, dose quantities, use and type of placebos. Challenges performed for the investigation of non-IgE-mediated allergies may include designs that make use of elimination and re-introduction diets
Safety	Supervised milk challenge in a controlled medical setting have an excellent safety record with no fatalities reported. Nonetheless, safety is increased by following basic challenge principles: patients should avoid medicines that may mask symptoms or indeed prevent the treatment of symptoms before undergoing the challenge resuscitation skills and equipment should be to hand a detailed clinical examination, to ensure the patient is well and free from active asthma, is mandatory before commencing any existing "rashes" should be clearly identified in order that confusion does not arise once the challenge has commenced use a low starting dose as most reactions occur early on in a challenge as do most severe allergic reactions challenges performed for the diagnosis of cow's milk-induced FPIES should be performed with a cannula in situ and facilities for ongoing supervision in the event of significant and prolonged dehydration
Follow-up postchallenge	A clear emergency and dietary plan, based on the challenge outcome, needs to be generated and communicated to the patient/family and healthcare practitioners. Appropriate emergency medications should be made available. Follow-up, usually by telephone, some 24 h postchallenge is ideal, as delayed symptoms are not uncommon—for example, eczema exacerbations

FPIES, food protein-induced enterocolitis syndrome; SPT, skin prick testing.

Table 4 Diagnostic cut-off values for specific IgE levels (based on plasma values, and SPT) for the diagnosis of CMPA

	≥kU/l	≥PPV
Predictive value of cow's milk-specific serum IgE levels[95]*		
All children	15	95
Infants ≤2 years[96]	5	95
	≥Weal size (mm)	**≥PPV**
Predictive value of skin prick tests[97]†		
Children > 2 years	8	95
Infants ≤2 years	6	95

PPV, positive predictive value; SPT, skin prick testing.
*Phadia ImmunoCAP.
†SPTs performed with commercial extracts.

test. As a result, the symptomatic improvement on an allergen exclusion diet followed by a return of symptoms on allergen reintroduction remains the gold standard for diagnosis. Classification of non-IgE-mediated reactions to cow's milk is challenging. One approach is to consider different CMPA syndromes, which allows discussion of their individual presentation; another is the recognition of a spectrum of inflammation responses that are manifesting in one or more commonly several parts of the intestinal tract at any one time. However, this approach tends to separate out GI from cutaneous presentations, and while we have taken this approach, there is a risk that the concept of cow's milk allergy as a systemic disease may be lost. The syndromes described below commonly overlap—for example, children with cow's milk-sensitive eczema commonly have GI-related symptoms and indeed these can be an important clue as to the role of cow's milk allergy in the underlying eczema.[31]

CMP-induced proctocolitis

This is a disease of infancy, usually presenting by 2 months of age and represents the benign end of the spectrum of non-IgE-mediated allergy to CMP.[34] Infants usually present with colic-like symptoms and visible fresh blood mixed with mucus in the stool, but otherwise thriving.[35] It is surprisingly more common in, but not exclusive to, breastfed babies whose mothers are ingesting cow's milk or soy protein.[36] Important differentials include intestinal infection and anal fissures. The diagnosis is usually made on the basis of a response to the exclusion of CMP, either from the lactating mother's diet and/or by substitution by an extensively hydrolysed formula (EHF) or amino acid formula (AAF). Bleeding should resolve within 72 h—although persistent bleeding may only respond to an AAF. The underlying mechanism is unclear.[32] Cow's milk and soy skin prick tests are typically negative and colonic biopsy (which is usually unnecessary) reveals a distal colitis with an eosinophilic infiltrate. Resolution is seen sooner than in IgE-mediated milk allergy with most infants tolerant by 12 months of age. CMP can be reintroduced in older children and this can safely be performed at home (although it is prudent to confirm negative skin test or specific IgE before doing this, in order to ensure there is no risk of an IgE-mediated reaction).

