

REVIEW

The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review

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Clinical and Experimental Allergy

Summary

The aim of this systematic review was to evaluate the efficacy of amino acid-based formulas (AAF) in patients with cow's milk allergy (CMA). Studies were identified using electronic databases and bibliography searches. Subjects eligible for inclusion were patients of any age with CMA or symptoms suggestive of it. Comparisons of interest were AAF vs. extensively hydrolysed formula (eHF), AAF vs. soy-based formula (SF) and AAF vs. cow's milk or cow's milk-based formula. Outcomes of interest were gastrointestinal (GI), dermatological, respiratory and behavioural symptoms as well as growth. A total of 20 studies [three head-to-head randomized controlled trials (RCTs), three cross-over challenge RCTs, seven clinical trials (CTs) and seven case reports (CRs)] were included in the review. In infants with confirmed or suspected CMA, the use of an AAF was shown to be safe and efficacious. Findings from RCT comparisons of AAF with eHF showed that both formulas are equally efficacious at relieving the symptoms of CMA in confirmed or suspected cases. However, infants in specific subgroups (e.g. non-IgE mediated food-induced gastro-enterocolitis-proctitis syndromes with failure to thrive, severe atopic eczema, or with symptoms during exclusive breastfeeding) were more likely overall to benefit from AAF, as intolerance to eHF may occur. In such cases, symptoms persisting despite eHF feeding usually remit on AAF, and catch-up growth may be seen. Meta-analysis of the findings was not possible due to lack of homogenous reporting of outcomes in the original trials. This systematic review shows clinical benefit from use of AAF in both symptoms and growth in infants and children with CMA who fail to tolerate eHF. Further studies are required to determine the relative medical or economic value of initial treatment with AAF in infants at high risk of eHF intolerance.

Keywords amino acid-based formula, cow's milk allergy, extensively hydrolysed formula, soy-based formula, systematic review

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Introduction

Cow's milk allergy (CMA), an immunological intolerance to milk proteins causing adverse clinical reactions, is one of the most common forms of childhood food allergy, affecting 2–3% of infants and young children [1]. In a large cohort study, formal mathematical analysis was used to identify groups of CMA patients with common features [2]. Analysis of symptoms at presentation and elicited by milk challenge revealed that patients appear to cluster naturally into three groups. Immediate onset reactions develop within minutes to 1 h after ingestion of small volumes of cow's milk and are associated with IgE sensitization. Intermediate reactors develop vomiting

and/or diarrhoea several hours after ingestion of moderate amounts of milk. Late reactions, which are usually T cell and not IgE-mediated, occur after at least 12 h, and sometimes not for several days, following ingestion of normal volumes of cow's milk [1–4]. The European Academy of Allergology and Clinical Immunology Task Force recognized these different clinical manifestations of intolerance to cow's milk protein as CMA [5].

In an Australian study, more than half of infants with CMA developed associated hypersensitivity to a few other foods including egg, peanut and nuts, i.e. oligo-food allergy [6]. In such cases, cutaneous manifestations like urticaria and atopic dermatitis (AD) affect up to 50%, compared with 56% for gastrointestinal (GI) and 20–30%

for respiratory symptoms [7]. In more severe cases, CMA may be associated with hypersensitivity to multiple food proteins, including extensively hydrolysed formula (eHF), soy milk, cow's milk, wheat, egg, peanut, nuts, meats, grains and vegetables, i.e. 'multiple food protein intolerance'/multiple food allergy syndrome [6, 8]. In these patients, milk may be one of a number of foods that induce hypersensitivity reactions manifesting as proctocolitis, enterocolitis, enteropathy, reflux esophagitis, AD or colic [8–10]. Significant delays in growth and development, as a result of either delayed diagnosis or inadequate treatment of CMA, have been reported [11]. The negative and emotional impact of childhood food allergy on caregivers and family activities can be severe [12]. However, the studies reported [6–8] may represent more severe cases than would be seen at the community level, as cases of simple monosensitization to cow's milk may not be referred to hospital.

A number of alternatives to cow's milk and cow's milk-based formulas are available, including soy-based formulas (SF), extensively hydrolysed formulas (eHF) and amino acid-based formulas (AAF). All have been shown to be nutritionally adequate for infant feeding [13]. Although guidelines in Europe [14] and United States [15] have been developed that discuss the types of alternative formulas available, the place of each formula in the management of infants with different forms of CMA remains unclear. In addition, there has been no attempt to review systematically the literature comparing the relative merits of each type of formula in the treatment of CMA.

The aim of this systematic review was to compare the efficacy of AAF with eHF, SF and cow's milk-based formula in the treatment of CMA. The results of appropriately designed studies, identified according to validated methodology, were analysed.

Methods

Identification and retrieval of studies

The review was planned, conducted and reported according to published guidelines [16–19]. A flow chart (Fig. 1) illustrates the principle processes undertaken. Potentially relevant studies were identified by searching electronic databases and were accessed on 26 July 2004 [20–24] and 09 August 2004 [25]. The search terms included: amino acid*, elemental, formula*, diet, allerg*, sensitiv*, cow*, intoleran*, milk. Bibliographies were checked and experts in the field contacted for additional studies.

