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BSACI guideline for the diagnosis and management of cow's milk allergy

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Summary

This guideline advises on the management of patients with cow's milk allergy. Cow's milk allergy presents in the first year of life with estimated population prevalence between 2% and 3%. The clinical manifestations of cow's milk allergy are very variable in type and severity making it the most difficult food allergy to diagnose. A careful age- and disease-specific history with relevant allergy tests including detection of milk-specific IgE (by skin prick test or serum assay), diagnostic elimination diet, and oral challenge will aid in diagnosis in most cases. Treatment is advice on cow's milk avoidance and suitable substitute milks. Cow's milk allergy often resolves. Reintroduction can be achieved by the graded exposure, either at home or supervised in hospital depending on severity, using a milk ladder. Where cow's milk allergy persists, novel treatment options may include oral tolerance induction, although most authors do not currently recommend it for routine clinical practice. Cow's milk allergy must be distinguished from primary lactose intolerance. This guideline was prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) and is intended for clinicians in secondary and tertiary care. The recommendations are evidence based, but where evidence is lacking the panel of experts in the committee reached consensus. Grades of recommendation are shown throughout. The document encompasses epidemiology, natural history, clinical presentations, diagnosis, and treatment.

Keywords aetiology, allergy, anaphylaxis, BSACI, desensitization, diagnosis, food, management, milk, prevalence, SOCC

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Executive summary (Grades of recommendations, see [1])

- Cow's milk allergy may be defined as a reproducible adverse reaction of an immunological nature induced by cow's milk protein. (A)
- Cow's milk allergy can be classified into IgE-mediated immediate-onset and non-IgE-mediated delayed-onset types according to the timing of symptoms and organ involvement. (A)
- The prevalence of cow's milk allergy is between 1.8% and 7.5% of infants during the first year of life. (B)
- Cow's milk allergy commonly presents in infancy with most affected children presenting with symptoms by 6 months of age. Onset is rare after 12 months. (B)
- Cow's milk allergy has a favourable prognosis, as most children will outgrow their allergy by adulthood. (B)
- Cow's milk allergy is more likely to persist in IgE-mediated disease and where there is greater sensitivity (higher specific IgE levels), multiple food allergies and/or concomitant asthma and allergic rhinitis. (B)
- The clinical diagnosis in IgE-mediated disease is made by a combination of typically presenting symptoms, for example urticaria and/or angio-oedema with vomiting and/or wheeze, soon after ingestion of cow's milk and evidence of sensitization (presence of specific IgE). The spectrum of clinical severity ranges from skin symptoms only to life-threatening anaphylaxis. Clinical assessment should include a severity evaluation to ensure affected individuals are managed at the appropriate level. (B)
- The clinical diagnosis of non-IgE-mediated disease is suspected by the development of delayed gastrointestinal or cutaneous symptoms that improve or resolve with exclusion and reappear with reintroduction of cow's milk. As with IgE-mediated disease,

non-IgE-mediated disease varies widely in clinical presentation from eczema exacerbations to life-threatening shock from gastrointestinal fluid loss secondary to inflammation [food protein-induced enterocolitis syndrome (FPIES)]. (B)
- Gastrointestinal symptoms of non-IgE-mediated cow's milk allergy are variable and affect the entire gastrointestinal tract. There are some well-recognized more easily identifiable conditions (e.g. eosinophilic proctitis), but symptoms are more commonly non-specific. Cow's milk allergy should be considered in these circumstances where symptoms fail to respond to standard therapy or where other features of allergy are present. (B)
- Lactose intolerance can be confused with non-IgE-mediated cow's milk allergy as symptoms overlap. The terms are thus frequently mistakenly used interchangeably. Lactose intolerance should be considered where patients present only with typical gastrointestinal symptoms. (B)
- The reported level of IgE required to support a diagnosis of IgE-mediated cow's milk allergy varies between studies and depends on the research population. A skin prick test (SPT) weal size ≥ 5 mm (≥ 2 mm in younger infants) is strongly predictive of cow's milk protein allergy. (C)
- A food challenge may be necessary to confirm the diagnosis in IgE-mediated disease where there is conflict between the history and diagnostic tests. (D)
- Food elimination and reintroduction is recommended for the assessment of non-IgE-mediated cow's milk allergy where there is diagnostic uncertainty. (C)
- The management of cow's milk allergy comprises the avoidance of cow's milk and cow's milk products and dietary substitution with an allergenically and nutritionally suitable milk alternative. (D)
- The choice of cow's milk substitute should take into account the age of the child, the severity of the allergy, and the nutritional composition of the substitute. Nutritionally incomplete substitutes can lead to faltering growth and specific nutritional deficiencies. (D)
- As cow's milk is the major source of calcium in infant diets, children on milk exclusion diets are at risk of a deficient calcium intake. A dietitian should assess calcium intake and dietary or pharmaceutical supplementation advised where appropriate. (D)
- Cow's milk allergy will resolve in the majority of children. Individuals should be reassessed at 6–12 monthly intervals from 12 months of age to assess for suitability of reintroduction. (B)
- The reintroduction of cow's milk may be graded according to the 'milk ladder' with less allergenic forms offered initially. More allergenic forms are then eaten sequentially as tolerated. Reintroduction can be performed at home or may need to be supervised in hospital. (D)
- Oral tolerance induction offers a novel treatment option to the small but clinically significant proportion of affected individuals whose cow's milk allergy persists. (C)
- Cow's milk allergy in adults more commonly arises in adulthood but may persist from childhood. This is frequently a severe form of allergy where up to 25% have experienced anaphylaxis. (C)

Introduction

Cow's milk protein allergy is most prevalent during infancy and early childhood when milk forms the greatest proportion of an individual's food intake. This guideline for the management of patients with cow's milk allergy will focus predominantly on this age group, although it will encompass older children and adults as cow's milk allergy persists in a small proportion of patients and can present in this group in its severest form. The guideline, which was prepared by an expert group of the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) including a lay commentator, addresses the clinical manifestations and management of cow's milk protein allergy with recommendations for families with milk allergic children. This guidance is intended for use by specialists involved in the investigation and management of individuals with cow's milk allergy.

Evidence for the recommendations was obtained from literature searches of MEDLINE/PubMed/EMBASE, NICE, and the Cochrane library (from 1946 to the cut-off date, March 2012) using the following strategy and key words – (hypersensitivity OR immune-complex disease OR atopic dermatitis OR eczema OR eczematous skin diseases OR colitis OR irritable bowel syndrome OR exanthema OR enteritis OR rash OR oesophagitis OR allergy OR skin prick test OR anaphylaxis OR contraindications OR IgE mediated adverse reactions) AND (milk OR caseins OR lactalbumin OR lactose OR lactic acid OR dairy). The experts' knowledge of the literature and hand searches as well as papers suggested by experts consulted during the development stage were also used [2]. Where evidence was lacking, a consensus was reached amongst the experts on the committee. The strength of the evidence was assessed by at least 2 experts and documented in evidence tables using the grading of recommendations as in a previous BSACI guideline [1], see Box 1. Conflict of interests were recorded by the BSACI. None jeopardized unbiased guideline development. During the development of the guidelines, all BSACI members were consulted using a web-based system and their comments carefully considered by the SOCC.

Box 1. Grades of recommendations [3, 4]

Grade of recommendation	Type of evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
E	Recommended best practice based on the clinical experience of the guideline development group

Definition and mechanism

Cow's milk allergy may be defined as a reproducible adverse reaction to one or more milk proteins (usually caseins or whey β-lactoglobulin) mediated by one or more immune mechanisms (A) [5]. The underlying immunological mechanism distinguishes cow's milk allergy from other adverse reactions to cow's milk such as lactose intolerance [6].

Cow's milk allergy is classified by the underlying immune mechanism, timing of presentation and organ system involvement. The commonest reactions are IgE-mediated occurring within minutes, the majority within an hour, following the ingestion of small amounts of cow's milk (A). Presentation varies in severity ranging from mild symptoms in the majority to, rarely, life-threatening anaphylaxis and involving the skin, respiratory tract, gastrointestinal tract, and cardiovascular system. Delayed reactions are typically non-IgE mediated, although some reactions are a combination of IgE- and non-IgE-mediated responses, presenting predominantly with gastro-oesophageal reflux, diarrhoea, and constipation and/or eczema. These usually present several hours, and up 72 h, after ingestion of larger volumes of milk [5, 7–10].

Cow's milk is largely ingested uncooked, but almost all commercially available cow's milk in the UK is pasteurized. Pasteurization involves heating cow's milk, but this does not significantly alter its allergenicity. Cow's milk is variously referred to as 'raw', 'fresh', or 'pasteurized'. In this guideline, to avoid confusion, pasteurized cow's milk will be consistently referred to as 'fresh' cow's milk.

Prevalence

Prevalence estimates vary because of differences in study design or methodology, and differences in study populations [11, 12]. This is particularly relevant in cow's milk allergy as it presents with a variety of clinical symptoms, many of which may be difficult to attribute to an allergic reaction, particularly in infants [13]. In addition, no single test or combination of tests is diagnostic so recognition of an affected individual is frequently delayed [14].

Symptoms suggestive of cow's milk allergy based on self-reports vary widely, and only about one in three children presenting with symptoms is confirmed to be cow's milk allergic using strict, well-defined elimination and open-challenge criteria [12, 15]. With these criteria, cow's milk allergy is shown to affect between 1.8% and 7.5% of infants in the first year of life (B) (Table 1). This may still be an overestimate as Venter and colleagues [16] confirmed cow's milk allergy, using the double-blind placebo-controlled food challenge for diagnosis, in only 1.0% of their population compared with a prevalence estimate of 2.3% using an open food challenge. Clinicians should therefore anticipate that between 2–3% of children have cow's milk allergy.

Natural history

Cow's milk allergy most commonly develops early in life, and almost all cases present before 12 months of age [17]. The outlook for cow's milk allergy is favour-

Table 1. Prevalence of cow's milk allergy in unselected populations diagnosed by oral challenge with fresh cow's milk

Authors, year	Prevalence
Halpern et al., 1973 [166]	20/1084 (1.8%)
Gerrard et al., 1973 [167]	59/787 (7.5%)
Jakobsson and Lindberg, 1979 [18]	20/1079 (1.9%)
Høst and Halken, 1990 [15]	39/1749 (2.2%)
Schrander et al., 1993 [168]	26/1158 (2.8%)
Saarinen et al., 1999 [19]	118/6209 (1.9%)
Venter et al., 2006 [16]	22/969 (2.3%)
Kvenshagen et al., 2008 [21]	27/555 (4.9%)

able, as most children outgrow their allergy during childhood (B).

Onset

Symptoms usually develop within a week of cow's milk introduction although may be delayed for many weeks, reported up to 24 and 36 weeks [15, 18]. Two studies report the average age of onset at similar ages of 2.8 ± 1.8 months [19] and at 3.5 ± 2.8 months [20], so most infants will manifest with symptoms by 6 months of age (B) [15, 18, 21]. In the majority of children, the triggering food is cow's milk *per se* or formulas or cow's-milk-based foods (e.g. porridge), although a small number react to cow's milk protein in maternal breast milk whilst exclusively breastfed [20].

Outcome

The natural history of cow's milk allergy has been thoroughly evaluated in a number of studies. Cow's milk allergic children were exposed to fresh cow's milk in controlled open challenges at regular intervals. Tolerance was established by a negative challenge followed by regular ingestion of age-appropriate quantities of cow's milk at home without symptoms (Table 2). All studies demonstrate a favourable outcome of cow's milk allergy, although with variable results, so predicting when tolerance will be acquired is still uncertain (B). Earlier studies before 2005 showed that cow's milk allergy carried a good prognosis with 80–90% of children tolerant by school age [7, 8, 22, 23], whilst studies since then have been less optimistic [20, 24, 25]. This suggests that the natural history of food allergy may be changing (D), but it is more likely this observation is caused by methodological differences. The latter three studies allowed clinicians to delay repeat challenges until there had been a reduction in sIgE levels (leading to underestimation of the time to resolution) [20, 24, 25], whereas in the earlier studies challenges were performed regularly in all participants regardless of sIgE concentration [8, 22, 23].

