

Original article

Dietary treatment of childhood atopic eczema/dermatitis syndrome (AEDS)

Objective: This review summarizes the research and clinical evidence in favour of dietary intervention aimed at eliminating allergenic foods in the management of atopic eczema/dermatitis syndrome (AEDS).

Data sources: The data source was PubMed, using a search algorithm selecting for clinical studies of AEDS, diet therapy and food allergy in all children to October 2003. Also included is a commentary based on the authors' clinical experience in the allergy unit of a university hospital in Italy.

Results: Fourteen prospective studies matched the entry criteria. Diverse trial designs, diagnostic criteria, types of dietary intervention and length of observation periods precluded meta-analytic methods. Allergenic food exclusion claimed efficacy in 13 of the 14 studies and was most useful in infants, in patients with elevated immunoglobulin E levels and/or multiple food sensitization and in patients with a diagnosis of food allergy.

Conclusion: Dietary intervention in the form of an elimination diet is efficacious in children with AEDS when a specific diagnosis of food allergy has been made. Diagnostic evaluation of food allergy should be performed in all children with eczema, particularly in younger children and those with severe forms of the disease.

**A. Fiocchi, G. R. Bouygue, A. Martelli,
L. Terracciano, T. Sarratud**

Department of Child and Maternal Medicine,
The Fatebenefratelli/Melloni University Hospital,
Milan, Italy

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Alessandro Fiocchi MD
Melloni Paediatrics
52 Via Melloni
20129 Milan
Italy

New cases of atopic eczema/dermatitis syndrome (AEDS) (1) are increasing dramatically (2, 3). A chronic condition which peaks in infancy with onset during the first 3 months of life, AEDS often anticipates the progression of atopic disease (4–6). Food allergy also peaks during the first year and food allergen sensitization at 12 months predicts allergic sensitization to common inhalant allergens at 3 years of age (7,8). The association of food-specific immunoglobulin E (IgE) antibody and 'atopic dermatitis' has enhanced the expectation among patients, their parents and their caregivers that restricted diets may alter the course or severity of disease. Common food allergens, such as egg, cow's milk or tomatoes, are frequently implicated (9,10). Food triggers of allergic skin symptoms, however, cannot account for the whole clinical spectrum and course of AEDS. Diagnosis must rest on a clinical, multifactor assessment basis. Diagnostic systematics varies (11) but pruritus, chronic/relapsing disease and personal/family history of atopy are considered major criteria (12,13). At least 47 different types of intervention against AEDS were reviewed from the literature in 2000 (14). However, there was no consensus

[and, earlier, even opposition (15)] regarding the efficacy of allergen dietary restriction, although food allergy as an etiological factor in AEDS was not at issue (16–19).

Aims and methods

Data retrieval and inclusion criteria

Literature was retrieved from the NCBI Pub Medical database using the following search algorithm to select for evidence linking pathogenic role of allergic sensitization to foods and assess the efficacy of dietary restriction in the treatment of infants and children with AEDS.

- # 1 atopic dermatitis <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>
- # 2 OR atopic eczema/
- # 3 or AEDS/
- # 4 OR/neurodermatitis/
- # 5 OR neurodermitis constitutionalis atopica
- # 6 AND food allergy/
- # 7 AND cow's milk allergy/
- # 8 AND egg allergy/
- # 9 AND wheat allergy/
- # 10 AND multiple food allergy/
- # 11 diet therapy/
- # 12 prevention and control/

Abbreviations: AD, atopic dermatitis; AEDS, atopic eczema/dermatitis syndrome; CMA, cow's milk allergy; DBPCFC, double-blind placebo-controlled food challenge; eHF, extensively hydrolysed formula; SPT, skin prick test.

13 child/
 # 14 OR infant/
 # 15 1975 January – 2003 October
 # 17 clinical studies.

Date of last search: 28 November 2003

Studies of all children up to 18 years diagnosed by a clinician using the criteria of Hanifin and Rajka (12) or their modification (20) were considered, regardless of the terminology used (atopic eczema, atopic dermatitis, or AEDS). The primary outcome measure to assess the efficacy of elimination of food(s) was improvement in clinical symptoms and secondary outcome measures were time off school, improvement in quality of life and need for topical steroids, antihistamines and emollients. Owing to the type of intervention reviewed (diet and nonpharmacological therapy), there are few controlled trials of dietary restriction efficacy in AEDS in the literature and thus blindedness of studies was not among the inclusion criteria. No language parameter was set.