Studies were deemed eligible for inclusion in the review if they conformed to pre-determined inclusion and exclusion criteria (Table 1). No restrictions were placed on studies with regard to year of publication, language (provided an English translation was available) and source. The following types of studies were included and are listed in order of priority:

- (1) Randomized controlled trials (RCTs).
- (2) Non-randomized controlled clinical trials (CCT).
- (3) Before and after clinical trials (CT).
- (4) Observational studies i.e. cohort or case reports (CRs).

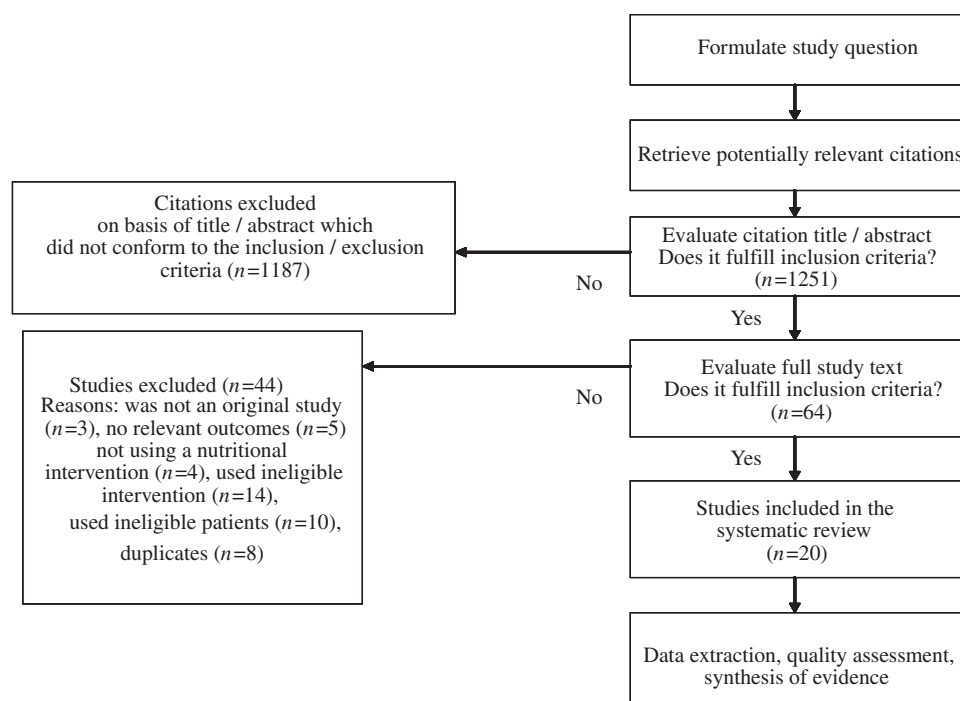


Fig. 1. Summary of study methodology stages and process of the systematic review.

Table 1. Criteria for inclusion of studies into the systematic review

Selection criterion	Inclusion criteria	Exclusion criteria
Population	All human studies All patients, of all ages Nutritional status either well-nourished or malnourished Proven cow's milk allergy (confirmed diagnosis e.g. DBPCFC, SPT) Suspected cow's milk allergy (diagnosis not specified e.g. reported intolerance/ adverse reaction to cow's milk, multiple food allergy including cow's milk) Immediate and delayed type reactions to cow's milk (IgE and non-IgE mediated)	Animal data
Intervention	All studies using amino acid-based formulas (100% amino acids). Route of administration oral or enteral (by tube) Studies comparing amino acid-based formula with soy-based formula and/ or extensively hydrolysed formula and/or cow's milk (formula)	
Outcome measures	Gastrointestinal symptoms (e.g. diarrhoea, bloody stools, vomiting) Dermatological symptoms (e.g. eczema, atopic dermatitis, urticaria) Respiratory symptoms (e.g. cough, rhinitis) Behavioural symptoms (e.g. irritability/distress, refusal to eat) Growth	

DBPCFC, double-blind placebo-controlled food challenge; SPT, skin prick test.

Any studies that did not comply with the inclusion criteria described in Table 1 were excluded from review. Following identification of potentially relevant studies based on titles and abstracts, full papers were obtained and evaluated by one researcher; a second assessor verified inclusion/exclusion decisions. A pre-determined data extraction table was designed to capture study characteristics and outcome data, and allow assimilation of data from differing study designs. Outcomes of interest were recorded based on the definitions provided by the original authors of each study and are shown in Table 1.

Quality assessment of included studies

These were assessed using two scales by K. R. and verified by a second assessor (P. W.) and also by independent assessment (Abacus International, UK). The scales were:

A. '*Quality of Evidence Quality Assessment Scale*' [26]: a six-point scale was adapted and used to score individual studies included in the review. The highest grade (score 1) was given to the RCTs and the lowest grade (score 6) was given where the evidence was inadequate owing to problems of methodology or where it was apparent there were conflicts of evidence.

B. *Jadad Assessment* [27]: this assesses the quality of reporting of RCTs. The highest grade (score 5) is only achieved by well-conducted double-blind RCTs with adequate description of randomization, blinding and dropouts. The lowest possible score on this scale is 0 although studies with scores of <3 may be regarded as poorly described.

Statistics

For planned meta-analysis, the method of Woolf [28] was chosen to calculate a weighted average of the log odds

ratio in each study, and a fixed effects model was intended to combine the treatment estimates, with heterogeneity to be investigated by the Mantel-Haenszel method [29]. An attempt was made to pool quantitative data for allergic and growth outcome measures, but due to a combination of inconsistent reporting of outcomes and limited numbers of comparable studies, meta-analysis of the findings was not possible.