Where studies have continued to assess children with increasing age, achievement of tolerance occurred well into adolescence, contradicting the popular notion that cow's milk allergy is unlikely to be lost if it has per-

Table 2. Natural history of cow's milk allergy expressed as percentage tolerant

	First author (year)													
Age (years)	Bishop (1990)† [7] (*n* = 97)	Høst (2002)*/† [8] (*n* = 39)			Vanto (2004)‡ [23] (*n* = 162)			Saarinen (2005) */‡ [22] (*n* = 118)			Skripak (2007)†/§ [24] (*n* = 807)	Levy (2007)†/§ [28] (*n* = 105)	Santos (2010)†/§ [20] (*n* = 139)	
	All	All	IgE	nIgE	All	IgE	nIgE	All	IgE	nIgE	IgE	IgE	All	IgE
1	–	56	24	100	–	–	–	45	38	66	–	–	9	–
1.5	–	67	–	–	–	–	–	–		–	–	–	23	–
2	28	77	–	–	44	30	59	51	–	–	9	–	34	–
3	–	87	–	–	69	–	–	–	–	–	–	19	40	5
4	56	–	–	–	77	59	93	–	–	–	26	–	46	16
5	–	92	–	–	–	–	–	81	74	100	–	31	53	22
6	78	–	–	–	–	–	–	–	–	–	44	–	56	28
8	–	–	–	–	–	–	–	–	–	–	56	–	63	37
8.6		–	–	–	–	–	–	89	85	100	–	–	–	–
9	–	–	–	–	–	–	–	–	–	–	–	38	–	–
10	–	92	–	–	–	–	–	–	–	–	64	–	66	43
11	–	–	–	–	–	–	–	–	–	–	–	41	–	–
12	–	–	–	–	–	–	–	–	–	–	77	–	–	–
14	–	–	–	–	–	–	–	–	–	–	83	–	–	–
15	–	97	–	–	–	–	–	–	–	–	–	–	–	–
16	–	–	–	–	–	–	–	–	–	–	88	–	–	–
18	–	–	–	–	–	–	–	–	–	–	93	–	–	–

Age – age when assessed, that is, underwent open food challenge with fresh milk; IgE, IgE mediated; nIgE, non-IgE mediated.
Study types (potentially influencing outcome)
*Birth cohort.
†Tertiary centre.
‡Regular challenges performed.
§Challenges performed only when sIgE levels have fallen.

sisted to school-age years [5, 22]. This indicates that there is no age at which outgrowing cow's milk allergy is impossible [8, 24].

Persistence

The ability to recognize the individual whose cow's milk allergy is likely to persist will help the clinician address parents' common questions about when their child will be able to reintroduce cow's milk. In general, non-IgE-mediated allergy resolves more rapidly that IgE-mediated allergy (C) [22]. The clinical traits that predict persistence are consistent between studies and over time, in contrast to timing of tolerance and levels of IgE as markers of tolerance (B). They were presentation with immediate symptoms [20, 22], presence of other food allergies, most commonly egg allergy [20, 22, 26] and concomitant asthma [8, 20, 24, 26–28] and allergic rhinitis [24, 27]. In addition, reactivity to baked milk on first challenge or exposure is also associated with persistence of fresh milk allergy [29].

Markers of tolerance

Many investigators have demonstrated that IgE levels, expressed either as SPT weal size or serum specific IgE (sIgE) level, could be useful in discriminating between children who remained hypersensitive and those who became tolerant (B) [23, 30, 31]. Vanto and colleagues [23], for example, showed that SPT weal size < 5 mm at diagnosis correctly identified 83% who developed tolerance at 4 years, whilst a weal size ≥ 5 mm correctly identified 74% with persistent cow's milk allergy. These cut-off levels vary from study to study, possibly because the composition of the groups studied differed. Garcia-Ara and colleagues [32] showed that sIgE levels predictive of clinical reactivity increased with increasing age. Nevertheless, independent of specific levels, higher maximum IgE levels are associated with reduced likelihood of developing tolerance [20]. In addition, a high proportion, nearly half in one study [5], who developed tolerance, continue to display some degree of skin reactivity.

Shek and colleagues [33] showed that there is a relationship between the amount by which sIgE levels to cow's milk fall and the likelihood of developing tolerance, with a greater decrease in sIgE levels indicative of an increased likelihood of developing tolerance. They were able to develop estimates of a child developing tolerance based on the decrease in sIgE levels, with a probability of tolerance of 0.31 for a decrease of 50%, 0.45 for a decrease of 70%, 0.66 for a decrease of 90%, and 0.94 for a decrease of 95%. These findings may be of practical significance reducing the need for food challenges as a guide for the reintroduction of cow's milk. IgG does not play a role in the pathogenesis of cow's milk allergy [5].

Clinical presentations

The allergic symptoms that an infant with cow's milk allergy presents with are determined by the mechanism of the individual's allergy.

IgE-mediated immediate-onset symptoms

Immediate-onset reactions (IgE mediated) to cow's milk affect the skin most commonly, then the gastrointestinal tract, and least frequently the respiratory system. Cardiovascular symptoms are rarely reported. Symptoms can range in severity from mild to life-threatening [34, 35]. Their onset is typically within minutes of exposure. Tables 3 and 4 list presenting symptoms and their reported frequencies (B).

Anaphylaxis to milk is therefore potentially fatal [36], and if there is such a history, intramuscular adrenaline should be prescribed for emergency use (B) [37]. Clinicians should therefore elicit a complete history of all

Table 3. Presenting symptoms in infants with immediate-onset reactions to cow's milk

Cutaneous
Pruritus without skin lesions
Urticaria
Angio-oedema
Atopic eczema exacerbation
Gastrointestinal
Vomiting
Diarrhoea
Bloody stools
Gastro-oesophageal reflux
Abdominal pain
Respiratory
Upper respiratory
Rhinitis
Nasal congestion
Lower respiratory
Wheeze
Cough
Stridor
Difficulty breathing
Cardiovascular
Anaphylaxis
Hypotony
Hypotension/shock
Prostration
General
Anaphylaxis
Irritability
Failure to thrive

References: [5, 20, 24].

Table 4. Reported symptom frequencies (%) in cow's milk allergic infants presenting with immediate symptoms

Symptom	Hill et al. [5] (n = 27)	Skripak et al. [24] (n = 807)	Santos et al. [20] (n = 66)
Skin	–	85	91
Pruritus	–	–	8
Urticaria	74	–	82
Angio-oedema	–	–	53
Eczema	19	–	6
GI	–	46	53
Vomiting	41	–	50
Diarrhoea	33	–	6
Respiratory	–	20	29
Upper respiratory	–	14	–
Lower respiratory	–	6	–
Cough	–	–	6
Wheeze	48	–	–
Dyspnoea	–	–	24
Rhinoconjunctivitis	–	–	8
Anaphylaxis	–	–	6
Poor growth	15	6	–
1 system involved	–	50	–
> 1 systems involved	–	47	67

symptoms to assess the severity of the reaction. Anaphylaxis may, for example, manifest in infants as pallor and floppiness [20]. Clinicians and carers can fail to realize the gravity of these symptoms considering them to be non-specific infant behaviour [13]. Anaphylaxis is not a feature of non-IgE-mediated cow's milk allergy.

Non-IgE-mediated predominantly delayed-onset symptoms*

**(In this section symptoms can be immediate or delayed)*

The presenting features of non-IgE-mediated cow's milk allergy are notoriously protean, and the onset is most frequently delayed, usually several hours, and in some instances several days after ingestion (B). Gastrointestinal symptoms are prominent. Peristalsis in the gut is controlled by complex neuronal networks (the enteric nervous system), and there are direct interactions between submucosal nerve fibres and mast cells or eosinophils [38]. Much of the evidence that cow's milk allergy plays a role in children with these presenting problems comes from observational studies demonstrating improvement in symptom patterns following exclusion of cow's milk protein from the diet. As the typical symptoms listed in Table 5 are also amongst the most common seen in infancy, the diagnosis of cow's milk allergy relies on recognition of suggestive symptom patterns. It is important to note in this respect that

Table 5. Common gastrointestinal symptoms in cow's milk allergy

Vomiting/posseting
Irritability (colic)
Dysphagia
Diarrhoea
Constipation
Failure to thrive
Blood in stools

symptoms are almost always multiple [39] and often fail to respond to standard management approaches. The diagnosis is supported by a personal and family history of atopy. These are important characteristics to seek actively from the history. Other features such as eczema are often present.

Vomiting/Posseting. Gastro-oesophageal reflux to some degree is universal in infancy. The vomiting or posseting tends to be effortless and does not upset the infant, and pain is not usually prominent. However, this is not the case in cow's milk allergic infants with vomiting who are often miserable, rather irritable babies who suffer frequent back-arching and screaming episodes. Feed refusal and aversion to lumps are also prominent features. These infants have usually had little or no response to standard antireflux medications. It is suggested that release of proinflammatory cytokines from activated T cells and degranulated eosinophils stimulates the enteric nervous system, thus triggering exaggerated transient lower oesophageal sphincter relaxations (TLOSRs) [40–42]. The combination of vomiting, oral aversion, and poor weight gain in infants should raise the possibility of eosinophilic oesophagitis [43].

Vomiting can also be a symptom of an immediate IgE-mediated reaction. In this circumstance, it is often profuse, occurring within minutes of exposure, and may coincide with other acute symptoms (B).

Irritability (Colic). Episodic irritability or crying in infancy is universal and often referred to as "colic" although the evidence that discomfort arises from the gastrointestinal tract is assumed rather than actual. Observational studies have suggested cow's milk allergy as a contributing factor in some infants demonstrating extreme colic [44, 45].

Dysphagia. True dysphagia is unusual in simple gastro-oesophageal reflux and is very suggestive of significant eosinophilic inflammation in the oesophagus [43, 46]. This can only be diagnosed by finding significant numbers of eosinophils in mucosal oesophageal biopsies. This symptom therefore always warrants endoscopy. So-called allergic eosinophilic oesophagitis (EoE) is distinguished from the eosinophilic infiltration found in reflux

oesophagitis by the number of eosinophils (15–20 per high power field) [47]. In some cases, the two conditions may coexist. Cow's milk protein is a major food cause of EoE, although other foods are commonly responsible (C) [48]. A therapeutic trial of cow's milk exclusion, followed by reintroduction, will determine whether cow's milk allergy plays a role (D).

Diarrhoea. Cow's milk allergic diarrhoea occurs because of failure of water reabsorption. The infant or child may be well in himself or herself, but usually has other manifestations of atopy. Most commonly there is no evidence of true enteropathy, and the child is thriving with normal serum protein levels. However, there is a specific entity of cow's-milk-induced small bowel enteropathy with protracted diarrhoea and the potential for faltering growth and hypoalbuminaemia. These features mandate small bowel biopsy, which shows mucosal changes similar to coeliac disease with varying degrees of villous atrophy and inflammatory infiltrates [49]. The inflammatory cells may include prominent eosinophils and, depending on the site and degree of infiltration, may give rise to a label of eosinophilic gastroenteritis.

Constipation. Constipation is a common symptom in infancy and early childhood and most often relates to inadequate fluid intake producing hard stools. It may, however, be a manifestation of cow's milk allergy, occasionally as a sole symptom, but more often coexisting with other allergic conditions. Infants and younger children can become very distressed with defecation and have great difficulty with much straining but then produce a soft stool. Older children in this category often have prominent abdominal pain. Cow's milk allergy should be considered in particular where other allergic conditions, rhinitis, eczema, or asthma, for example, are also present as a high proportion of such children have been shown to improve when cow's milk protein is excluded from their diet [50]. Rectal eosinophilia has been demonstrated, and there is evidence that higher rectal pressures are required for internal anal sphincter relaxation in the cow's milk allergic child [51].