Results

Fifteen studies fulfilled the inclusion criteria (21–35) and were tabulated. These papers differed so markedly in study populations (Table 1), types of intervention, trial design, duration (Table 2) and outcome assessment

methods (Table 3) as to withstand systematization or meta-analysis. Definition of atopic dermatitis was defined according to clinical criteria in all studies, sometimes with a specific reference (e.g. Hanifin's criteria). In three studies 'severe' eczema was considered an inclusion criterion whereas three other considered 'refractory' eczema as sole entry criterion. A selection bias appeared in all studies as children with eczema were referred for assessment to either dermatological or paediatric allergy clinics. Their caseloads are not representative of the whole population of infants and children with AEDS. The disparity between entry criteria was matched by differences in sample size. In total, 823 children were assessed; 142 in caseloads recruited on the 'refractory' disease criterion (25,28,30), 137 in studies concerned with 'severe' disease (22,29,33) and 544 in studies which did not specify the severity of symptoms for enrolment (21,23,24,26,27,29,31,32) (Table 1). There was no uniformity in the exclusion/trial of foods as part of the dietary intervention. Two studies eliminated cow's milk and egg (21,23), two prohibited only eggs (27,34), four studies substituted formulae [either elemental (25,31,36) or cow's milk hydrolysates (31,32,36) to their patients while two others excluded cow's milk and eggs from the diet of the nursing mother (24,27)]. The elimination of cow's milk and/or eggs (22), of 'suspect' foods (26), of three (28), or six (29) foods has also been recommended

Table 1. Overview of dietetic interventions in the literature on cow's milk allergy (CMA): caseload characteristics

Study	Outcome measures	Sample size and demographics
(21)	clinical diagnosis of 'atopic eczema'	36 children (20 completed the trial) Age 2–8 years attending a dermatology clinic
(22)	clinical diagnosis of 'severe atopic dermatitis'	59 children. No age reported No dropout reported.
(23)	atopic eczema	53 children and young adults (40 completed the trial) Age 1–23 years
(24)	established atopic eczema	19 breast-fed infants
(25)	severe, refractory, widespread atopic eczema	37 children
(26)	atopic dermatitis	91 children 0–5 years (referrals to dermatological clinic) 16 healthy controls 61 SAFT-positive (including 38 lost at follow-up)
(27)	atopic dermatitis	138 children 0–3 years (33 aged 3–6 months; 25 aged 7–11 months; 46 aged 11–24 months; 34 aged 24–36 months)
(28)	severe atopic dermatitis unresponsive to topical treatment	12 children aged 0.8–4.1 years (mean 2.64; SD 0.95)
(29)	severe atopic dermatitis (>30%*) with poor response to conventional therapy or with clear history of food intolerance	62 children (median 2.9 years). 37 with exceptionally severe AD
(30)	refractory atopic dermatitis (>12%*)	85 nonbreast-fed children (median age 2.3 years; range 0.3–13.3 years)
(31)	atopic dermatitis	45 nonbreast-fed children allergic to cow's milk and requiring a substitute formula for at least 6 months (mean age 14 months; range not reported)
(32)	atopic dermatitis (Hanifin's criteria)	27 children aged 2.5–15.7 months (median age not reported)
(33)	suspected multiple-food induced severe atopic dermatitis	16 children aged 5–24 months (median age not reported) outpatients attending dermatology clinic
(34)	atopic dermatitis specific IgE to egg	62 'young children' (age reported only as mean ± SD; 11.3 months in the diet group and 17.2 months in the control group)
(35)	atopic dermatitis CMA at DBPCFC	73 infants Age 1.6–9 months (median 5.7 months)

*Percentages indicate body area.