CMP-induced enteropathy

Unlike patients with CMP-induced proctocolitis, infants with enteropathy usually have protracted diarrhoea, sometimes associated with vomiting.[32] This may result in malabsorption and faltering growth; making a firm diagnosis is therefore very important. The natural history is similar to other forms of non-IgE-mediated milk allergy—that is, presenting in infancy and resolving by 1–2 years. Again, the underlying immune mechanism is unclear, with no association with raised cow's milk-specific IgE but nonetheless

cow's milk-specific, involving T cell responses.[37] The differential diagnosis includes infection, and diagnosis is usually made on a combination of clinical response to exclusion and, if necessary, endoscopic small-bowel biopsy. Histological findings include mucosal inflammation and distortion of the villous architecture with a "patchy" distribution; features may be difficult to distinguish from untreated coeliac disease.[38]

Food protein-induced enterocolitis syndrome

The food protein-induced enterocolitis syndrome (FPIES), despite being described as far back as 1967,[39] remains an underdiagnosed condition for which CMP is a common trigger. While conditions such as CMP-induced proctocolitis, enteropathy and eosinophilic gastoenteropathies may all present with overlapping clinical features,[40] FPIES represents the severe end of the spectrum of GI CMPA.[41] FPIES is an acute, cell-mediated, GI food hypersensitivity characterised by severe protracted diarrhoea and vomiting, pallor and hypotonia, most commonly following ingestion of cow's milk or soy-based formula (50% of infants react to both), although solid food allergens, particularly rice, has also been implicated.[42 43] Unlike IgE-mediated reactions, symptoms usually appear between 1 and 3 h after ingestion. Progression can occur to a state of dehydration; hypovolaemic shock is described in 20% of cases.[38 44 45] The combination of vomiting, lethargy and resulting acidosis in the infant may lead to a false diagnosis of sepsis; however, symptoms typically recur upon reintroduction of the food. Failure to recognise the link with a dietary allergen may lead to multiple admissions.[45] A raised white blood cell count (with a predominance of neutrophils) is also consistently found in FPIES. The presence of the above findings in association with bloody diarrhoea may also lead to a clinical suspicion of infective diarrhoea, coagulation defects or intussusception.[46] However, the absence of fever, presence of eosinophilic debris in the stools and negative stool cultures can help differentiate these conditions. Symptoms rapidly resolve on a diet free of allergens. Patients with FPIES classically have no specific IgE and are negative on SPT. Endoscopy is often unhelpful, as infants may remain well between challenges.[47] Atypical cases have been described with detectable IgE to the causal protein and with a more prolonged course of allergy.[43]

The diagnosis is made based on clinical criteria with a standardised oral challenge if doubt remains.[48] These criteria include the onset of exclusive GI symptoms before 9 months of age, which are consistently present on further exposures after a period of relief with removal of the offending allergen(s). In contrast to IgE-mediated CMPA or even non-IgE-mediated conditions such as CMP-induced proctocolitis, there are no reports of infants developing FPIES while exclusively breast feeding. The cornerstone of management in children with FPIES is targeted dietary exclusion, preferably under the supervision of a paediatric dietitian. Reports show that 2 years from presentation, 60% and 25% of patients lose their sensitivity to cow's milk and soy, respectively[49 50] Confirmation of resolution requires a supervised food challenge with facilities to deal with the hypotension and shock that may arise.[43] It is prudent to cannulate children before such challenges.

Allergic dysmotility

CMPA may present with a range of GI motility abnormalities; including vomiting, gastro-oesophageal reflux (GOR) and diarrhoea. Allergic GI motility disorders are common in infancy and early childhood.[51] Symptoms are shared by many IgE and non-IgE CMP-induced disorders.[40] The timing of onset of such symptoms is typically more delayed and protracted. The exact mechanisms of delayed-onset allergic GI motility disorders are slowly being unravelled with a focus on interaction of inflammatory cells such as mast cells and eosinophils with the enteric nervous system ("neuroimmune" interaction). For example, in the human stomach, studies have demonstrated that mast cells can degranulate in a matter of minutes after cow's milk exposure, with associated disruption of normal gastric peristalsis. CMP may also trigger transient lower oesophageal sphincter relaxations resulting in GOR episodes.[52]