Unwell infants with vomiting and loose stools. Infants may uncommonly present in the neonatal period with profuse vomiting and diarrhoea with evidence of acidosis and shock. This tends to appear between one and three hours after ingestion of cow's milk. Other food proteins have also been implicated including soya and rice [52]. These infants are often misdiagnosed as having sepsis, and the differentiation between the two can be very difficult. However, the so-called food protein-induced enterocolitis syndrome (FPIES) is not associated with fever, and stool cultures will always be negative although the peripheral white cell count is high. Recurrent symptoms may occur always upon reintroduction of the offending food protein. Reports of this syndrome in breastfed infants or children over 9 months of age are rare [53].

Well infants with bloody stools. There is a well-recognized entity of allergic distal colitis in well, often happy, thriving, breastfed babies who simply present with blood and mucus streaking in otherwise normal stools. This settles within 48 h of cow's milk protein elimination from the mother's diet and generally resolves by 1 year of age. Endoscopy is unnecessary but if performed demonstrates eosinophilic infiltration in a distal colitis.

Eczema. There are three different patterns of clinical reactions to foods in children with eczema:

- Immediate-onset (non-eczematous) reactions. Clinical symptoms include cutaneous reactions such as erythema, pruritus and urticaria, and/or non-cutaneous respiratory or gastrointestinal symptoms or even anaphylaxis;
- Isolated eczematous reactions (i.e. flare ups) after hours or days; or
- Mixed reactions of a combination of eczematous reactions following on from preceding acute symptoms [54].

Lactose intolerance

Lactose is a disaccharide that is found exclusively in mammalian milk where it is the predominant carbohydrate. Effective utilization follows hydrolysis by the intestinal brush border enzyme lactase into its constituent monosaccharides, glucose, and galactose that can then be absorbed by intestinal enterocytes. If lactase activity is low or absent, undigested lactose (lactose malabsorption) may induce symptoms of lactose intolerance. Although it is commonly confused with cow's milk allergy (and the terms are mistakenly used interchangeably), lactose intolerance is not immunological in origin and thus not an allergic condition [6].

There are three types of lactose intolerance: primary, secondary, and congenital. In primary lactose intolerance (lactase non-persistence), lactase activity starts to decrease within a few months of life. This down-regulation is genetically determined with the prevalence in affected populations varying according to ethnicity and the historical use of dairy products in the diet. The age of onset of symptoms of lactose intolerance also varies with earlier onset at < 5 years of age in higher prevalence populations. Secondary lactase deficiency implies the loss of brush border lactase expression secondary to inflammation or structural damage, usually a gastroin-

testinal infection. Where an infectious aetiology is not found, coeliac disease, Crohn's disease, and immune-related and other enteropathies should be considered. Secondary lactase deficiency can present at any age and is usually reversible with resolution or treatment for the underlying cause. Congenital lactase deficiency is an extremely rare condition, mainly described in small populations in Finland and Russia, where lactase activity is absent from birth. It is a lifelong disorder and is characterized by infantile diarrhoea and faltering growth with first mammalian milk contact [55].

The typical symptoms of lactose intolerance that include abdominal discomfort, bloating, flatulence, and explosive diarrhoea arise from the colonic bacterial fermentation and the osmotic effects of unabsorbed lactose. These symptoms overlap with those of non-IgE-mediated cow's milk protein allergy, so the two conditions may be confused with one another. However, unlike milk allergy, in primary lactase deficiency, symptom onset is typically subtle and progressive over many years, with most diagnosed in late adolescence or adulthood, although it can present with relatively acute milk intolerance. Furthermore, individuals with lactase deficiency need not always be symptomatic with lactose ingestion as tolerance to milk products may be partial so dietary changes alone may be sufficient to avoid symptoms. Dietary changes include, for example, taking small portions spread throughout the day, eating yogurt as bacteria in yogurt partially digest the lactose, simultaneously consuming solid foods which delay gastric emptying, thereby providing additional time for endogenous lactase to digest dietary lactose or eating aged cheeses which have a lower lactose content than other cheeses [56].

Dietary history is unreliable as a means to confirm or exclude the presence of lactose intolerance because symptoms are prone to subjectivity and because symptoms may vary and be modified by the amount of dairy in an individual's diet and the amount of lactose contained in different products. A strict lactose exclusion trial for at least 2 weeks with resolution of symptoms, and their subsequent recurrence with reintroduction of dairy foods, can be diagnostic. The hydrogen breath test, a measure of exhaled hydrogen after the ingestion of a lactose meal, is the least invasive diagnostic test. Lactose intolerance is managed by total or partial exclusion of dietary lactose depending on the individual's tolerance (B).

Diagnosis

Early and reliable diagnosis of cow's milk allergy is important to initiate the appropriate diet where confirmed or to avoid unnecessary dietary restrictions where not. The diagnosis of cow's milk allergy is more easily accomplished when there is a relation between the ingestion of cow's milk and onset of symptoms and when it can be demonstrated that the symptoms are the consequence of an immunological reaction.

IgE-mediated cow's milk allergy

The diagnosis of IgE-mediated food allergy is based on the combination of clinical history and examination, allergy tests such as SPTs and/or sIgE and, when indicated, oral food challenges (OFCs). SPT's and sIgE levels serve to detect the presence of sIgE antibodies (tissue bound and circulating IgE antibodies, respectively) but cannot differentiate between sensitization alone and clinical allergy. It is an unequivocal history of allergic symptoms after cow's milk exposure coupled with evidence of sensitization that help make 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 an OFC can resolve diagnostic uncertainty. The algorithm in Figure 1 gives a suggested practical clinical approach for the diagnosis of IgE-mediated cow's milk allergy based on expert opinion and available data (C).

SPT and sIgE. Allergy testing should only be carried out if there is clinical suspicion of cow's milk allergy as it has poor predictive value as a screening tool. Traditionally, taken with a good clinical history, cut-off levels for SPT weal size of ≥ 3 mm larger than the negative control or sIgE ≥ 0.35 kU/L have been used to support a clinical diagnosis (C) [57–59]. However, if the clinical history is weak, SPT weals of between 3 and 5 mm may be clinically irrelevant and low levels of sIgE may be found in children without clinical cow's milk allergy [60]. Higher cut-offs have been proposed, which are associated with higher specificity and positive predictive values (PPV), although in younger children (< 2 years) smaller SPT weals and lower serum sIgE are more likely to be predictive of milk allergy than in older children [61]. Increasing SPT weal size and magnitude of sIgE levels do not appear to correlate with increased clinical severity but do correlate with greater likelihood of clinical allergy [62, 63].

SPT. Skin prick tests have been used for decades to prove or exclude sensitization to allergens, as they are easy to perform, inexpensive, well tolerated, and the results are immediately available. Using an OFC as a reference standard, a number of studies have demonstrated a SPT weal diameter at and above which a positive reaction invariably occurred [61, 64, 65] (Table 6). These studies have put forward different values depending on the extract used (commercial vs. fresh milk), placement of test (back vs. forearm), type of population studied, and prevalence of atopic dermatitis in the study

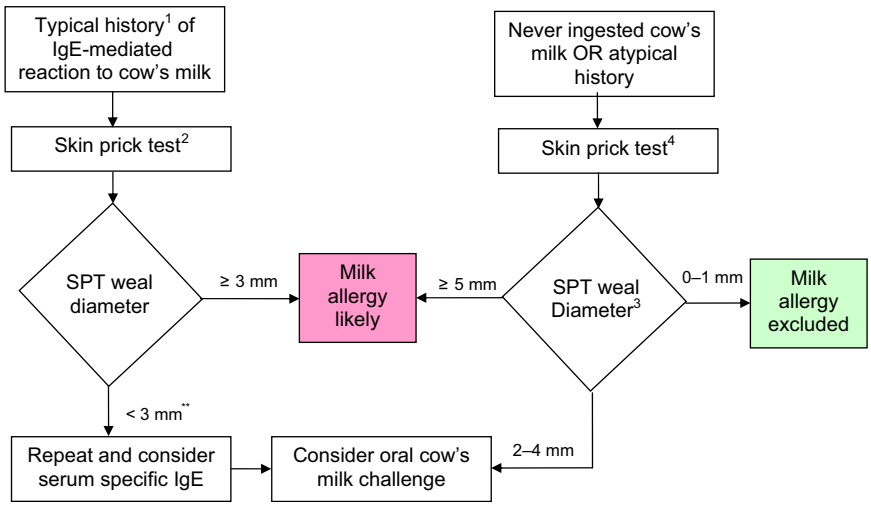

Fig. 1. Algorithm for the diagnosis of IgE-mediated cow's milk allergy. 1. A typical history is the immediate onset of symptoms, for example urticaria, angio-oedema, vomiting, abdominal pain, wheezing, or breathlessness. 2. Skin prick test (SPT) weals should always be given as diameters in excess of negative control. 3. Clinical allergy may be found in young infants with an SPT weal diameter of 2 mm particularly if there is associated flare. 4. Not recommended as a screening test for milk allergy.

population. A weal size of ≥ 5 mm (≥ 2 mm in an infant ≤ 2 years) is associated with a higher specificity [61, 66]. It has been suggested that weal sizes of ≥ 8 mm (≥ 6 mm in infants < 2 years) are 100% specific for positive challenge and that there is no need to undertake oral challenge to confirm diagnosis in these cases (C) (Table 7). SPTs with fresh cow's milk resulted in non-significant larger weal diameters than with commercial extracts [67]. Negative skin test results are useful for confirming the absence of IgE-mediated reactions, with negative predictive values exceeding 95% (C) [62, 63, 68, 69].

Serum Specific IgE. Cow's milk sIgE can be measured using standardized *in vitro* assays providing a quantitative measurement. At the cut-off level of 0.35 kU/L the

Table 6. Performance of skin prick testing in the diagnosis of cow's milk allergy

References First author (year)	Number of patients	Age	Method of diagnosis	Prevalence of milk allergy (%)	Prevalence of eczema (%)	PPV at stated SPT cut-off (mm)		Specificity (%) at stated SPT cut-off (mm)	
						PPV	Cut-off	Specificity	Cut-off
Sampson (1997) [70]	196	0.6–17.9 years	DBC	50	100	66	3	51	3
Eigenmann (1998) [66]	61	Child–Adolescent (Median 4.6 years)	DBC	56	100	78	3	68	3
Sporik (2000) [61]	339	1–192 months (=16y)	OC	42				100	8
								100	6 (< 2 years)
Garcia-Ara (2001)* [73]	161	Mean 6.5 months	OC	44	23	60	3	62	3
*Saarinen (2001) [169]	239	Median 6.9 months	OC	49		92	8	98	8
*Roehr (2001) [170]	71	2 months to 11.2 years (median 13 months)	DBC	63	100	81	3	69	3
*Osterballe (2004) [171]	455	3 years	OC	3	16	59	3	100	3
*Verstege (2005) [172]	149	3 months to 14 years	DBC/OC	49	87	76	3	95	9 (< 1 year)
								95	15
*Mehl (2006) [173]	341	3 months to 14 years (Median 13 months)	DBC/OC	49	90	95	9	70	3
*Calvani (2007) [174]	104	Mean 3.6 years	DBC/OC	27	50	50	3	65	3
						95	15		

PPV, positive predictive value; OC, open challenge; DBC, double-blind placebo-controlled food challenge; sIgE, specific IgE.
*Fresh milk used for SPT. Where results are stratified by age, this is shown in the 'cut-off' column.