Results

Part 1: identification of studies

A total of 1251 studies were identified by the search strategy (Fig. 1). Following evaluation of the title/abstract, 64 papers were deemed potentially relevant and obtained in full. On the basis of full text, 20 complied with the inclusion criteria [8, 10, 30–47]. The other 44 studies were excluded, due to not being an original experimental study, e.g. a review ($n = 3$; [48–50]); reporting no relevant outcomes ($n = 5$; [51–55]); not utilizing a nutritional intervention ($n = 4$; [56–59]); using an ineligible nutritional intervention ($n = 14$; [6, 12, 59–70]); using ineligible subjects ($n = 10$; [71–80]); or because they were duplicates (abstracts) of papers already selected for inclusion ($n = 8$; [81–88]).

The following eligible studies were identified:

RCTs: $n = 6$; [8, 10, 33–35, 44]

CCTs: none were identified

CTs: $n = 7$; [30–32, 36–38, 42]

CRs: $n = 7$; [39–41, 43, 45–47]

The population included consisted exclusively of children aged 2 days to 12 years. The diagnosis of CMA was

confirmed in 10 reports: four RCTs [10, 33–35] and six non-RCTs [39–41, 43, 46, 47]. Ten other studies included subjects with suspected CMA: two RCTs [8, 30], and eight non-RCTs [31, 32, 36–38, 42, 44, 45]. Subjects were classified as suspected CMA cases if it was not made clear whether or not an internationally accepted method of diagnosis [e.g. double-blind placebo-controlled food challenge (DBPCFC)] had been used. Results are presented in Tables 2–7. Further tables providing additional data on studies included in Tables 2–7 are available from the corresponding author.

Amino acid-based formulas vs. extensively hydrolysed formula (n = 16).

(a) RCTs (n = 6)

(i) *Head-to-head comparisons:* In three RCTs, infants were given an AAF or an eHF for a prolonged period of 6–9 months [33, 34, 44].

(ii) *Cross-over challenge trials:* In three RCTs, subjects received only one open or DBPCFC with eHF and AAF [8, 10, 35]. In two of these RCTs, some patients in the comparator arm also received soy-based or cow's milk-based formula [8, 10].

(b) CTs (n = 5)

There were five before and after CTs eligible for analysis [31, 32, 36–38]. One study [36] included some of the patients who were also described in another CT [37], but reported different outcomes, so both were included.

(c) CRs (n = 5)

Five case reports compared AAF with eHF in infants who failed to tolerate eHF but were subsequently treated with AAF [39, 43, 45–47].

Amino acid-based formulas vs. soy-based formula (n = 6).

(a) RCTs (n = 2)

(i) *Head-to-head comparisons:* No studies were identified.

(ii) *Cross-over challenge trials.* Two cross-over challenge RCTs included SF [8, 35].

(b) CTs (n = 2)

Two CTs included SF before treatment with AAF [32, 36].

(c) CRs (n = 2)

Two CRs described infants who failed to tolerate eHF and also SF, who were subsequently treated with AAF [43, 45].

Amino acid-based formulas vs. cow's milk-based formulas (n = 6).

(a) RCTs (n = 2)

(i) *Head-to-head comparisons:* No studies were identified.

(ii) *Cross-over challenge trials:* Two cross-over challenge RCTs that included cow's milk or cow's milk-based formula were compared with AAF and with eHF [8, 10].

(b) CTs (n = 2)

Two CTs compared cow's milk or cow's milk-based formula with AAF after therapy [30, 42].

(c) CRs (n = 2)

Two CRs described infants who had failed to tolerate cow's milk or cow's milk-based formula, who were subsequently treated with AAF [40, 41].

Assessment of quality of included studies

On the 'Quality of Evidence Assessment Scale' six RCTs [8, 10, 33–35, 44] scored the highest grade of 1. Seven CTs [30–32, 36–38, 42] scored 4 and the seven CRs [39–41, 43, 45–47] scored 5.

Using the Jadad scale [27], three RCTs [8, 10, 44] attained the highest score of 5; the others scored 4 [35], 3 [34] or 2 [33], respectively. The methodology of three of the six RCTs was poorly described or planned with regard to methods of randomization, blinding and recording of number of drop-outs [33–35].

Part 2: clinical findings

Amino acid-based formula vs. extensively hydrolysed formula (Tables 2–5).

(a) RCTs [8, 10, 33–35, 44]

(i) *Head-to-head comparisons:* Table 2 summarizes three head-to-head RCTs comparing AAFs with eHFs [33, 34, 44]. Two RCTs included infants with confirmed CMA and AD at approximate age 6 months [33, 34]. The other included very young infants with suspected CMA and GI symptoms [44]. In all three RCTs, improvements in GI and dermatological symptoms occurred following treatment with both AAF and eHF and no significant differences were found between interventions. In the two RCTs of infants with AD and CMA, both AAF and eHF significantly decreased SCORAD scores after 8 months treatment, with significant reduction in serum IgE [33, 34]. The RCT of infants with GI disorders reported a significant increase in plasma albumin levels only with eHF [44].

The two RCTs of infants with confirmed CMA and AD reported significant growth differences for AAF compared with eHF [33, 34]. One demonstrated increase in both relative weight and length [33] and the other demonstrated only length [34] in those receiving AAF, but not in those receiving eHF. In contrast, the RCT involving suspected CMA infants with GI disorders reported no differences in weight for age and length for age Z scores, but increase of weight for length Z scores in only the eHF group [44]. All RCTs reported similar energy intakes in those treated with AAF and eHF [33, 34, 44].