CMPA has been suggested as the underlying cause in up to 40% of diagnosed gastro-oesophageal reflux disease (GORD) in infants and young children.[53] In these patients, reflux symptoms usually resolved within 2 weeks of commencing a suitable hypoallergenic formula. It may be clinically difficult to distinguish food protein-induced reflux episodes from other causes of reflux, and both may coexist. Clinical features associated with food protein-induced GORD are feeding difficulties that may be associated with persistent crying, colic-like symptoms and abnormal posturing such as back arching known as Sandifer's syndrome.[53 54] These children often have had little or no response to a multitude of anti-reflux medications. Significant aversive feeding, including feed refusal and gagging on solids is often associated with GORD.[55] CMP influences the ability of the stomach to distend (known as poor compliance) and rhythmically contract. This manifests as an inability to eat large volumes of food, vomiting on liquids more than solids and delayed gastric passage such as vomiting of curdled milk. The differential diagnosis includes eosinophilic oesophagitis (EO), a diagnosis made by the presence of >15 eosinophils in one high-power field oesophageal biopsy.[56] Typically, infants with EO do not respond to treatment with proton pump inhibitors, but studies have shown improvement after treatment with a pauciantigenic or elemental diet. In older children and adolescents with EO, swallowed corticosteroid aerosols may provide some relief.

CMA has also been implicated as a cause of constipation.[57] The neural-inflammatory response in the lower GI tract may cause insensitivity of the external anal sphincter with normal relaxation when open so an infant may strain excessively but pass normal consistency stools.[58] However, a causal relationship has not been unequivocally demonstrated. CMPA should be considered as a cause of intractable constipation in young infants who develop hard and infrequent stools in relation to the dietary introduction of CMP.[59] This clinical presentation may mimic Hirschsprung's disease. Increased numbers of mucosal eosinophils on rectal biopsy suggest an allergic aetiology, while the presence of submucosal ganglia excludes Hirschsprung's disease.[60] Empirical treatment of CMP-induced constipation relies on either EHF or amino acid-based formula, as well as strict CMP elimination for at least 4 weeks. In responders, reintroduction of CMP may be attempted after 3–6 months. Tolerance to CMP develops in some by 18–24 months of age, but the problem may persist into adolescence.[61]

Allergic eosinophilic gastroenteropathies

First described by Kaisher in 1937, this heterogeneous group of conditions is characterised by eosinophilic inflammation in the gut.[62] These enteropathies are classified according to the site of the inflammation and it is the depth and severity of the inflammation that influences the presenting symptoms. The spectrum of pathologies (often with overlapping symptoms) includes EO, the most common of these conditions, eosinophilic gastroenteritis and eosinophilic gastro-enterocolitis. While EO is clearly associated with the atopic phenotype, the underlying mechanism remains uncertain. The local production of eotaxin, a potent eosinophil chemoattractant, appears to be pivotal. Treatment consists of the supervised dietary-exclusion, which may be guided by APT, which has been shown to be effective in a subset of younger children.[63] Inhalant allergens may also be implicated in older children and adolescents with EO. However, exclusion diets are seldom enough to control symptoms and other treatments such as antihistamines, steroids, sodium chromoglycate and leukotriene receptor antagonists are required.[64]

Table 5 Historical points that influence the likelihood that food—for example, cow's milk is exacerbating eczema

How severe is the eczema and when did it start?	Underlying food allergy is more likely in early-onset, more severe eczema, especially if it resistant to conventional treatment.
Is eczema being managed appropriately?	Management regimens are often suboptimal. Consider cumulative number of tubes of steroid preparation used monthly, and potency of steroid.
Is there a family or personal history of atopy?	An atopic family history (particularly maternal), is common in food allergies children. Siblings of children with food allergy have an increased chance of having food allergies themselves.
Are there associated symptoms?	Consider food allergy in children with eczema and gastro-intestinal symptoms such as gastro-oesophageal reflux, diarrhoea/constipation, failure to thrive, irritability and sleep disturbance.
Was infant breast fed?	The course of the eczema in relation to the amount of cow's milk exposure in the diet (or via breast milk) can provide an important clue to its possible role. For example, it may be relevant that eczema first presented when cow's milk formula was introduced following a period of exclusive breast feeding. Was an infant formula used in the nursery while breast feeding was established?