Table 2. Dietary interventions in cow's milk allergy: design of intervention and study

Study	Dietary intervention [concomitant treatment]	Trial design and duration
(21)	egg and cow's milk elimination diet (soy as substitute) [antihistamine]	double-blind, crossover, placebo [soy]-controlled. Two 4-week periods separated by a 4-week period of free diet.
(22)	exclusion of milk and/or egg [not reported]	open design; observations of various duration.
(23)	egg and cow's milk elimination diet (soy as substitute). [antihistamine + topical steroids]	double-blind controlled crossover trial Two 6-week periods separated by a 6-week period of free diet.
(24)	egg and cow's milk elimination from the mother's diet (soy as substitute).	2 groups: (n = 19) double-blind, crossover trial with exclusion of egg and cows' milk (n = 18) open exclusion of 11 foods followed by double-blind challenge to mothers whose infants seemed to respond.
(25)	antigen avoidance (hospitalization, exclusive elemental formula feeding for 30 days (median) [reduction of pet and dust mite antigens at home]	open for 12 months. After eczema clearance, food challenges at 7-day intervals
(26)	elimination of foods causing food immediate-contact hypersensitivity [FICH] (cow's milk, egg, peanut or soy).	open, variable observation period
(27)	egg elimination diet in infants and breast-feeding mothers [use of concomitant medication not reported]	single-blind, controlled trial
(28)	2–4-week egg, wheat and cow's milk elimination diet [use of concomitant medication not reported]	open for 2–4 weeks. Results confirmed with open reintroduction of foods in 8/12 children.
(29)	six-food elimination diet. In subgroup with exceptionally severe disease: hospitalization and exclusive feeding with an elemental formula (Vivonex) for a median duration of 30 days [antihistamine + topical steroids]	open for 6 weeks
(30)	elemental diet (eliminating all but five to eight foods) + n = 27: whey hydrolysate; n = 32 casein hydrolysate formula vs. n = 26 unrestricted diet. [antihistamine + topical steroids]	parallel, single-blinded (6 weeks)
(31)	n = 22 infants median age 6 months: extensively hydrolysed whey formula median age 17 months: amino acid-derived formula.	parallel, randomized, prospective study (9 months)
(32)	cow's milk elimination diet without (group a) and with (group b) <i>Lactobacillus</i> GG substitute: extensively hydrolysed whey formula.	parallel, randomized, prospective (group a) open (group b) (1 month)
(33)	elemental diet (home-made meat-based formula)	open for (4 weeks) followed by DBPCFC with cow's milk, egg and wheat
(34)	general advice + egg exclusion diet vs general advice vs. general advice only [emollients + topical steroids]	randomized controlled trial open to parents but blinded to assessor. (4-weeks)
(35)	Extensively hydrolysed whey formula (Alfaré of Pepti-Tutteli, n. 42) Amino acid-derived formula. (Neocate, n. 31)	Open, randomized, controlled multicenter trial (6 months)

as well as an elemental diet based on a small number of foods (30,33) (Table 2). The main limitation of published trials in this field is the lack of blindedness. One study (24) compared the effect of an exclusion diet with a placebo under double-blinded conditions but only in a subset of patients. Another study (32) carried out a blinded comparison of probiotic supplementation, but the allergy arm of the study was open. In mitigation, it must be said that finding suitable placebo is difficult. An amino acid elemental formula could substitute for cow's milk, but the two studies assessing its use against a whey hydrolysate are open studies (31,35) (Table 2). Well-controlled, prospective assessment of cow's milk restriction is ruled out by ethical concerns. Other confounding factors present in all these studies are not always acknowledged. The most conspicuous is a method for evaluating eczema for which a consensus is yet to be reached, although specific scoring systems have been devised (36,37). Thus studies rely on home-made scores, but some are difficult to use (38) and evidence or consensus on which is the best are still lacking (39,40). Another confounder is the method used for

diagnosing food allergy in these children. In some studies, children are sensitized to one or two foods but do not undergo formal demonstration of food allergy by oral provocation tests (22,25,34). In other studies children are sensitized by multiple foods (33) or are described as suffering from atopic dermatitis but without specifically referring to the foods they are sensitized by or allergic to. Only two studies enjoy the ideal situation when an allergic reaction to the study food is confirmed at double-blind, placebo-controlled food challenge (DBPCFC) (31,35). A third factor is the problem of the evaluation of compliance with dietary advice. Dietary restrictions are increasingly hard to enforce among older children and in children undergoing stringent dietetic prescriptions the phenomenon ought to be taken into account. Of further limitation are the high drop-out rates [reported as 44 (21), 25 (23) and 41% (30)]. All told, 112 out of 823 children (or 13.6%) were lost to follow-up in the studies considered. A further confounder of study interpretation is the concomitant administration of nondietetic therapeutic intervention, e.g. pharmacological treatment (Table 1)