(ii) *Cross-over challenge trials:* Table 3 displays details and results of three cross-over challenge RCTs [8, 10, 35]. Infants and children with confirmed CMA [10, 35] and

Table 2. Results from randomized controlled trials (RCTs) comparing amino acid-based formula (AAF) vs. hydrolysed formula (HF) in patients with confirmed or suspected cow's milk allergy (CMA)

	Isolaure et al. [33]		McLeish et al. [44]		Niggemann et al. [34]	
	Baseline	9 months	Baseline	24 weeks	Baseline	6 months
Outcome measures						
Vomiting (no./day)	-	-	-	0.1 vs. 0.1	-	-
Stools/day	-	-	-	1.8 vs. 1.4	-	-
Atopic dermatitis/eczema severity (mean SCORAD score)	21 vs. 17	4 vs. 5 at 8 months Significant differences compared with control in both groups ($P = 0.0001$)	-	-	18.5 vs. 14.7 (24.6 mean for whole group)	10.7 mean for whole group Significant improvement in both groups ($P = 0.0001$) 12.2 at 3 months
Blood total IgE (kU/L)	35 vs. 44	9 vs. 9 at 2 months 17 vs. 31 at 8 months Significant differences compared to control in both groups ($P = 0.002$)	-	-	16 vs. 30	-
Plasma albumin (g/L)	-	26 vs. 43 at 2 months	37 vs. 35	38 vs. 41 Significant increase in eHF group only ($P < 0.05$)	-	-
Plasma EAA ($\mu\text{mol/L}$)	-	973 vs. 670 Significant differences compared to control in both groups at 3 months ($P = 0.0008$)	-	-	-	-
Plasma BCAA ($\mu\text{mol/L}$)	-	406 vs. 255 Significant differences compared to control at 3 months ($P = 0.0009$)	-	-	-	-
Plasma highly NAA ($\mu\text{mol/L}$)	-	1351 vs. 1087 Significant differences compared to control at 3 months ($P = 0.009$)	-	-	-	-
Energy intake (kcal/kg)	-	124 vs. 112 at 12 months age ($P = 0.44$)	-	Similar in both groups (% estimated average requirement)	-	Similar in both groups
Weight for age Z score	-	-	-0.89 vs. -1.21	-0.68 vs. -1.16	-	-
Length for age Z score	-	-	-0.37 vs. -0.41	-0.42 vs. -0.74	-	-
Relative weight (%)	0.6	Significant increase in AAF group compared to eHF group ($P = 0.09$)	-	-	-	-
Relative length (SD)	-0.3	Significant increase in AAF group compared with eHF group ($P = 0.006$)	-	-	-	-
Weight for length Z score	-	-	-0.82 vs. -1.22	-0.43 vs. -0.73 Significant increase within eHF group ($P < 0.05$) but not within AAF group	-	-
Weight for length (%)	-	-	-	-	-	Stable, similar, development in both groups
Length SDS score	-	-	-	-	-	Significant increase within AAF group ($P < 0.04$) but not within the eHF group
MUAC (% of standard)	-	-	95.5 vs. 87.0	98.0 vs. 92.0	-	-

*Proportion of infants likely to have cow's milk sensitive enteropathy (CMSE).

eHF, extensively hydrolysed formula; SCORAD, scoring atopic dermatitis; EAA, essential amino acids; BCAA, branched chain amino acids; NAA, nitrogenous amino acids; SD, standard deviation; SDS, standard deviation score; MUAC, mid upper arm circumference; -, data not reported.

Table 3. Results of randomized controlled cross-over challenge trials comparing amino acid-based formula (AAF) vs. cow's milk/cow's milk-based formula (CM/CMF) vs. hydrolysed formula (HF) vs. soy-based formula (SF) in patients with confirmed or suspected cow's milk allergy (CMA)

Outcome measures	Sampson et al. [10]				Hill et al. [8]				Caffarelli et al. [35]			
	AAF	eHF	CMF	AAF	eHF	SF	CMF	AAF	pHF (whey)	eHF (casein)	eHF (whey)	SF
Age 11 months – 12 years <i>n</i> = 28, confirmed CMA												
Time to resolution of symptoms	-	-	-	< 2 weeks	-	-	-	-	-	-	-	-
Patients with improvement of symptoms	-	-	-	18/18	-	-	-	-	-	-	-	-
Patients with vomiting	0/28	1/28	-	0/18	4/10	2/7	1/1	0/16	0/17	0/16	1/16	0/16
Patients with diarrhoea	-	-	-	0/18	5/10	1/7	0/1	0/10	0/17	1/16	0/16	0/20
Patients with GI symptoms	0/28	-	8/22	-	-	-	-	-	-	-	-	-
Patients with eczema	-	-	-	0/18	1/10	4/7	0/1	2/10	4/17	0/16	1/16	0/20
Patients with rash/skin symptoms'	0/28	1/28	17/22	-	-	-	-	0/10	3/17	1/16	1/16	0/20
Patients with 'respiratory symptoms'	0/28	1/28	16/22	-	-	-	-	0/10	2/17	0/16	0/16	0/20
Patients with irritability	-	-	-	0/18	6/10	4/7	1/1	-	-	-	-	-
Patients with hypotension	-	-	-	-	-	-	-	0/10	2/17	0/16	0/16	0/20
Patients with 'growth failure'	-	-	-	0/18 post-AAF treatment	2/10 before AAF treatment	2/7 before AAF treatment	0/1 before AAF treatment	-	-	-	-	-

eHF, extensively hydrolysed formula; pHF, partially hydrolysed formula; GI, gastro-intestinal; -, data not reported.