CMP "sensitive" eczema

Atopic eczema is a chronic inflammatory skin disorder associated with raised serum IgE, allergen sensitisation and an atopic family history. A well-established and strong association exists between eczema and IgE-mediated food allergy. Hill *et al* found that up to 64% of infants whose eczema commenced before 3 months of age had a high risk for concomitant IgE-mediated food allergy to egg, cow's milk and/or peanuts.[65] Most children with IgE-mediated food allergy will have a background of eczema and this possibly reflects a causal role of an impaired skin barrier increasing the likelihood of allergen sensitisation by the cutaneous route.[66–68] However, the possible role of foods causing worsening of established eczema by a non-IgE-mediated mechanism remains controversial. A number of studies have used double-blind placebo-controlled food challenges to demonstrate that food allergens, and in particular, CMPs are able to induce delayed eczematous reactions in children even in the absence of an immediate, histamine-mediated, component.[29 69 70] However, attempts to show that dietary exclusions can objectively influence the course of atopic eczema have remained unconvincing. A review of 14 interventional studies suggests that dietary interventions, when guided by allergy testing, were efficacious, especially in younger children <2 years of age.[71] A later systematic review of dietary exclusions for improving established eczema in adults and children only identified one paper in children showing a positive effect.[72]

While SPT and specific IgE blood testing are extremely helpful in detecting IgE-mediated food allergy in children with eczema,[73] their role in non-IgE-mediated reactions is less clear. The role of APT, which elicits T cell-mediated reactions, may slightly enhance diagnostic power. As discussed earlier in this review, use of the APT is subject to much variability and is therefore not in routine practice in the UK.[29 30] The need for different testing modalities reflects the mixed IgE-mediated and cell-mediated mechanism that appears to underlie this condition. The gold standard test investigation for identifying the possible causative role of a food in the exacerbation of eczema remains an exclusion-reintroduction diet. A recent European Academy of Allergy and Clinical Immunology (EAACI) position paper on eczematous reactions to food in atopic eczema offers a useful review of the area.[31] Important clues to the possible role of non-IgE-mediated reactions to milk causing a worsening of eczema are outlined in table 5. The possible role of cow's milk allergy is now reflected in the National Institute of Clinical Excellence guidelines for the management of atopic eczema in children,

which recommends a 6–8-week trial of an EHF or AAF in place of cow's milk for bottle fed infants <6 months with moderate to severe eczema, particularly if there is a history of gut dysmotility or failure to thrive.[74]

Management of IgE and non-IgE-mediated CMPA

The mainstay of treatment for CMPA infants is the avoidance of all CMP (this includes CMP-derived infant formulas and other dairy products). The requirement for complete milk avoidance is very much dependent on the nature of the individual child's allergy.[75] While the majority of children with either IgE or non-IgE-mediated reactions should avoid CMP completely, a significant number may tolerate a small amount of extensively heated (baked) dairy.[27] Although CMP β-lactoglobulin can be detected in the breast milk of 95% of lactating women (0.9–150 μg/l), this amount will be of no consequence to most CMPA infants and strict maternal elimination is not always necessary.[18 76] However, if CMPA symptoms persist in the breastfed infant, a strict maternal CMP exclusion diet may be required. When this dietary intervention is adopted, it is important to consider the adequacy of the lactating mother's dietary intake, specifically her calcium and protein requirements. Avoidance diets therefore need to be individually tailored under the care of a paediatric dietitian. The importance of a safe and balanced diet, while anticipating the acquisition of tolerance to CMP, remains the goal of treatment.

Choosing a hypoallergenic formula for use in the CMPA infant

In the absence of human milk, a hypoallergenic infant formula will need to be selected. European recommendations are now published which aim to facilitate this decision.[2] Hypoallergenic formulae can be defined using clinical criteria or through analysis of constituent proteins. The clinical definitions state that a hypoallergenic formula should be tolerated by 90% CMPA infants (with a 95% CI).[77] Formulae are also classified according to the degree of protein hydrolysis; EHF contain peptides with molecular weights <3000 Da, whereas partially hydrolysed formulae (PHFs) contain peptides with molecular weights ranging between 3000 and 10 000 Da (table 6).[78] PHFs do not meet the clinical criteria of hypoallergenicity and should not be used for infants with CMPA. Casein-based EHF formulae have been used in the treatment of children with CMPA for >60 years. Whey-based EHFs were subsequently introduced and have an equivalent hypoallergenicity.[79] While an EHF is suitable for the majority of CMPA