Table 7. Positive predictive value for food-specific IgE and skin prick tests

≥ 95% Specific IgE levels (U/mL) positive predictive values		
Milk	15	
Infants ≤ 2 years		5
Egg	7	
Infants ≤ 2 years		2
Peanut	15	
Tree Nuts	15	
Fish	20	
≥ 95% Skin prick tests (weal diameter in mm) positive predictive values		
Milk	8	
Infants ≤ 2 years		6
Egg	7	
Infants ≤ 2 years		5
Peanut	8	
Infants ≤ 2 years		4

Reference: Du Toit et al. [175].

performance characteristic of sIgE to cow's milk was similar to that of a positive SPT (weal diameter of ≥ 3 mm), with a good sensitivity but poor specificity [70]. There is a relationship between increasing levels of cow's milk sIgE and the likelihood of clinical reactivity to cow's milk, although many individuals with positive tests for cow's milk sIgE lack clinical reactivity. A number of studies have proposed a range of predictive cut-off values for the diagnosis of cow's milk allergy (Table 8). The studies demonstrate that although there is a relationship between serum sIgE levels and challenge outcome, there is poor agreement between cut-off levels identified at different centres and this is again thought to be related to the variation in study populations [71]. Predictive cut-off values are found to be lower in younger children and increase with age [70, 72, 73] with these diagnostic cut-off values remaining valid regardless of total serum IgE [74]. It is consequently difficult to suggest standardized cut-offs for cow's milk sIgE above which an OFC would not be required. Each case would therefore need to be judged on its own merit. The measurement of sIgE to cow's milk in the absence of a history of cow's milk ingestion is discouraged, as in this circumstance, the test has poor sensitivity and low negative predictive value; an oral challenge would be required if the sIgE level is positive but low.

Oral food challenge. The recent DRACMA guidelines highlight that OFCs may be considered in the initial diagnosis although in practice, OFCs are rarely required

Table 8. Performance of serum specific IgE by ImmunoCAP in the diagnosis of cow's milk allergy

References First author (year)	Number of patients	Age	Method of diagnosis	Prevalence of milk allergy (%)	Prevalence of eczema (%)	PPV at stated sIgE cut-off (kU/L)		Specificity (%) at stated sIgE cut-off (kU/L)	
						PPV	Cut-off	Specificity	Cut-off
Sampson (1997) [70]	196	0.6–17.9 years	DBC	50	100	95	32	98	32
Garcia-Ara (2001) [73]	161	1–12 months (median 5 months)	OC	44	23	95	5	95	2.5
								99	5
Roehr (2001) [170]	71	2 months to 11 years (median 13 months)	DBC	63	100	59	0.35	38	0.35
						86	17.5	96	17.5
Saarinen (2001) [169]	239	Median 6.9 months	OC	49		92	3.5	94	3.5
						58	0.35	49	0.35
Sampson (2001) [72, 133]	62	3 months to 14 years (median 4 years)	DBC	66	61	100	32	100	32
						95	15	94	15
Celik-Bilgili (2005) [60]	398	1 month to 16 years	DBC/OC	49	88	90	88.8 25.8 (< 1 year)		
Mehl (2006) [173]	341	3 months–14 years (median 13 months)	DBC/OC	49	90	95	27.5	49	0.35
Komata (2007) [176]	861	0.2–14 years (median 1.3 years)	DBC/OC	25	74	95	50.9 5.8 (< 1 year) 57.3 (> 2 years)		
Van der Gugten (2008) [177]	213	0.2–15.5 years (median 3 years)	DBC	44	84	100	23 (< 2.5 years)		

PPV, positive predictive value; OC, open challenge; DBC, double-blind placebo-controlled food challenge; sIgE, specific IgE.
Unless otherwise stated sIgE is directed against 'cow's milk'. Where results are stratified by age, this is shown in the 'cut-off' column.

to make the diagnosis of cow's milk allergy (D) (Figure 1) [75]. Double-blind placebo-controlled food challenges are the reference standard for the diagnosis of food allergy, but they are time-consuming and expensive and hence usually limited to research [76, 77]. Open challenges can be used to confirm both IgE- and non-IgE-mediated reactions to cow's milk (following an elimination diet) and are usually adequate for clinical purposes [78, 79]. A blinded challenge may, however, be necessary where symptoms are atypical or subjective.

The challenge food in cow's milk allergy is either baked or fresh milk (Figure 2). As baked milk is less allergenic in this context where a positive challenge is unexpected, it may be used initially as reactions are less likely to be severe (D). In addition, as cow's milk allergic individuals develop tolerance to baked milk before fresh milk, using this form may identify individuals developing tolerance earlier (see Milk reintroduction).

Molecular diagnosis. Current allergy tests assay total specific IgE to crude allergen and thereby only allow for binary recognition (i.e. yes or no). They do not provide any information about constituent components of the allergen involved. Not all recognized parts are equally important or even clinically relevant [80]. Molecular diagnostic allergy testing (component-resolved diagnostics) is now commercially available for food allergens, including cow's milk, and its use has been reviewed recently [81]. Although a number of studies have made use of these novel techniques [82–88], only three are comparable with standard clinical diagnostic methods [83, 87, 89] and used OFC's as the outcome measure. No advantage over the usual diagnostic tests was found by the comparative evaluation of SPT and sIgE (measured with ImmunoCAP; Thermo Fisher Scientific Inc., Waltham, MA, USA) with the component-based microarray assay Immuno Solidphase Allergen Chip (ISAC®; VBC Genomics Bioscience Research, Vienna, Austria) (D). When evaluating natural cow's milk allergens (*Bos d* 4,5,6 and 8), no single allergenic component was found to be superior at discriminating between clinically irrelevant sensitization and genuine cow's milk allergy. Studies have suggested that, in persistent disease, casein sensitization [32, 83] and presence of certain epitopes [90] are more likely. Subjects with severe systemic reactions demonstrated stronger IgE reactivity to more components; however, the testing did not allow differentiation between subjects without symptoms and subjects with severe or gastrointestinal symptoms [85, 86].

The specificity of the microarrays has been demonstrated to be high, but this does not currently translate into an acceptable negative predictive value to make this technology a reliable instrument of exclusion screening in the setting of cow's milk allergy. Using the ISAC® method, there appeared to be no single sensitization profile identified in subjects with persistent cow's milk allergy. Although the studies are promising, the clinical application of molecular diagnosis remains to be assessed and currently the use of component-resolved diagnostics in cow's milk allergy is not routine (E).

Tests not recommended for diagnosing cow's milk allergy. Combining allergy tests has not been shown to improve diagnostic accuracy, and other proposed tests for diagnosing food allergy (e.g. histamine, tryptase, and chymase assays) have had too few studies to allow conclusions to be drawn regarding their use [91].

Methods that are not useful for diagnosing cow's milk allergy include those without validity and/or evidence, such as hair analysis, kinesiology, iridology, electrodermal testing (Vega), and those methods without valid interpretation such as lymphocyte stimulation tests and food-specific IgG and IgG4 [92].

Non-IgE-mediated cow's milk allergy

Gastrointestinal symptoms. In non-IgE-mediated cow's milk allergy presenting with gastrointestinal symptoms only, the diagnosis is dependent on a careful detailed clinical history and examination as none of the currently available diagnostic tests are of use in the assessment. Elimination diets and milk reintroduction remain the diagnostic gold standard (C) [58, 93]. Return of symptoms would suggest a non-IgE-mediated allergy, and the exclusion diet would need to be maintained. Usual clinical practice, however, is to introduce an elimination diet only, and if the symptoms improve or resolve, to maintain dietary exclusion until assessing the child for the development of tolerance. At this time, reintroduction can be considered. (see Milk reintroduction).

Eczema. Sensitization to food allergens, as evidenced by elevated IgE levels, is very common in children with eczema [94] and was reported at 27.4% for cow's milk [95]. However, sensitization does not necessarily indicate clinical allergy [96]. In immediate-onset reactions allergy tests (SPTs or sIgE assays) to selected foods identified by careful history can be used to recognize the responsible food or foods. Isolated delayed reactions are rare, and tests in this scenario are unhelpful [97]. Mixed reactions account for more than 40% of all food reactions in patients with eczema and are the most difficult to diagnose as the history is frequently absent owing to the severity of the eczema. Allergy tests are frequently positive [54].

The possible role of milk allergy in moderate to severe eczema not controlled by topical corticosteroids may be assessed with elimination–reintroduction diets in the following clinical scenarios:

Baked milk challenge

1. Small crumb of biscuit
2. Large crumb of biscuit
3. 1/16 of biscuit
4. 1/8 of biscuit
5. 1/4 of biscuit
6. Remainder of biscuit

- Challenge food is a malted milk biscuit.
- The biscuit should ideally contain whole milk protein (< 1 g per biscuit).
- 15- to 30-min observation periods between doses.
- 60-min observation period (minimum) at the end of the challenge.

Fresh milk challenge

1. One drop of cow's milk placed on lower oral mucosa
2. 0.1 mL cow's milk
3. 0.25 mL cow's milk
4. 0.5 mL cow's milk
5. 1.0 mL cow's milk
6. 2.5 mL cow's milk
7. 5.0 mL cow's milk
8. 10 mL cow's milk
9. 20 mL cow's milk
10. 50 mL cow's milk
11. 100 mL cow's milk

- Challenge food is fresh milk.
- Challenge is suitable for infant formulas.
- 10-min observation period after step 1, followed by 15- to 30-min observation periods between subsequent doses.
- 60-min observation period (minimum) at the end of the challenge.

Fig. 2. Cow's milk oral open-challenge protocols (hospital based). 1. The rate of dose escalation, interval between doses, and observation period after challenge can vary depending on risk assessment in individual cases. Slower up-dosing is recommended to ensure safety and thereby promote reintroduction. 2. In non-IgE-mediated food protein-induced enterocolitis syndrome, immediate allergic symptoms are unusual and delayed symptoms can occur up to 2 h after ingestion. The entire portion can therefore be given in 3 feedings over 45 min, but with a prolonged observation period of 4 h [76, 178].

- Breastfed infants under 6 months old with or without other evidence suggestive of cow's milk allergy (i.e. positive allergy test, other clinical manifestations of allergy such as colic, diarrhoea, vomiting, faltering growth, and/or a family history of atopy) [98].
- Bottle-fed infants and children under 2 years of age with or without other evidence suggestive of cow's milk allergy.
- Older children (> 2 years of age) with other evidence suggestive of cow's milk allergy, which in these circumstances include a child who has always vomited, had diarrhoea and now has constipation, has another known food allergy, has allergy tests positive to milk, and/or has a family history of atopy. Other food triggers identified by parental history and allergy tests should also be considered.
- Older children (> 2 years of age) with high levels of total IgE without environmental triggers, particularly when another food allergy is present.

It is not sufficient to use the elimination diet alone as improvement in the eczema may be coincidental (E). Diagnostic elimination should be implemented only after the eczema has been stabilized with standard eczema care of emollients, appropriate strength topical corticosteroids, and antibacterial treatment as needed [54].

Diagnostic dietary elimination should be maintained for at least 6 weeks [98], after which each excluded food should be individually introduced with caution using a titrated challenge protocol (e.g. Figure 3) (C). Cautious reintroduction is preferable as more severe, and immediate reactions may occur after a period of dietary elimination [99]. Observation for any clinical reaction for up to 72 h is then recommended. If no reaction is observed, the child should continue to consume the food over the next 5–7 days, taking a daily dose corresponding to the average age-appropriate portion size, whilst being observed for any deterioration in his or her eczema. In cow's milk allergy, baked milk is reintroduced first followed by fresh milk using a similar reintroduction procedure and a titrated challenge protocol (e.g. Figure 2).

Dietary avoidance

Avoidance advice. The treatment following the diagnosis of cow's milk allergy is complete avoidance of cow's milk and foods containing cow's milk (D). Verbal and written advice should be provided on the avoidance of dairy-based solids and foods with cow's milk proteins as hidden 'ingredients' and measures to avoid contamination (see Appendix A: Patient information sheet – cow's milk allergy). Advice should be adapted to the age of the child and include education to other carers of the child, for example grandparents, nurseries, childminders, so as to minimize accidental cow's milk ingestion outside the home. It is preferable that all children diagnosed with cow's milk allergy are assessed at least once by a dietitian to discuss avoidance, appropriate meals and milk substitute choice, nutritional adequacy, and reintroduction. Failure to involve a dietitian may lead to inappropriate feeding, prolonged unnecessary exclusion, and nutritional deficiencies. Children should be reviewed at 6–12 monthly intervals for assessment of tolerance and possible cow's milk reintroduction.