infants with suspected CMA [8] were challenged orally with AAF, eHF and other formulas in short-term challenge trials. More infants and children developed GI, respiratory and behavioural symptoms when orally challenged with eHF compared with AAF but these differences were not significant. Complete symptom resolution within 2 weeks, before the commencement of one RCT, was seen in all patients treated with AAF [8]. In another RCT, two of 10 infants receiving AAF and one of 16 infants receiving eHF developed eczema [35]. This trial showed that all alternative formulas provoked significantly fewer clinical reactions than cow's milk. In the third study, two of 25 children with CMA tolerant to AAF reacted to eHF on DBPCFC [10].

(b) CTs [31, 32, 36–38]

Table 4 presents details and findings of five CTs (pooled size 138 cases) in patients (age 3 weeks–16 months) with intolerance to eHF subsequently treated with AAF. Three CTs reported time to complete symptom resolution of <2 weeks of commencing AAF following failure to tolerate eHF [31, 37, 38]. One CT in infants with protein-induced enterocolitis showed treatment with AAF induced significant reduction in daily vomiting episodes, crying time and stool output, after eHF had failed [31]. A CT in infants with persistent gastroesophageal reflux symptoms and eczema despite eHF feeding reported that AAF induced significant reduction in non-cutaneous symptoms in 13 of 16 infants [37]. Another study reported 12 young children with severe eczema persisting on eHF but resolving with AAF [32].

Two CTs in infants with persistent GI symptoms, which resolved on AAF, reported significant increase in mean weight and height Z scores [36] or body weight index [37]. Increased growth was seen in infants with food protein-induced enterocolitis who failed to tolerate eHF and were given AAF was reported in another CT, with a mean weight gain of 30 g/day [31].

(c) CRs [39, 43, 45–47]

Table 5 summarizes results from CRs in which infants who had failed to tolerate eHF were successfully treated with AAF. One CR of an infant with confirmed CMA shows resolution of symptoms within 3 days of commencement of AAF after previously failing to tolerate eHFs and SF [43]. Another CR of a 1-month-old infant with confirmed CMA described weight gain from the 3rd–50th percentile over 4 months after changing from partially hydrolysed formula to AAF [46]. A third CR reported a neonate with vomiting episodes, gastritis, angio-oedema with poor growth when ingesting cow's milk, soy milk or eHF but settling completely following AAF feeding [45]. An additional report reported fatal anaphylaxis in one pre-term twin receiving casein hydrolysate, and allergic colitis in her twin, responding to AAF [47]. A final CR described one child with persistent atopic eczema when ingesting eHF, which resolved when commenced on AAF [39].

Table 4. Results of clinical trials (CTs) comparing amino acid-based formula (AAF) vs. hydrolysed formula (HF) in patients with suspected cow's milk allergy (CMA)

	Kuzminskiene and Vaiciulioniene* [32]		Vanderhoof et al. [31]		de Boissieu et al. [37]		Ammar et al.* [38]		de Boissieu and Dupont† [36]	
	Before	4–12 weeks	Before	2 weeks	Before	Mean age 6.2 months (ranges 1–16) n = 16, suspected CMA	Before	Median age 3 months (ranges 15 days–13 months) n = 30, suspected CMA	Mean age 5.3 months ± 3.8 months n = 52, suspected CMA	
Outcome measures										
Time to resolution/improvement of symptoms										
Patients with resolution of symptoms	0/12	-	0/28	25/28	0/16	13/16†	-	-	-	-
Patients with vomiting	-	-	10/28	-	9/16	1/16	-	-	-	-
Overall vomiting (no./day)	-	-	-	0.21 (P = 0.028)	-	-	-	-	-	-
Patients with diarrhoea	-	-	12/28	-	9/16	3/16	17/30	-	-	-
Patients with bloody stools	-	-	15/28	3/28	-	-	-	-	-	-
Stools/day	-	-	-	0.5 (P = 0.041)	-	-	-	-	-	-
Patients with digestive symptoms	-	-	-	0.73 after 2 days	-	-	25/30	-	47/52	-
Patients with regurgitation	-	-	-	-	-	-	18/30	-	-	-
Lactitol/mannitol ratio	-	-	-	-	-	-	6.58 ± 2.92%	3.47 ± 1.58% (P = 0.0004)	-	-
Patients with eczema/rash/cutaneous symptoms	-	0/10 in those that took AAF	-	-	-	-	6/30	-	23/52	-
Atopic dermatitis/eczema severity (SCORAD score)	-	-	-	-	35 (mean from 13/16 infants)	16 (P < 0.05) (mean from 13/16 infants)	-	-	-	-
Patients with angio-oedema	-	-	-	-	-	-	-	-	6/52	-
Patients with respiratory symptoms	-	-	-	-	2/16	0/16	-	-	-	-
Patients with irritability	-	-	18/28	-	-	-	-	-	-	-
Patients with irritability/crying	-	-	-	-	14/16	3/16	-	-	-	-