Table 3. Dietary interventions in cow's milk allergy in children with AEDS: selection criteria and evaluation of food-allergy

Study	Outcome measures	Food allergy diagnosis
(21)	unpublished composite score including the number of areas affected, itching, sleeplessness and use of antihistamines	not reported
(22)	clinical improvement	SPT and clinical history
(23)	areas affected, day- and night-time itch and use of topical steroid	not reported
(24)	unpublished 60-point numerical score	not reported
(25)	unpublished combined disease severity score of surface area plus erythema score topical corticosteroids as per British National Formulary	total and specific IgE
(26)	unpublished clinical score [described in the study]	skin application food test [SAFT]
(27)	clinical	specific IgE (RAST) – no oral provocation test
(28)	unpublished dermatological score, based on distribution and severity of lesions	SPT, RAST confirmed sensitization in 8/12 patients. single-blinded, challenge with egg, cow's milk and wheat after the exclusion diet
(29)	clinical	history of food intolerance
(30)	unpublished skin severity score (extent and severity) plus parental record of itch, sleep loss and global improvement	not reported
(31)	SCORAD index	cow's milk allergy confirmed at DBPCFC
(32)	SCORAD index. Other outcome measures were the concentrations of fecal α_1 -antitrypsin, tumour necrosis factor- α , eosinophil cationic protein before and after dietary intervention.	cow's milk allergy: clinical history confirmed at SPT in 30%, RAST in 37% of infants.
(33)	previously published (62) severity score based on skin lesion interpretation	no challenge confirmation
(34)	previously published (63) composite severity score based on readings of 16 body sites; eczema in extent percentage	multiple food allergy (more than three positive SPT responses to foods) RAST positive to egg (unspecified cut-off point). No SPT. Suggestive history in 7 cases.
(35)	SCORAD index	cow's milk allergy confirmed at DBPCFC

and environmental measures (25,29). The limited duration of many of the studies is also a drawback: most studies investigated only short- to medium-term effects. Three studies evaluated patients 6 (35), 9 (31) and 12 (25) months into diet therapy, each with favourable conclusions. In a disease with marked seasonal variations, it can be impossible to draw conclusions from studies of 2, 4 (21,28,32–34) or 6 weeks (29,30). Finally, many of these studies have a lack of statistical power because of poor study design and only in one study of cow's milk allergy in children (31) was the effect of a substitute assessed against placebo use. Case-controlled cross-over studies can be fitted to logistic regression models but these studies may not have sufficient statistical power to evaluate the multiple outcomes of an exclusion diet on AEDS (14). A few studies focused on the risks of exclusion diets in AEDS. We know that children with eczema show a reduced pattern of growth during the first year of life (41) and this can reflect a nutritional disorder because of food allergy. These disorders may be aggravated by inappropriate diet, sometimes with dramatic effects (42). Another case in which eczema can develop in the absence of food allergy even in little children is phenylketonuria (PKU), when the appropriate metabolic diet can prevent both atopic eczema and the allergic sensitization to foods (43). A study showing that feeding an amino acid formula resulted in improved growth compared with feeding an eHF suggests that the more anallergic are the diet substitutes, the more adequate is their nutritional value (35). Thus, a full nutritional history has to be taken when exclusion diets are planned for children with AEDS.