Avoiding cow's milk products. Cow's milk as an ingredient is found in a very wide variety of commonly consumed foods and is probably the most difficult allergen to avoid. Although consumers expect the presence of cow's milk in some foods, many others would require expert dietetic knowledge to anticipate its presence, or it may be in a form that the lay consumer might not recognize as cow's milk (Table 9). Labelling legislation has consequently been introduced to ensure that consumers are given comprehensive ingredient information, thereby making it easier for people with food allergies to identify foods they need to avoid. In November 2005, the European Union issued legislation for pre-packaged foods that a list of 14 allergens, including cow's milk, must be indicated by reference to the source allergen if used in the production of the food and still present as an ingredient [100]. This law is currently being extended to foods sold unpackaged; however, until fully enforced, care should be taken over all foods sold loose and unwrapped as, for example, ham may contain casein, pastry may be glazed with cow's milk, and biscuits may use margarine containing whey. Similar legislation in the United States since 2004 requires that food containing any of eight major food allergens, again including cow's milk, must clearly list the food allergen on the label in simple language [101].

These laws do not address voluntary disclaimers such as 'this product does not contain cow's milk, but was prepared in a facility that makes products containing cow's milk' or 'this product may contain traces of cow's milk'. Such statements often deny consumers the ability to make informed decisions. Blanket eliminations should be avoided as they substantially increase dietary restrictions that may be unnecessary except for those individuals with previous severe reactions (e.g. anaphylaxis or FPIES) to baked milk traces.

Suitable milk substitutes

Cow's milk is a staple food in human nutrition providing energy, protein, calcium and phosphorous, riboflavin, thiamine, B12, and vitamin A [102]. It is used in the manufacture of many nutritionally important foods, such as yogurt and cheese, and therefore, the choice of substitute milk must address the nutrients lost with exclusion. During breastfeeding and in children 2 years and older, a substitute milk may not always be necessary if adequate energy, protein, calcium, and vitamins can be obtained from other sources. In infants not breastfed and children < 2 years old, replacement with a substitute milk is mandatory.

Breast milk. Breast milk is suitable for most infants with cow's milk allergy. Cow's milk protein β-lactoglobulin can be detected in the breast milk of most lactating women although in concentrations that will be of no consequence to most cow's milk allergic infants [103, 104]. Mothers should therefore be encouraged to continue breastfeeding and usually do not require dietary dairy restrictions unless the infant has symptoms whilst being breastfed.

However, small amounts of cow's milk proteins found in breast milk can elicit symptoms in exclusively breastfed infants never given cow's milk [104, 105]. The population prevalence is reported at 0.4–0.5% [18, 19, 105].

As hypoallergenic formulas contain small amounts of β-lactoglobulin, cow's milk allergic infants reacting to breast milk are more likely to require an amino acid formula when weaned [106, 107]. Mothers excluding cow's milk should be assessed for their own need for

Important: Read before starting reintroduction

Background

- Most children with cow's milk allergy grow out of it in early life. As the allergy resolves with time, many children will initially tolerate well-cooked (baked) milkproducts, then lightly cooked milk products, and finally uncooked fresh milk.
- It is appropriate to try reintroduction of baked milk products at home in young children who have had a previous mild reaction to milk (e.g. mild rash, gastro-oesophageal reflux). Children who have had more severe symptoms may need to have a reintroduction performed under hospital supervision
- This protocol informs parents how to perform the milk reintroduction at home.
- Your dietitian/doctor/nurse will advise when it is appropriate to try each stage of reintroduction. Use the following information only as a guide. There may be variations for individual children, which your dietitian or doctor will explain.

Guidance notes

- You may stay at each stage for longer than as shown above, but do not increase to the next dose more quickly.
- Try to give the dose every day. If you miss several days (e.g. child unwell), give a smaller dose when you restart and build up.
- Do not increase the dose if your child is unwell.
- If you start to see symptoms, reduce the dose to a level that is tolerated.
- Symptoms of a reaction can usually occur up to 2 h after the last dose (worsening of eczema usually occurs after some hours, or the next day).
- Do not allow other foods (see 'milk ladder') until 1 whole milk containing biscuit is tolerated, or you have spoken to your dietitian/doctor/nurse.
- Do not worry if your child does not like to in itially eat milk products. This is quite common.

Week 1:

1. Postpone the reintroduction if your child is unwell.
2. Have oral antihistamines available.
3. Obtain a malted milk biscuit containing < 1 g of baked cow's milk powder or protein (do not use a biscuit with any type of undercooked cow's milk, e.g. a cream filling).
4. Begin by rubbing a small amount of the biscuit on the inner part of the child's lips.
5. Wait for 30 min and allow your child to continue normal activities.
6. Observe for any signs of an allergic reaction. These may include itching, redness, swelling, hives (nettle-sting type rash), tummy pain, vomiting or wheezing
7. If there have been no symptoms give your child a small crumb of the biscuit.
8. Give a small crumb of biscuit once a day for a week
9. Follow the dose increases below as tolerated.

Week 2

- Large crumb to be eaten daily (2 days)
- 1/16 biscuit to be eaten daily (2 days)
- 1/8 biscuit to be eaten daily (3 days)

Week 3

- 1/4 biscuit to be eaten daily

Week 4

- 1/2 biscuit to be eaten daily

Week 5

- 1 whole biscuit to be eaten daily

Fig. 3. Protocol for home baked cow's milk reintroduction.

calcium and vitamin D supplementation. All infants over 6 months receiving breast milk as their main feed should be given vitamin D supplementation in the form of vitamin drops [108].

Hypoallergenic formulas. A hypoallergenic formula is one that meets the defined criterion [109] of 90% clinical tolerance (with 95% confidence limits) in infants with proven cow's milk allergy (Table 10) [109, 110]. Only amino acid and extensively hydrolysed formulas meet this criterion and are the formulas of choice for the treatment of cow's milk allergy. Partially hydrolysed formulas are available in the UK, and although they may have some use in milder forms of digestive disorders, they are not hypoallergenic and therefore should not be used for the treatment of suspected or proven cow's milk allergy or diagnostic exclusion diets. Lactose-free formulas contain intact cow's milk protein and should not be used in proven or suspected cow's milk allergy. Some individuals highly sensitized to

Table 9. Food items and ingredients that contain cow's milk protein

Butter, butter fat, butter milk, butter oil
Casein (curds), caseinates, hydrolysed casein, calcium caseinate, sodium caseinate
Cheese, cheese powder, cottage cheese
Cow's milk (fresh, condensed, dried, evaporated, powdered (infant formulas), UHT)
Cream, artificial cream, sour cream
Ghee
Ice cream
Lactalbumin, lactoglobulin
Low-fat milk
Malted milk
Margarine
Milk protein, milk powder, skimmed milk powder, milk solids, non-fat dairy solids, non-fat milk solids, milk sugar
Whey, hydrolysed whey, whey powder, whey syrup sweetener
Yogurt, fromage frais

cow's milk may react to residual cow's milk proteins in extensively hydrolysed formulas (EHFs) and will thus require an amino acid formula (AAF) [111].

Extensively hydrolysed formulas—As different EHFs are derived from different protein sources and are designed to meet the needs of whole protein intolerance (cow's milk allergy) and malabsorption conditions, there are differences between brands. Although many infants will tolerate all protein hydrolysates, the following should be considered when choosing an EHF for an individual:

a)*The protein source*. The hydrolysate may be based on whey or casein proteins from cow's milk or be derived from soya and pork. The latter may not be suitable in some religions.
b)*The size of peptides*. The presence of larger peptides is associated with higher allergenicity. It may therefore be preferable to use a hydrolysate with the greatest percentage of peptides under 1000 Daltons.
c)*Palatability*. Hydrolysed protein is bitter in taste. Differences in taste are related to protein source (i.e. casein, whey, bovine), degree of hydrolysation, and the presence or absence of lactose. Palatability may influence formula choice, especially in older infants or where a less hydrolysed formula can be tolerated.

Amino Acid formulas—Amino acid formula (AAFs) are suitable first line formulas for cow's milk allergy but are usually reserved, because of their higher cost, for those infants with (D)

- multiple food allergies,
- severe cow's milk allergy,
- allergic symptoms or severe atopic eczema when exclusively breastfed,
- severe forms of non-IgE-mediated cow's milk allergy such as eosinophilic oesophagitis, enteropathies, and FPIES,
- faltering growth and
- reacting to or refusing to take EHF at nutritional risk.

Amino acid follow-on formulas are available for use in children over 1 year old, and are useful when milk allergic infants (who meet the criteria for an amino acid milk) require additional energy, calcium, and iron or a flavoured product.

Soya formulas. Soya protein formulas are nutritionally adequate substitutes, although provide no nutritional advantage over cow's milk protein formulas (Table 10) [112, 113]. Native soya protein has lower bioavailability than cow's milk protein and has a lower content of the essential amino acid methionine (and carnitine which is synthesized from methionine and is used in fatty acid metabolism). Therefore, soya protein infant and follow-on formulas available in Europe must fulfil certain compositional criteria to ensure that only protein isolates are used and that the minimum protein content is higher than that found in cow's milk formulas (2.25 g/100 kcal vs. 1.8 g/100 kcal) [114]. Methionine and carnitine supplementation is also recommended [115].

Several brands of infant soya protein formulas can be prescribed for children with milk allergy. It is generally agreed that they are considerably more palatable and less expensive than extensively hydrolysed (EHF) and amino acid (AA) formulas and are therefore a popular choice as substitute formula (E). Other dairy replacement products made from soya are also available (e.g. cheese and yogurts) which can be helpful for weaning infants. However, there remain issues with the development of soya allergy, risks of developing peanut allergy, and risks of phytoestrogen exposure in male infants.

Concomitant soya protein allergy affects about 1 in 10 infants with cow's milk allergy, occurring equally in IgE-mediated and non-IgE-mediated cow's milk protein allergy [59, 116]. Adverse reactions to soya in a single small study occurred more commonly in infants under 6 months than in those 6–12 months old (5 of 20 vs. 3 of 60) [59].