Patients with 'colicky pain'	-	-	-	-	10/30	-	-	-	-
Mean time spent crying (min/day)	-	-	-	60 ($P = 0.003$) 120 after 2 days	-	-	-	-	-
Patients with malaise	-	-	-	-	-	-	-	8/52	-
Patients with growth failure	-	-	-	-	10/30	-	-	16/52	-
Patients with poor weight gain	-	-	4/28	-	-	-	-	-	-
Patients with weight gain	-	-	-	-	-	-	-	-	-
Mean weight gain (g/day)	-	-	-	30	13/16	-	-	27.5 ± 10.8	-
Mean weight Z scores	-	-	-	-	-	-	-	-1.04	-0.02 ($P < 0.001$)
Mean height Z scores	-	-	-	-	-	-	-	-0.86	0.16 ($P < 0.001$)
Body weight index (%)	-	-	-	-	90.2	97.9 (13/16) ($P < 0.001$)	-	-	-

*Abstract.

†Describes some of the patient population from de Boissieu et al. [46] but reports different outcomes.

‡Resolution of non-cutaneous symptoms.

eHF, extensively hydrolysed formula; SCORAD, scoring atopic dermatitis; -, data not reported.

Amino acid-based formula vs. soy-based formula (Tables 3–5).

(a) RCTs [8, 35]

Two short-term cross-over challenge trials included SF [8, 35], and have been described in the previous section reporting AAF vs. eHF. One study [8] reported adverse effects of SF challenge in patients asymptomatic on AAF and the other [35] reported no adverse effects of AAF on children who were shown to be tolerant to soy.

(b) CTs [32, 36]

Two CTs included SF [32, 36], and have been described in the previous section (1b). In one, 12 infants with severe atopic eczema were intolerant to SF, which resolved on AAF [32]. The other CT of 52 infants with predominantly GI symptoms were intolerant to SF and eHF but symptoms settled on AAF [36].

(c) CRs [43, 45]

Two CRs [43, 45] have been described in the previous section (1c). An infant developed soy enterocolitis following rotavirus gastroenteritis, persisting with eHF but resolving with AAF [43]. A second infant had vomiting spells, angio-oedema and gastritis, failing to grow when ingesting SF or eHF, but recovering fully on AAF [45].

Amino acid-based formula vs. cow's milk or milk-based formula (Tables 3, 6 and 7).

(a) RCTs [8, 10]

Two cross-over challenge studies reported the effect of AAF on children with CMA. One documented tolerance to AAF in 18 infants with a history of probable CMA [8] and the other tolerance to AAF in 20 children with confirmed CMA [10].

(b) CTs [30, 42]

Table 6 details results of two CTs [30, 42]. In one CT, relative weight for height scores improved significantly [42]. The other CT of infants with suspected CMA and multiple food protein intolerance reported restoration of normal growth pattern in patients with previous growth delay [30].

(c) CRs [40, 41]

Two CRs are documented in Table 7 [40, 41]. In one, an infant with hyper-IgE syndrome, confirmed CMA, eczema and poor growth improved on AAF [40]. In the other, a child suffered brain damage following an adverse reaction to cow's milk at 6 months of age and tolerated AAF subsequently [41].

Discussion

This systematic review was conducted according to published guidelines and is the first to collate all intervention studies comparing safety and efficacy of AAF, eHF and SF in CMA. Our findings suggest distinct differences between children with uncomplicated CMA and those with more complex GI manifestations or multiple food allergy. We point out however that all of the studies examined

Table 5. Studies comparing amino acid-based formula (AAF) vs. hydrolysed formula (HF): case reports (CRs)

Trial	Quality of evidence score [26]	Patient group	Method of diagnosis	Intervention	Length of follow-up	Results
Kelso and Sampson [43], CR	5	Confirmed CMA, <i>n</i> = 1. Age 7 months. Previously on eHF and SF	SPT	Before therapy, <i>n</i> = 1 After AAF, <i>n</i> = 1	1 month	Guaiaac positive stools, 1/1
Bruel <i>et al.</i> [47], CR	5	Confirmed CMA, <i>n</i> = 2. Age 2 days (twins born 31.5 weeks gestation). Commenced initially on eHF (one twin died on day 7 from severe acidosis associated with leucopenia). Surviving twin diagnosed with allergic colitis	SPT (surviving twin)	Before therapy, <i>n</i> = 1 (surviving twin)	12 months	Time to resolution of symptoms, 3 days; guaiac positive stools, 0/1 Bloody stools, 1/1
Rigourd <i>et al.</i> * [45], CR	5	Suspected CMA, <i>n</i> = 1. Age 48 h. Intolerance to pHF and incomplete response to eHF, SF and BM	Not stated	After AAF, <i>n</i> = 1 Before therapy, <i>n</i> = 1 After AAF, <i>n</i> = 1	Not stated	Bloody stools, 0/1; normal growth 1/1 Vomiting, 1/1; angio-oedema, 1/1; FTT, 1/1 Vomiting, 0/1; angio-oedema, 0/1; resolution of symptoms, 1/1; weight gain improved (no data given) AD, 1/1
Dutau <i>et al.</i> * [39], CR	5	Confirmed CMA, <i>n</i> = 1. Age not stated. Previously on eHF	Clinical history, SPT, oral food challenge, specific IgE	Before therapy, <i>n</i> = 1	Not stated	
Siu <i>et al.</i> [46], CR	5	Confirmed CMA, <i>n</i> = 1. Age 1 month. Previously on pHF (whey), then 24 h bowel rest before AAF	CM-specific IgE positive	After AAF, <i>n</i> = 1 Before therapy, <i>n</i> = 1 After AAF, <i>n</i> = 1	4 months	AD, 0/1; resolution of symptoms, 1/1 Diarrhoea, 1/1 Diarrhoea, 0/1; catch-up growth achieved—body weight increased from 3rd to 50th percentile for age at 5 months

* Abstract.