Table 6 Hypoallergenic formulae available in the UK for children <1 year of age

Formula	Protein source	Protein/100 ml (g)	Molecular weight of feeds (Da)	Osmolality (mOsm/kg H_2O)	Per 100 ml calcium (mg), iron (mg) and vitamin D (μg)	Additional information
Nutramigen 1 and 2 (Mead Johnson)	Hydrolysed casein	1.9 and 1.7	60.4% <500 35% 500–1000 4.1% 1000–2000 0.2% 2000–3000	290 and 365	Calcium 64 and 94 Iron 1.22 and 1.2 Vitamin D 1.02 and 1.1	Clinically insignificant lactose content. Nutramigen 2 suitable from 6 months of age
Pregestimil (Mead Johnson)	Hydrolysed casein	1.9	60.4% <500 35% 500–1000 4.1% 1000–2000 0.2% 2000–3000	330	Calcium 78 Iron 1.22 Vitamin D 1.25	Contains 55% MCT, clinically insignificant lactose content.
Pepti Junior (Cow and Gate)	Hydrolysed whey	1.8	28.2% < 500 35.2% 500–1000 28.3% 1000–2000 5.9% 2000–3000	190	Calcium 54 Iron 0.9 Vitamin D 1.3	Contains 50% MCT, clinically insignificant lactose content.
Pepti (Milupa)	Hydrolysed whey	1.6	28.2% < 500 35.2% 500–1000 28.3% 1000–2000 5.9% 2000–3000	240	Calcium 52 Iron 0.5 Vitamin D 1.5	Contains prebiotics and 38 % of carbohydrates from lactose
Pepdite (SHS)	Hydrolysed soy and pork collagen	2.1	64% < 1000 34.2% 1000–5000	237	Calcium 45 Iron 1.0 Vitamin D 1.3	Not commonly used for the management of CMPA. Lactose and sucrose not added as ingredients
MCT Pepdite (SHS)	Hydrolysed soy and pork collagen	2.0	64% < 1000 34.2% 1000–5000	290	Calcium 45 Iron 1.0 Vitamin D 1.3	Not commonly used for the management of CMPA. 75% MCT, lactose and sucrose not added as ingredients
Neocate LCP (SHS)	Amino acids	1.9	Not available	360	Calcium 68.5 Iron 1.0 Vitamin D 1.2	Truly hypoallergenic, no CMP β-lactoglobulin and lactose free, with LCP
Nutramigen AA (Mead Johnson)	Amino acids	1.89	Not available	350	Calcium 64 Iron 1.22 Vitamin D 0.85	Truly hypoallergenic, no CMP β-lactoglobulin and lactose free, with LCP

CMP, cow's milk protein; CMPA, cow's milk protein allergy; LCP, long-chain phospholipids; MCT, medium-chain triglycerides.

infants, between 2% and 10% of CMPA infants with IgE-mediated disease continue to react to EHF and will require an AAF.[80] This is related to the residual CMP β-lactoglobulin (0.84–14.5 µg/l) detected in EHF. It is important to note that the exact percentage of children that continue to react to EHF in non-IgE-mediated allergies is not well established. However, Latcham *et al* found that 29.7% of the children in their retrospective study with non-IgE-mediated GI allergies were intolerant to EHF.[33] A recent systematic review by Hill *et al* found that EHFs are efficacious at relieving the symptoms of CMPA in the majority of infants. However, infants with non-IgE-mediated food-induced gastro-enterocolitis and proctitis syndromes with faltering growth, severe atopic eczema, or with symptoms during exclusive breast feeding were more likely overall to benefit from AAF.[81] The choice of a suitable hypoallergenic formula is also dependent on the coexisting clinical diagnoses and the palatability of the formulae.