A large cohort study showed an association between intake of soya protein formula in the first 2 years of life and later development of peanut allergy [117]. However, in a randomized controlled study in which infants with cow's milk allergy were fed either a soya protein formula or an extensively hydrolysed formula, the use of soya protein did not increase the risk of development of peanut sIgE antibodies or of clinical peanut allergy [118]. In addition, a data analysis of an atopy cohort study Koplin and colleagues [119] found no association between soya protein formula consump-

Table 10. Substitute formulas available in the UK for cow's milk allergic infants

Type of formula	Example (alphabetical order)	Manufacturer	Composition[1] Protein source	Carbohydrate	Minerals (mg/100 ml)
EHF[2]	Aptamil Pepti 1 and 2 (2 suitable from 6 months)	Milupa	Hydrolysed whey 73% peptides < 1000 Da	Fish oils (omega 3 and 6). Lactose and maltodextrin	Calcium 52 Iron 0.5
	Althéra	Nestlé	Hydrolysed whey 95% peptides < 1000 Da	Palm, coconut, rapeseed and sunflower oil. Maltodextrin, lactose	Calcium 41 Iron 0.73
	Nutramigen 1 and 2 (2 suitable from 6 months)	Mead Johnson	Hydrolysed casein 95% peptides < 1000 Da	Palm, coconut, soya and sunflower oil. Glucose syrup, modified corn starch, fructose. Lactose free	Calcium 77 and 94 Iron 1.22 and 1.2
	MCT Pepdite	Nutricia SHS	Hydrolysed soya and pork collagen 64% peptides < 1000 Da	Coconut, maize, palm kernel and walnut oil. 75% fats MCT. Glucose syrup. Lactose free.	Calcium 49 Iron 1.0
	Pepdite	Nutricia SHS	Hydrolysed soya and pork collagen 64% peptides < 1000 Da	Coconut, soya and sunflower oil. Glucose syrup. Lactose free.	Calcium 45 Iron 1.3
	Pepti Junior	Cow and Gate	Hydrolysed whey 57% peptides < 1000 Da	Coconut, soya and fish oil; 50% MCT. Glucose syrup Lactose content insignificant	Calcium 76 Iron 1.2
	Pregestimil	Mead Johnson	Hydrolysed casein 95% peptides < 1000 Da	Corn, soya and sunflower oil; 55% MCT. Corn syrup and corn starch. Lactose free.	Calcium 94 Iron 1.8
	Similac Alimentum	Abbott	Hydrolysed casein 95% peptides < 1000 Da	Sunflower and soya oil. 33% MCT Sucrose, modified corn starch. Lactose free.	Calcium 71 Iron 1.2
AAF[3]	Neocate LCP	Nutricia SHS	Amino acids	Coconut, canola and sunflower oil. Glucose syrup. Lactose free	Calcium 65.6 Iron 1.0
	Neocate Active (suitable from 12 months)	Nutricia SHS	Amino acids	Coconut, canola and sunflower oil. Glucose syrup. Lactose free.	Calcium 95.1 Iron 1.3
	Neocate Advance (suitable from 12 months)	Nutricia SHS	Amino acids	Coconut, canola, and sunflower oil. Glucose syrup. Lactose free.	Calcium 50 Iron 0.62
	Nutramigen AA	Mead Johnson	Amino acids	Palm, coconut, soya and sunflower oil. Glucose syrup and tapioca starch. Lactose free.	Calcium 64 Iron 1.22
Soya[4]	Infasoy	Cow and Gate	Whole soya	Glucose syrup. Suitable for vegans	Calcium 54 Iron 0.8
	Wysoy	SMA Nutrition	Whole soya	Glucose syrup.	Calcium 67 Iron 0.8

AAF, amino acid formulas; EHF, extensively hydrolysed formulas; Da, dalton; MCT, medium chain triglycerides.

Additional information:

[1]Composition information sourced from commercial data sheets 2013;

[2]EHF: Use with caution in infants with severe milk allergy or with symptoms with breast milk, lower hydrolysation (i.e. lower % peptides < 1000 Da) poses potential risk of allergic reaction to formula, Pepdite, Pepti Junior, and Pregestimil suitable for milk allergy but more commonly used for multiple malabsorption or short bowel syndrome;

[3]AAF: reserved for infants with multiple food allergies, severe cow's milk allergy, allergic symptoms, or severe atopic eczema when exclusively, breastfed, severe forms of non-IgE-mediated cow's milk allergy such as eosinophilic esophagitis, enteropathies, and FPIES, infants with faltering growth, and those reacting to or refusing to take EHF at nutritional risk;

[4]Soya formulas should not be used in infants < 6 month old or in suspected soya allergy.

tion as randomly allocated feed and peanut sensitization, but by contrast, if parent selected, a significant association was noted. Parents were more likely to choose a soya infant feed in the presence of either maternal or sibling cow's milk allergy. The association between soya consumption in infancy and subsequent peanut sensitization is not causal but instead the result of preferential use of soya protein formulas in infants with atopy (e.g. eczema) and thus at greater risk of other sensitizations. Therefore, the current evidence does not support a causal relationship between soya exposure and the subsequent development of peanut allergy.

Phytoestrogens are naturally occurring plant-derived compounds that possess weak oestrogenic activity. The main phytoestrogens in soya are isoflavones, which are present in soya protein formulas in concentrations four orders of magnitude (i.e. 10 000 times) higher than in human breast milk. Phytoestrogens in high dose have been shown in animal studies to adversely affect the development of reproductive organs and fertility [120]. There is no evidence from limited data of similar effects in humans, however, as a precaution in 2003 the Committee on Toxicity of Chemicals in Food advised that infants under 6 months should not be fed soya milk as a sole source of nutrition unless a mother wished her infant to have a vegan diet.

Therefore, soya formulas should not be the first line choice of substitute milk for infants < 6 months old with cow's milk allergy (E). An EHF (or AA preparation where hydrolysates are not tolerated) should be given. If after 6 months of age soya protein formula is considered because of lower cost or better palatability, tolerance to soya protein should first be established. Exceptions may arise where, for example, refusal to take EHF/AA places the infant at nutritional risk or in vegan families unable to breastfeed or symptomatic with breast milk.

Where soya is chosen as a milk substitute, a soya *formula* should always be used in children under 12 months old because of its complete nutritional value (E). Soya-based drinks (see Alternative 'milk' beverages) may be suitable in older children but only if supervised by a dietitian.

Unsuitable (or less desirable) milk substitutes

Heated and processed fresh cow's milk. All fresh cow's milk is pasteurized before it is marketed. This relatively low temperature and short time heating process of 70–80°C for 15–20 s, which is designed to reduce potential pathogen load, has no impact on the allergenicity of cow's milk.

Technological processing designed to prolong the shelf-life of milk may have minor effects on the allergic potential of cow's milk through modification of whey proteins. Examples include sterilization of milk by heating for an extremely short period of time at temperatures required to kill spores (135°C for 1–2 s) and evaporation for the production of powdered formula milk. The changes to the milk proteins by these processes may explain why some individuals claim to tolerate these milks, but not fresh milk, when cow's milk is reintroduced.

Other mammalian milks. Homology of protein composition between mammalian milks correlates with phylogenetic relatedness. Cow's milk proteins thus have greater similarity with those of goat's and sheep's milk and less with milk from camels, donkeys, horses, pigs, and reindeer [121]. Consequently, most cow's milk allergic individuals are also allergic to goat's milk [122], whilst more than 80% tolerate donkey's milk [123]. However, milk from camels, donkeys, horses, pigs, and reindeer is not widely available, and there are also uncertainties about the suitability of their chemical and nutritional composition and hygiene. As a consequence of the nutritional concerns, the European Food Safety Agency and the Department of Health issued statements that recommend against the use of these other mammalian milks as a suitable infant formula [124]. They should therefore not be recommended to individuals with cow's milk allergy.

Alternative 'milk' beverages. There are a large variety of so-called cow's milk replacements available in supermarkets and health stores. These may be based on almond, coconut, hazelnut, hemp, oat, potato, quinoa, rice, or soya (see above re: Soya formulas). The majority have poor nutritional value compared with cow's milk, as most are low in energy and extremely low in protein. Some are devoid of calcium (e.g. organic brands), and there are large variations in the vitamin content. Recommendations on the use of alternative 'milks' are as follows:

- They are not suitable for infants as a main drink under 1 year of age. A nutritionally complete formula should always be chosen, preferably to 2 years of age (although they can be used for cooking).
- Their use in children should be under the close guidance of a dietitian as shortfalls in energy, protein, calcium, riboflavin, vitamin A and D, and essential fatty acids are likely without an alternative dietary source. Weight and growth should be regularly monitored.
- They are not available on prescription and therefore should not be suggested to families with financial constraints where a more suitable complete formula can be prescribed.

- Their use in older children and adults should be under the supervision of a dietitian to ensure adequate calcium intake.
- Care should be taken to ensure that specific ingredients are not allergenic to a particular individual, for example nut milks and nut allergy, soya milks and soya allergy.
- Rice milk should not be used under age 4.5 years due to its natural inorganic arsenic content [125, 126].

Calcium availability and replacement

As cow's milk is a good nutrient source, dietary exclusion without provision of suitable dietary substitute can lead to nutritional deficiencies. Whilst many of the nutrients can be obtained from other foods, dairy products are a principal source of dietary calcium [127]. Factors to consider when assessing calcium intake are dietary calcium content, bioavailability, and absorption.

Calcium is better absorbed from breast milk than infant formulas and cow's milk (66% vs. 40% vs. 24%) [128]. Infant formulas are consequently over fortified to 140% of the calcium content of breast milk to compensate for reduced absorption. Calcium absorption is also decreased in the absence of lactose, so lactose-free milks and soya milks are also overfortified [129]. The additional fortification thus ensures that cow's milk allergic infants fed hydrolysed, amino acid, or soya formulas maintain adequate calcium intake.

A dietitian should assess all children on dairy exclusion diets for calcium intake (D). This can be performed initially using the diet history, but where milk intake is less than 500 mL per day, a more thorough assessment using a dietary diary is required. If the child is not achieving the recommended intake for his or her age (Table 11), supplementation will be required if dietary manipulation is not possible. Calcium phosphate supplements are better absorbed than calcium carbonate or lactate [130].

Calcium-rich foods (aside from milk) include nuts, seeds, pulses, shellfish, tinned fish (particularly where the bones are eaten), calcium-fortified cereals, and tofu (Table 12). Their usefulness as calcium sources depends on bioavailability, which varies from 4% for sesame to 11% for soybeans and 38% for certain vegetables (kale and celery) [131].

Milk reintroduction

The natural history of all types of cow's milk allergy is to resolve during childhood (Table 2). The speed with which this tolerance develops varies greatly, so the appropriateness and timing of reintroduction should be individually assessed. Non-IgE-mediated allergy will resolve more rapidly than IgE-mediated allergy [22]. Clinical and laboratory indices can be used to guide reintroduction; those associated with slow resolution include a history of severe reactions, the presence of other food allergies, asthma, and rhinitis [8, 20, 22, 24, 26–28], and a SPT weal size $\geq$ 5 mm at diagnosis [23].

A reduction in sIgE over time accompanies the development of clinical tolerance [24], and repeat measurements at 6–12 monthly intervals may be of value in determining when to consider performing reintroduction (B). A follow-up study established that a 99% reduction in cow's milk sIgE levels after 12 months translated into a 94% likelihood of achieving tolerance within that time span, whilst a 50% reduction in titre of the sIgE over the same period was associated with a 30% probability of resolution of the allergy [23]. A 70% reduction was associated with a 45% probability of resolution [33]. Others suggest that this predictability applies only to those individuals with concomitant atopic dermatitis [132]; however, clinical experience shows that a substantial reduction in sIgE levels over time is associated with the development of clinical tolerance.

Children who grow out of their cow's milk allergy become tolerant to milk in baked form before fresh milk and fresh milk products because baking reduces protein allergenicity. Therefore, reintroduction of baked milk as an ingredient is attempted before reintroduction to fresh milk (D). The effects of heat on cow's milk proteins are determined by the protein structure, with sequential epitopes (caseins and serum albumin) having higher thermal stability than heat-sensitive conformational epitopes (whey proteins α-lactalbumin, β-lactoglobulin, and lactoferrin). Baking (or thermal processing) thus reduces allergenicity by destroying the conformational epitopes but has limited effect on the sequential epitopes [133]. Allergenicity is further reduced by the matrix effect where cow's milk proteins interact with other ingredients within processed foods, which results in decreased availability of the protein for interaction with the immune system [134]. A study of 100 milk allergic children aged between 2.1 and

Table 11. Recommended calcium intake*

Age	Adequate intake (mg/day)
0–12 months	525
1–3 years	350
4–6 years	450
7–10 years	550
11–14 years (male)	1000
11–14 years (female)	800
15–18 years (male)	1000
15–18 years (female)	800

*UK recommendations differ from those of other countries (e.g. US).