CMA, cow's milk allergy; eHF, extensively hydrolysed formula; SF, soy-based formula; SPT, skin prick test; pHF, partially hydrolysed formula; BM, breast milk; FTT, failure to thrive; AD, atopic dermatitis; CMA, cow's milk.

Table 6. Results of clinical trials (CTs) comparing amino acid-based formula (AAF) vs. cow's milk/cow's milk-based formula (CM/CMF) in patients with suspected cow's milk allergy (CMA)

Outcome measures	Kanny et al. [30]		Isolaure and Sampson [42]	
	Before	After (4–9 months)	Before	After (6 months)
Patients with GI troubles	6/26	–	–	–
Patients with AD	25/26	–	–	–
SCORAD score	54	15* 26 after 2–3 months	–	–
Patients with asthma	1/26	–	–	–
Patients with anaphylaxis	2/26	–	–	–
Patients with FTT	5/26	1/26 [†]	–	–
Weight for height Z score (mean)	–	–	– 3.1	–1.2 (<i>P</i> = 0.03)

*Result reported in 23/26 infants.

[†]Patient found to have gluten intolerance.

GI, gastro-intestinal; AD, atopic dermatitis; SCORAD, scoring atopic dermatitis; FTT, failure to thrive; –, data not reported.

represent children referred for secondary or tertiary assessment, and note a lack of evidence based on primary care, where it is probable that simple monosensitization is more common.

Evidence from head-to-head RCTs shows AAF and eHF are equally effective in resolving GI and skin symptoms in uncomplicated CMA. Owing to the high efficacy of both formulas, published studies have not been adequately powered to detect significant overall differences, and studies of appropriate magnitude are unlikely to occur. Findings from cross-over challenge RCTs are consistent, in that no significant differences between AAF and eHF were observed, although fewer infants and children reacted adversely to AAF than to eHF when orally challenged with these formulas. Some differences were reported in terms of biological parameters. In one RCT, a significant increase in plasma albumin was observed only in the eHF group [44]. The relevance of this is unclear, as this trial contained different forms of CMA, including complex surgical patients.

The formulas are nutritionally adequate and all meet European Union commission guidelines [89], although there are clear differences in amino acid profiles due to their different nitrogen sources. However, evidence from RCTs suggests possible differences in linear growth with AAF in comparison with eHF in infants with confirmed CMA. Two RCTs reported increase in relative length [33] or length SDS score [34], not observed in the eHF treatment groups. In another RCT [8], increase in weight was observed following AAF treatment in cases with growth failure and an incomplete clinical response to eHF. It is possible this difference may be related to subtle effects of residual antigenicity of eHF or differences in energy/protein intake. By contrast, one RCT showed that growth

(weight for length) was significantly greater in the eHF than in the AAF group [44]. Despite the significant differences in linear growth reported in these studies, the evidence favouring AAF over eHF is not convincing given the uncertainty of length measurements in infants in a routine clinical setting. In all three head-to-head RCTs [33, 34, 44] insufficient baseline data were given for interpretation of growth parameters, and the description of how growth was measured and by whom was inadequate in two of these studies [33, 34]. To resolve these uncertainties, future studies should use validated growth parameters such as Z scores. The most clinically relevant parameter for future studies may be body composition, which may allow some insight as to whether easily measured changes in body weight are a truly relevant measure of growth in such cases.

The CTs identified an important group of infants with suspected CMA and intolerance to eHF who responded favourably to AAF. Studies suggested 2–10% of infants with uncomplicated CMA may be intolerant to eHF [10, 63, 65], rising to 40% in pre-term and term infants with more complex forms of the disease [12, 60, 90]. Such infants more frequently developed symptoms while being exclusively breastfed and manifested delayed non-IgE-mediated GI reactions to cow's milk, including gastroesophageal reflux disease, enterocolitis or proctitis and gastroenteritis syndromes [8, 9, 31, 37, 69, 76] as well as severe atopic eczema [8]. Many of these infants with intolerance to eHF suffer from multiple food allergy. Their slowly evolving reactions to eHF are likely to be T cell mediated and triggered by residual T cell epitopes in hydrolysed formula [12]. Intolerance to these relatively minor residual antigens in eHF or breast milk is consistent with underlying impairment of low dose tolerance, a

Table 7. Studies comparing amino acid-based formula (AAF) vs. cow's milk/cow's milk-based formula (CM/CMF): case reports (CRs)