Use of soy formula

Before the availability of hypoallergenic formulae, the only alternative to CMP-based formula for infants with CMPA, were derived from soy. Soy-based formulas remain popular in the UK with distinct advantages including favourable taste, absence of lactose and suitability for vegans.[82] The prevalence of concomitant soy allergy in infants with CMPA differs between IgE and non-IgE-mediated disease. Klemola *et al* and Zeiger *et al* found that 10% and 14% of infants with IgE-mediated CMPA, respectively, have concomitant soy allergy, whereas associated soy allergy in non-IgE-mediated CMPA is much higher (up to 50%), especially in enterocolitis/enteropathy syndromes.[83–85] Recent concerns (based on animal studies) relate to the possible effects of soy on young infants due to phytoestrogens. As a precaution, the Committee of Toxicity of Chemicals in Food recommended that soy formula should only be consumed after the age of 6 months.[86]

Use of other mammalian milks

It is commonly believed that non-dairy mammalian milks such as goat's, ewe's, mare's and donkey's milk provide an acceptable alternate infant formula for use in CMPA infants.[87] There is, however, a close homology between the allergenic proteins in goat and cow's milk with an associated high potential to induce allergic reactions in CMPA infants.[88] Anaphylaxis to goat's milk has also been described in cow's milk allergic children.[88] In addition to the allergic risk of goat's milk formula, there are also nutritional concerns: there are therefore European and UK statements that recommend against the use of goat's milk for infants <1 year of age.[89]

Vitamins and minerals

All hypoallergenic formulae are fortified with vitamins and minerals; however, many infants may not consume sufficient quantities to provide them with their recommended requirements. The intake of vitamins and minerals can be achieved by improving the weaning diet of the infant, a process that requires careful monitoring by a paediatric dietitian. Breastfed infants above 6 months of age and CMPA infants consuming <500 ml of formula per day should be prescribed a multivitamin that contains vitamin D. Calcium intake should be reviewed, as both vitamin D and calcium-deficient rickets has been documented in food-allergic children.[90] The recommended nutrient intake for vitamin D is 8.5 µg/day between ages 0–6 months and 7 µg/day from 6 months to 3 years and for calcium is 525 mg for infants below 1 year and 350 mg for child between 1 and 3 years of age. While most hypoallergenic formulae for infants <1 year contain between 50 and 70 mg of calcium per 100 ml, it can be difficult to achieve calcium requirements children consuming lower volumes of formulae without any dairy products. The ingestion of calcium-enriched soy products in weaned infants will increase calcium intake for CMPA infants who are tolerant of soy, but in many cases, calcium supplementation may be required.

Medical management of IgE-mediated reactions

Patient and carers should be educated and empowered to recognise and respond to reactions when they occur. This process requires an individualised emergency plan, which includes an antihistamine and if indicated, an epinephrine auto-injector.[91] The successful treatment of CMP-induced anaphylaxis relies on early administration of epinephrine, ideally via the intramuscular route. Reactions of a milder nature typically settle spontaneously, or after the administration of an antihistamine. The presence of asthma—especially when poorly controlled—has been shown to be a major risk factor for the occurrence of more severe allergic reactions to cow's milk.[25]

Follow-up and the development of tolerance

The natural history of both IgE and non-IgE-mediated reactions is for the development of tolerance during childhood. The follow-up of cow's milk allergic patients is important to ensure a nutritionally complete diet, reinforce avoidance advice, to revise the management of allergic reactions, and to assess for the development of tolerance.[92–94] Significant advances have been made with respect to the use of serial SPT, IgE (and IgE allergen components) as a guide to the development of tolerance. A final determination of tolerance is, however, only made when an age-appropriate quantity of CMP is tolerated. In non-IgE-mediated allergy, a history of uneventful dietary indiscretion may provide a useful clue that tolerance has developed. In the absence of IgE sensitisation, home milk challenges are often used to test if tolerance has been achieved; however,

if reactions were previously severe or suggestive of the FPIES, then a hospital-based challenge is indicated.

There is a long literature that suggests that desensitisation to cow's milk is possible for children with CMPA; this is true even in those with previous severe symptoms to CMP.[95–97] These procedures are, however, not without risk and should only be undertaken in experienced centres.

CONCLUSION

Adverse reactions to cow's milk encompass a diverse spectrum of conditions ranging from lactose intolerance to life-threatening IgE-mediated anaphylaxis. There have been significant advances in our understanding of the diagnosis, management and underlying pathophysiology of these conditions. Current management relies on allergen exclusion together with careful dietary supervision to ensure that nutrition is not compromised. Recognition and prompt treatment of reactions together with awareness of comorbidities also contribute to optimal management.

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