Table 12. Calcium content in selected foods

Food group	Food type and calcium content (in mg/100 g of food)
Nuts	Almond (240), Brazil nut (170), hazelnut (140), peanut (60), pistachio nut (110), walnut (94)
Seeds	Sesame seeds (670), tahini paste (680)
Pulses	Canned baked beans (53), cooked chick peas (46), cooked red kidney beans (71), cooked soya beans (83)
Fish	Tinned pink salmon (91), canned sardine (540), canned pilchards (250)
Shellfish	Canned crab (100), prawns (110), shrimp (110)
Cereals	Brown bread (186), white bread (177), some breakfast cereals contain added calcium
Vegetables	Broccoli (56), cabbage (52), celery (45), curly kale (150), okra (160), olives (61), parsnip (50), watercress (170)
Fruit	Dried apricots (73), blackberries (41), blackcurrants (60), dried figs (250), oranges (47), rhubarb (raw) (93)
Others	Tofu (510), whole egg (57), egg yolk (130), egg white (5)
Cow's milk	Formulas (118) *for comparison*
Calcium-fortified foods	Most non-organic milk substitutes, for example hemp, nut, oat, rice, soya (100)
	Some non-dairy desserts, for example soya yogurts (100)
	Some breads (90 g per slice)
	Calcium-fortified water and fruit drinks (120)
	Calcium-fortified breakfast cereals (140 per bowl)
	Meals and dishes made with calcium-fortified milk-free substitutes, for example custard, white sauce (100)

17.3 years showed that 75% were able to tolerate challenges with baked milk products. Subjects who reacted on heated milk challenge had significantly larger SPT weals and higher milk-specific and casein-specific IgE levels [135].

Although there is a paucity of published evidence to support the practice, home reintroduction of baked milk products has become routine practice through experience in allergy services in the UK (D). Home reintroduction may be attempted in children who have had only mild symptoms (only cutaneous symptoms) on noteworthy exposure (e.g. a mouthful of fresh milk) and no reaction to milk in the past 6 months and in IgE-mediated disease, a significant reduction in sIgE/SPT weal diameter (D) (Figure 3 and Box 2) [76]. Reintroduction should proceed at the rate recommended as a single study has demonstrated that rapid high-dose exposure may result in severe reactions in a small number of patients [136].

The addition of baked milk to the diet may accelerate the further development of tolerance, including to fresh milk [29]. Consequently, once tolerance is established, greater exposure through ingestion of less processed cow's milk according to the 'milk ladder' (Figure 4), limited by the individual's tolerance, can be encouraged (D). Affected individuals and their families should, however, be advised to proceed with caution as the classification in a 'milk ladder' of milk-containing foods from low to high allergenicity is imperfect and may thus result in a bigger than anticipated step-up in exposure. The difficulties with classification are that

- In devising a 'milk ladder', there is very little evidence on the effect of processing on the allergenicity of specific foods.
- Whilst many commercially manufactured and home-made foods contain milk, recipes for similar products differ widely in the quantity of milk protein per portion, the type of milk protein used (i.e. whole milk protein or whey powder), the length of time and temperature at which it is cooked, and the presence of other ingredients that may affect IgE binding sites.

Therefore, the 'milk ladder' should be used only as a guide (D).

A fresh milk challenge is recommended in individuals who have achieved full tolerance of all baked milk products (D).

Oral tolerance

Whilst most children will grow out of their cow's milk allergy usually by 5 years of age, a significant proportion will remain allergic. Traditionally management of these individuals has been limited to dairy exclusion with replacement by dietary alternatives. However, as accidental ingestion of cow's milk occurs frequently, those who remain allergic will be at continued risk of allergic reactions [137].

Oral tolerance induction (OTI) as a treatment for cow's milk allergy offers a promising management option in individuals where it persists beyond an age at which it is expected to resolve (C). The concept of OTI follows the same principles as immunotherapy in other allergic conditions. It involves the administration of increasing doses of cow's milk during an induction phase, starting with a dose small enough not to cause a reaction and continuing to a target dose or until the treated individual's symptoms preclude further dose increments. This is followed by a maintenance phase with regular intake of the maximum tolerated amount of cow's milk [138].

Since the early report on OTI by Patriarca and colleagues [139], there have been a number of observational studies [140–144] and randomized trials [145–150] on the outcomes of OTI to cow's milk in children. Although there is little uniformity in the methodology of these studies with differences in particular in the study population age and treatment protocols, there is agreement on outcome. Four clinical patterns of reactions occur; non-responders, partial responders developing partial tolerance defined as able to take

Box 2. Home reintroduction should not be attempted if any of the following features are present

- Previous cow's milk allergy symptoms that significantly affected breathing [cough, wheezing, or swelling of the throat, for example cough, stridor, or choking sensation or throat tightness (in older children)], the gut (i.e. severe vomiting or diarrhoea), or the circulation (faintness, floppiness or shock)
- A less severe reaction with only trace exposure
- Regular asthma preventative inhaler treatment and/or poorly controlled asthma.
- Multiple or complex allergy
- No significant reduction in SPT wheal diameter/sIgE level since diagnosis
- High sIgE levels without history of any prior milk exposure (e.g. exclusively breastfed or hypoallergenic formula fed infants with severe eczema)
- Parents who are unable to comprehend or adhere to the protocol
- Children with any of these features should undergo a supervised challenge in hospital. In children at highest risk, a supervised baked milk challenge is preferable

more than 5 mL but less than 150 mL of cow's milk, responders developing full tolerance (i.e. able to tolerate at least 150 mL of cow's milk and eat dairy and cow's-milk-containing products) requiring regular intake to maintain full tolerance [151], and responders who remain tolerant even after periods of dietary elimination [138]. A recent systematic review and meta-analysis of four published randomized trials showed that the probability of achieving full tolerance was 10 times higher in children receiving OTI compared with elimination diets alone and that the probability of developing partial tolerance was over 5 times higher [152].

There are risks of adverse reactions associated with OTI with symptoms occurring as frequently as in one in six doses. These predominantly affect the skin and gastrointestinal tract and are thus mild to moderate in severity. Anaphylactic reactions that require treatment with adrenaline have, however, been reported [153, 154].

Although OTI in cow's milk allergy has been more widely studied than in allergy to hen's egg [155] and peanut [156], there are still a number of unanswered questions requiring further research to establish which subjects to treat, what protocol to use, whether the treatment actually achieves true tolerance with a long-lasting effect or just temporary desensitization and data on long-term safety. Most authors thus do not currently recommend OTI for routine clinical practice [152, 157].

Pharmaceutical agents containing milk

Where cow's milk is used in the manufacture of pharmaceutical agents, traces of milk protein may persist in sufficient amounts to elicit reactions in highly sensitive cow's milk allergic individuals. Agents that should be considered are probiotics cultured in media that include milk proteins or others that contain lactose as an inactive ingredient.

Current legislation does not require manufacturers to evaluate residual allergen content in probiotic preparations or to indicate on the label the characteristics of their culture medium. Where the probiotic growth medium includes milk proteins, these may remain in the commercial product at levels high enough to elicit a positive SPT response and clinical reaction [158]. In high-risk cow's milk allergic children where there are clinical indications for using probiotics, it is advisable to use products clearly labelled to contain no food allergens or to undertake a screening SPT with the product if uncertainty remains (D) [159].

Pharmaceutical grade lactose is obtained from skimmed milk by coagulating and filtering out cow's milk proteins and is widely used as an excipient in pharmaceutical formulations including tablets, oral suspensions, intravenous formulations, and dry powder inhalers for asthma. As this is regarded an efficient process, product information inserts do not warn consumers of the possibility of allergic reactions to cow's milk protein in lactose-containing medicines [160]. Allergic reactions are consequently highly unlikely in most allergic individuals. Clearly, where they do occur, lactose-free alternatives are recommended [161].

Cow's milk allergy in adults

Cow's milk allergy in adults may arise *de novo* in adulthood or persist from childhood. In adults, cow's milk allergy is rare with an estimated prevalence of 0.49–0.6% [162, 163]. Adult patients are more likely to be sensitized by both casein and the whey proteins α-lactalbumin and β-lactoglobulin than children who are sensitized to casein proteins with only a minority sensitized to both [164]. Compared to children, cow's milk allergy is more likely to be severe and persistent. Characterization of cow's milk allergy in adults has been reported [164], with two-thirds developing it in adulthood. Two-thirds also presented with severe symptoms affecting the respiratory and cardiovascular systems, of whom about 25% had experienced anaphylactic shock. None of the 30 patients studied became tolerant during a period of observation ranging from 3 to 40 years. There was no correlation between IgE levels and symptom severity.

The majority of adults report concomitant asthma and have more severe disease with an increased likelihood of inadvertent exposure. Therefore, emergency treatment with adrenaline should always be considered with a written emergency treatment plan and appropriate avoidance advice provided (C). Advice on

More denatured/Low protein dose
Less allergenic

Less denatured/High protein dose
More allergenic

Stage 1	Stage 2	Stage 3	Stage 4
Small crumb of a biscuit containing <1 g of whole cow's milk protein per biscuit. Build up to 1 biscuit over 5 weeks as tolerated. This will include shop bought biscuits that contain cow's milk with protein content listed as < 1 g of protein per biscuit.	Other baked products containing cow's milk protein, for example biscuits, cakes, muffin, waffles, scotch pancakes. Butter. Margarine. Cheese powder flavouring.	Products containing cooked cheese or whole cow's milk as a heated ingredient, for example custard, cheese sauce, pizza, rice pudding. Chocolate. Chocolate coated items. Fermented desserts. Yogurt. Fromage frais.	Uncooked cheese Uncooked non-yogurt desserts, for example ice cream or mousse. Cow's milk UHT milk followed by pasteurised milk and then unpasteurised milk (if this form is preferred by the family).

NOTES:
1. Affected individuals and their families are advised to proceed with caution as the classification in a 'milk ladder' of milk-containing foods from low to high allergenicity is imperfect and may thus result in a bigger than anticipated step-up in exposure.
2. At all stages start with a small amount and gradually increase.
3. Each individual products in Stage 3 is to be introduced in trace amounts first as they have more milk protein and a lower degree of heat treatment or protein denaturation. There is also variability in milk protein between products.
4. If a reaction occurs, the culprit food should be stopped and reintroduction should be continued with food from a lower stage in smaller amounts.

DEVELOPMENT OF 'MILK LADDER' (rationale for classification)
1. The 'milk ladder' considered factors that influence the allergic potential of cow's milk food stuffs in their stage classification: volume or quantity, effect of heating (including duration and degree of heating), and wheat matrix effect [135].
2. Classification:
   - Stage 1: small quantity, baked and matrix.
   - Stage 2: larger quantity, baked and matrix OR traces without matrix or with minimal heating.
   - Stage 3: larger quantity, less heating, and less matrix OR all with some degree of protein change with heating or manufacturing.
   - Stage 4: fresh milk products.

Fig. 4. Classification of cow's-milk-containing foods ('Milk ladder').

alternative sources of calcium should be supplied. Periodic follow-up is useful to review diet, allergic reactions due to inadvertent exposure, comorbidities, for example asthma control, and medication (D). However, as cow's milk allergy is likely to persist and severity correlates poorly with sIgE, changes in titres should not be used routinely as a marker for improvement.

Future research

- Auditing the use of home reintroduction – protocols, indications, and safety (Appendix B).
- Auditing supervised hospital food challenges to evaluate different protocols, that is, rates of up-dosing and intervals between doses.
- Prevalence of soya allergy in milk allergic infants, and prevalence in IgE-mediated and non-IgE-mediated cases.
- Natural history of severe non-IgE-mediated milk allergy.
- Auditing of the efficacy and safety of the 'milk ladder'.
- Investigation of oral tolerance induction for the treatment of milk allergy – efficacy and safety; safety of home up-dosing; safety and efficacy of long-term treatment [165].

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These guidelines inform the management of milk allergy. Adherence to these guidelines does not constitute an automatic defence for negligence, and conversely non-adherence is not indicative of negligence. The expert group will be monitoring clinical management changes, for example, with national audits. Any significant changes will trigger a review of these guidelines. It is anticipated that these guidelines will be reviewed 5 yearly with an assessment at the half point of this period.

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Appendix A: Patient information sheet – cow's milk allergy

What is cow's milk allergy?

Cow's milk and cow's-milk-containing foods (called dairy products) can cause reactions when eaten either because the affected individuals are allergic to the proteins in cow's milk or because they cannot digest the sugar (lactose) in the milk. The presenting symptoms of cow's milk protein allergy are usually more widespread and can involve the skin, respiratory system, gut, and circulation. The symptoms of lactose intolerance affect only the gut with stomach ache, bloating, and diarrhoea.