Trial	Quality of evidence score [26]	Patient group	Method of diagnosis	Intervention	Length of follow-up	Results
Heyman <i>et al.</i> [41], CR	5	Confirmed CMA, multiple food allergies, <i>n</i> = 1. Age 3.5 months	Positive SPT to CM and SF at 27 months of age	AAF, <i>n</i> = 1 Started 2/3 strength enteral, progressing to oral	Not stated	Diarrhoea, 1/1 Diarrhoea, 0/1; resolution of symptoms 1/1; catch-up growth achieved (no data given)
Hernandez-Trujillo <i>et al.</i> [40], CR	5	Confirmed CMA, hyper IgE syndrome, MFA, <i>n</i> = 1. Age 3 weeks	Positive SPT to CM, RAST, atopy patch test and DBPCFC	Before therapy, <i>n</i> = 1 After AAF, <i>n</i> = 1	2 months	Rash/skin symptoms, 1/1; mean BEC (mm ³), 6310; mean blood total IgE (U/mL), 8454 Rash/skin symptoms-improved (no data given); growth velocity improved (no data given); mean BEC (mm ³), 2100; mean blood total IgE (U/mL), 2747

CMA, cow's milk allergy; SPT, skin prick test; SF, soy-based formula; MFA, multiple food allergy; RAST, radioallergosorbent test; DBPCFC, double-blind placebo-controlled food challenge; BEC, blood eosinophil count.

regulatory mechanism dependent on the cytokine TGF- β [91]. In support of this, impaired generation of duodenal TGF- β producing lymphocytes has been demonstrated in infants with allergy to cow's milk and other antigens [92].

Not all studies reported complete resolution of symptoms on transfer from eHF to AAF although the numbers that do not achieve complete resolution is relatively small. In one CT, three of 28 did not achieve full resolution of symptoms although all were able to demonstrate a gain in weight [31]. One investigator [35] suggested atopic eczema induced by AAF was attributable to contamination by equipment previously used in the manufacture of hydrolysed formula. Another investigator [37] documented three cases of failed response to an AAF prepared in a dedicated factory and thus unlikely to have been contaminated by milk proteins. It is possible the diarrhoea may have been caused by enteropathy-associated carbohydrate malabsorption [93], which may account for poor response to AAF in a minority of infants with eHF-induced enterocolitis [31, 59]. Whether such carbohydrate malabsorption may indirectly affect immune responses through changes in the gut flora is unknown. Some of the AAF used in these studies [31, 44, 59] are lactose and sucrose free with carbohydrate provided as maltodextrin. Lipid constituents have included safflower oil, coconut oil and soy oil. Soy lipid emulsions have the potential, albeit very rarely, to cause hypersensitivity reactions to AAF in highly allergic infants [94]. There is recent evidence in mice that lipid antigens may directly induce allergic T-helper type 2 T cell responses, following presentation by the non-classical MHC molecule CD1 [95]. However, there is so far no confirmation of such a phenomenon in humans.

There was a lack of studies directly comparing AAF vs. cow's milk or SF. For the former comparison, this was due to the ethical implications of assigning infants with known or suspected CMA to a cow's milk formula comparator arm. For the latter comparison, this may relate to consensus statements advising against use of SF in the treatment of CMA [14, 15, 96, 97]. However, before and after type studies showed that infants who failed to tolerate cow's milk or SF had improvement in symptoms and growth when transferred to AAF [31, 36, 37].

The studies reported had several methodological limitations. In general, there was inconsistent data reporting, with some studies only reporting symptom frequencies at the start or at the end of the trial, making it difficult to compare effects. Few studies reported time to symptom resolution, despite its relevance as an outcome measure in CMA. Benefits of AAF were reported within 2–3 days in one study [37] and within 2 weeks in others [8, 31, 38]. More studies including this outcome measure are needed. Amongst studies in infants, we identified an overall lack of high quality (level 1) studies, and planned meta-analyses were impossible to undertake due to a lack of

homogeneous study design or consistency in outcome reporting. Future studies need to assess the impact of long-term AAF use, and it may be that the introduction of other proteins during weaning is necessary. Recent animal studies suggest that prolonged absence of whole dietary protein after weaning may impair immunological maturation and the development of tolerance [98, 99]. This is yet to be demonstrated in humans, and such considerations would appear relevant only to the small number of infants receiving exclusive long-term AAF intake who are unable to tolerate any other solids.

In conclusion, this analysis has demonstrated that for infants with CMA who completely tolerate eHF, there was no additional benefit from the use of AAF. However, a clear need for AAF in infants with CMA and intolerance to eHF was demonstrated. These infants are more likely to have developed symptoms during exclusive breastfeeding [9, 55] and to have severe atopic eczema [8], reflux esophagitis [76] or a food-induced enterocolitis-proctitis syndrome with failure to thrive [31, 37]. We emphasize that severity of symptoms should be an important determinant. Simple rectal bleeding has been shown to have a benign outcome in infants, and many cases proved not to relate to food allergy [100]. This suggests that more severe symptomatology is necessary to warrant use of AAF, and that cow's milk challenge should be undertaken in infants in whom rectal bleeding is the primary reason for considering AAF use.

The cost of different treatment options for CMA needs to be balanced against the cost of hospitalization, investigation and increased morbidity in infants in whom effective treatment is delayed. For infants intolerant to eHF, the available evidence favours early use of AAF. The evidence concerning primary use of AAF at presentation, in infants with high risk for eHF intolerance (e.g. symptomatic while exclusively breastfed), is so far less clear. One potential future stratagem for the sick high-risk infant might be an initial period of several weeks' stabilization with AAF, before moving to eHF if the challenge was successful. Further studies of the medical and economic value of such an approach are required to demonstrate any potential reductions in morbidity and the cost of hospitalization and/or investigation.

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