Cow's milk allergy is common in infants and young children, usually developing before 6 months of age. It affects about 1 in 50 infants, but is much less common in older children and adults, as most affected children will grow out of their allergy. However, in a small minority of individuals, milk allergy is lifelong.

The proteins in cow's milk are similar to those in more closely related (goats, sheep, buffalo) than less closely related (donkeys, horses, camels) animals. As allergy is a reaction against the proteins in cow's milk, individuals who are allergic to cow's milk will also be allergic to goat's milk.

Heating does not change the allergic potential of cow's milk; so allergic individuals will also react to boiled milk. However, when milk is baked with wheat, binding between the milk and wheat hides the milk proteins, thereby reducing its allergic potential. Individuals allergic to cow's milk will often be able to tolerate baked milk before they can tolerate fresh or raw milk.

What are the symptoms of cow's milk allergy?

In infants, cow's milk allergy can present broadly in one of two ways, either with the typical symptoms of food allergy involving the skin, respiratory system, gut, and (rarely) circulation where onset follows soon after ingestion or with delayed mostly gut symptoms or eczema.

The typical immediate-onset symptoms include rash, hives, and swelling which can spread all over the body; runny nose, sneezing, and itchy watery eyes; coughing, wheezing, and trouble with breathing; choking, gagging, vomiting, stomach cramps, and diarrhoea; pallor and drowsiness. Allergic reactions to cow's milk are mild to moderate in most children, but can progress, although rarely, to the severer symptoms of pallor and drowsiness or even into severe allergy called anaphylaxis.

Delayed-onset symptoms are by their nature more difficult to identify as being caused by cow's milk allergy because they can occur hours or even days after milk ingestion and because they often mimic common ailments in infancy such as colic, reflux, and constipation. These symptoms include vomiting, abdominal cramps, diarrhoea, and constipation. Cow's milk allergy should be considered in infants who respond poorly to the medical treatment for these symptoms and who in addition may be particularly irritable, refuse feeds, experience difficulty swallowing and are losing or not gaining weight.

Milk allergy can also be an important factor in infants and children with moderate to severe eczema, particularly where the eczema does not respond to adequate treatment with steroid and moisturizing creams. These children can present with acute skin symptoms (hives, itch, and swelling) in addition to their eczema or with worsening of the eczema itself.

Will the allergy resolve?

Cow's milk allergy will resolve in most children. About two-thirds will be able to drink milk by the time they go to school. In the remaining one-third, tolerance will continue to increase as they get older with only about 1 in 20 still allergic as adults.

Infants and young children can be tested about every 6 months by offering them a crumb of a baked milk biscuit. If they show tolerance, it can be tested by initially increasing the amount of biscuit eaten and then having contact with fresh milk. If a test for tolerance fails, the individual returns to his or her avoidance diet and tries again after a further 6 months. This reintroduction, or putting dairy back into an individual's diet, should not be attempted without the advice of your dietitian, doctor, or nurse.

How is cow's milk allergy diagnosed?

The diagnosis of cow's milk allergy in immediate-onset symptoms is based on the combination of history of a previous reaction confirmed by allergy skin tests or blood tests. As these tests are commonly negative in delayed-onset cow's milk allergy or where cow's milk allergy is associated with eczema, diagnosis in these cases can only be confirmed by symptomatic improvement following dietary exclusion of cow's milk.

What is the treatment?

The treatment for cow's milk allergy is to avoid milk until the allergy resolves. As cow's milk is an excellent source of protein and calcium, it is important to replace it in an infant's diet with appropriate alternatives to maintain growth and nutrition. The most suitable milk will depend on the child's age, the severity of the allergy, and whether he or she can tolerate soya.

Cow's milk alternatives

Breastfeeding	Breastfeeding mothers may need to exclude dairy from their diets as infants with severe allergy may react to the cow's milk protein in breast milk
Hydrolysed infant formula *Aptamil Pepti* *Althera* *Nutramigen* *Similac Alimentum*	Specialized hypoallergenic formula made from heat and chemically changed cow's milk. Contain small amounts of cow's milk protein. Available only on prescription
Amino acid infant formula *Neocate* *Nutramigen AA*	Made from protein building blocks with no cow's milk protein. Indicated in severe forms of cow's milk allergy. Available only on prescription
Soya formula *Infasoy* *Wysoy*	Made from soya protein. Not recommended for under 6 months. Choose brands with added calcium, and monitor weight gain
Fresh soya milk	Suitable for older children who tolerate soya. Choose brands with added calcium and monitor weight gain

It is important to find out how strict the cow's milk avoidance needs to be in an allergic child. Some children will develop symptoms with the tiniest (trace) amount of milk – even milk proteins passed through a mother's breast milk – whilst others can tolerate baked or processed cow's milk or even small amounts of fresh milk. It is easier to identify obvious sources of dairy products, but cow's milk is added to many manufactured foods. It is important therefore to read the food ingredient label carefully.

How to read a label for a milk-free diet

Look out on labels for any of the following ingredients	
Butter, butter fat, butter milk, butter oil	Lactalbumin, lactalbumin phosphate
Butter acid, butter esters	Lactoglobulin, lactoferrin margarine
Casein, caseinates, hydrolysed casein	Milk solids (non-fat milk solids, milk sugar, Milk protein, skimmed milk powder)
Calcium caseinate, sodium caseinate	Animal milks (goat's milk)
Cow's milk (fresh, dried, evaporated, condensed, powdered, UHT)	Sour cream, sour cream solids
Cheese, cheese powder, cottage Cheese	Sour milk solids
Cream, artificial cream	Whey, hydrolysed whey, whey powder whey syrup sweetener
Curds	Yogurt, fromage frais
Ghee	
Ice cream	
Milk is sometimes found hidden in the following	
Biscuits, baked goods	Savoury snacks
Pastry, batter	Soups, gravies
Processed meat	

EU law and the US FDA demand that milk as an ingredient must be clearly labelled on pre-packed manufactured foods. All milk-containing products must be identified by the word 'milk' so that it can be easily identified.

Check ingredient labels every time you buy foods as products are often altered and ingredients may have changed. Lists of milk-free foods can be obtained directly from food manufacturers and supermarket chains. They can be very helpful in identifying which foods are safe to eat. Products that are sold loose (or unpackaged) do not need ingredient labels and in addition are at risk of cross-contamination. These include products from bakeries, delicatessens, butchers, and self-service counters.

What about nutrition?

Dairy products are important sources of energy, protein, calcium, and vitamins. Whilst many of these nutrients can be obtained from other foods, cow's milk is the main source of dietary calcium. When dairy is removed from an individual's diet, it is important to ensure that there is enough calcium from other foods.

What is lactose intolerance?

Lactose intolerance occurs where an individual is not able to digest the lactose sugars in dairy products. These individuals have a deficiency in the gut enzyme lactase. As the lactose is not broken down and absorbed, it ferments in the gut and produces symptoms of bloating, excessive flatulence or wind and watery, explosive diarrhoea.

Individuals with lactose intolerance can have some dairy contact without symptoms, depending on the degree of lactase deficiency, the concentration of lactose in the cow's milk product, and the amount of dairy ingested. They will also, unlike cow's milk allergic individuals, naturally be able to drink lactose-free milks.

Resources

1 British Dietetic Association Food Allergy and Intolerance Specialist Group. Cow's milk free diet for infants and children. Available at: www.bda.uk.com
2 Department of Allergy and Immunology, Royal Children's Hospital, Melbourne. Cows milk allergy. Available at: www.rch.org.au/clinicalguide
3 Food Allergy and Anaphylaxis Network. How to read a label for a milk-free die. Available at: www.foodallergy.org

Appendix B: Cow's Milk Allergy Audit

Name of Trust:_____

1 Main specialty of consultant managing patients with cow's milk allergy (CMA).
Which of the following best describes your specialty?

[ ] Paediatric Allergist
[ ] Paediatrician with an interest in Allergy
[ ] Paediatric Gastroenterologist with an interest in Allergy
[ ] General practitioner with an interest in Allergy
[ ] Adult Allergist or Immunologist consulting in paediatric allergy clinic
[ ] Specialist paediatric allergy dietitian
[ ] Advances nurse practitioner/Specialist paediatric allergy nurse
[ ] Other. Please specify:_____

2 What setting do you see children with milk allergy?

[ ] Dedicated paediatric allergy clinic
[ ] Dedicated paediatric gastroenterology clinic
[ ] General paediatric clinic
[ ] Combined adult and paediatric allergy clinic
[ ] General practice
[ ] Specialist dietetic clinic
[ ] Other. Please specify_____

3 How frequently do you attend the BSACI?

[ ] Annually
[ ] Every two years
[ ] Other. Please specify:_____

4 Is your main CPD Allergy

[ ] Yes
[ ] No

5 How many paediatric allergy clinics does your service provide every week?

[ ] Less than one
[ ] One
[ ] Two
[ ] More than two

6 How many new paediatric patients does your clinic see annually?

[ ] Less than 200
[ ] 200 – 500
[ ] 500 – 1000
[ ] More than 1000

7 In a routine consultation in your clinic (as per question 2), does the child with CMA and his or her family see (Tick ALL applicable answers):

[ ] Clinician
[ ] Dietitian
[ ] Specialist nurse
[ ] Other. Please specify:_____

8 As part of a routine consultation in your clinic, which allergy tests do you use to investigate CMA?

[ ] Skin prick tests to cow's milk using commercial reagents
[ ] Prick prick tests to fresh cow's milk
[ ] Skin prick tests to specific cow's milk proteins e.g. casein, β- lactoglobulin
[ ] Blood tests assaying serum specific IgE to cow's milk
[ ] Blood tests assaying serum specific IgE to specific cow's milk proteins
[ ] Other. Please specify:_____

9 Clinical scenario 1: You are presented with a 7-month-old female infant who you diagnose with CMA. She has been exclusively breast-fed. Her mother has dairy in her diet. She has been difficult to feed, frequently vomits and has loose stools. When weaned she had an allergic reaction to baby rice containing milk powder with an urticarial rash, profuse vomiting, pallor and drowsiness.
Which infant formula would you consider? (You can select more than one):

[ ] Amino-acid formula
[ ] Extensively hydrolysed formula
[ ] Infant soya formula
[ ] Cereal or nut based drink, e.g. Almond milk
[ ] Goat's milk

10 Clinical scenario 2: You are presented with a 7-month-old female infant who you diagnosed with CMA. She has been exclusively breast-fed. Her mother has dairy in her diet. She has been a well thriving contented baby. When weaned she had an allergic reaction to baby rice containing milk powder with an urticarial rash and mild vomiting only.
Which infant formula would you consider? (You can select more than one):

[ ] Amino-acid formula
[ ] Extensively hydrolysed formula
[ ] Infant soya formula
[ ] Cereal or nut based drink e.g. Almond milk
[ ] Goat's milk

11 When evaluating an infant with diagnosed CMA for prescription of a substitute formula, which of the following criteria would prompt you to select an amino-acid formula over an extensively hydrolysed formula? (you can select more than one)

[ ] First choice substitute formula for any CMA
[ ] Child with multiple food allergies
[ ] History of an anaphylactic reaction to milk

[ ] Clinical presentation of Food protein-induced enterocolitis syndrome
[ ] Failure to thrive
[ ] Refusal to drink extensively hydrolysed formula

12 Does your clinic perform oral challenges to diagnose CMA?

[ ] No
[ ] Yes

If yes, are the oral challenges:

[ ] Open challenges
[ ] Double blind placebo controlled challenges

13 Does your service perform oral challenges to assess tolerance in children with CMA?

[ ] No
[ ] Yes

If yes, are the oral challenges:

[ ] Open challenges
[ ] Double blind placebo controlled challenges

And, do you perform challenges to

[ ] Baked milk
[ ] Fresh milk

And, do you advise challenges with baked milk

[ ] at home only
[ ] in hospital only
[ ] at home or in hospital (based on clinical assessment