Interpretation of the results

With such limitations, the task of sifting meaningful clinical data from the literature appears daunting and it is not surprising that the claims of proponents of diet therapy in atopic dermatitis have been considered optimistic. Primary outcomes (improvement in signs and symptoms as rated by the clinician) are consistently reported in the literature (Table 4). Secondary outcomes are sometimes omitted and thus defy analysis. One study (30), though limited by a dropout rate of 46%, does not mention reduction in severity of eczema or extent of lesions in children treated with an elemental diet and a casein hydrolysate. A nonstatistically significant (but still clinically important) reduction of symptoms was however, observed in children treated with an elemental formula and a whey hydrolysate. In studies claiming efficacy of dietary treatment, this is reported within a 25–100% range, which suggests that allergen restriction is effective in at least some subsets of children with AEDS. Peak efficacy was reported in children under 2 years of age (22,24,25), while older children had a lower rate of response (21,23,30). This supports the observation that, among infants, food allergy is a more relevant trigger of AEDS. Furthermore, the response rate is higher in children with the more severe presentation of atopic dermatitis (44). In studies of 'severe' or 'refractory' forms of disease (25,28,29,33), diet therapy was found to be effective in 52–80% of cases. Surprisingly, several authors have considered the effects of dietary intervention in whole populations of children with AEDS irrespective of

Table 4. Dietary interventions in cow's milk allergy: results and comments

Study	Results	Comments
(21)	13 improved; 1 worsened; 6 no change SPT unrelated to clinical response	evaluation method similar to SCORAD. The possibility of soy [placebo] allergy was not excluded. High dropout rate (16/36)
(22)	clinical improvement in 80% after dietary exclusion. younger children did best. Severity of the eczema did not matter	definition of food allergy and evaluation of eczema unclear. Variable duration of the observation period
(23)	clinical improvement in 25% of cases after dietary exclusion	no definition of food allergy. high dropout rate. Adults included.
(24)	clinical improvement in 23%.	poor blinding method. Small sample.
(25)	improvement in 73%. Severity score fell to 27% of pretreatment. 3/27 patients required topical corticosteroids.	open design, lack of definition of food allergy. 4/37 patients responded by anaphylactic shock to reintroduction.
(26)	(FICH) egg: 72%, cow's milk: 47%, peanut: 34%; soy: 1.7%. (SAFT +) 39% response to elimination diet	open design, 62% dropout rate, nonstandardized test. Interesting for the evaluation of FICH as predictor response to diet.
(27)	effect only in 3–6-month-old infants old with egg allergy	blinded evaluation of egg allergy in children allergic to various foods including egg.
(28)	effect on 8 children (66%). 3 had diagnosis confirmed at the reintroduction.	recruitment throughout the year, excluding seasonal variation.
(29)	whole group: effect in 52% (14% drop-out).subgroup: effect in 73% (no drop-out).	small sample. Open design. Results confirmed by open reintroduction
(30)	46% dropout rate (35 in the diet group, 4 in the control group). median reduction in percentage surface area whey hydrolysate group = 17.8%; casein hydrolysate group 5%; control group 4.9%. skin severity score: whey hydrolysate group, 21.8%; casein hydrolysate group, 13.5%; control, 15.9%. improvement in the skin severity score was more than 20% in 58% of the diet group vs. 73% in control group. diets were found ineffective.	a specific calculation should be produced for the whey hydrolysate group. Good randomization. One of the few blinded studies (though single-blind). no diagnosis of food allergy. most of the drop-outs are in the diet group
(31)	atopic eczema improved significantly and progressively all round: from 17 to 5 in We group and from 21 to 4 in Aa group.	SCORAD indicated that children were mainly affected by mild AD. selected population
(32)	SCORAD improved from 21 to 19 in group a, from 26 to 15 in group b. concentrations of α -1-antitrypsin and fecal TNF- α decreased only in group b.	diagnosis of cow's milk allergy. the only study with laboratory evaluation of efficacy.
(33)	concentration of fecal ECP unaltered. severity score improved in 100% of cases	these data contradict the data of the previous paper (in a similar group and study design) suggesting that diet is effective only when associated with <i>Lactobacillus</i> GG. no blinding of L GG open, unblinded. no statistical evaluation.
(34)	affected surface area 3% vs. 8.7% ($p = 0.02$). severity score 3.2% vs. 9.9% ($p = 0.04$).	egg avoidance can be useful but effect magnitude is not great.
(35)	SCORAD decreased from 24.6 to 12.2 at three months and 10.7 at 6 months. No difference between AA and eHF groups	the study is mainly designed to evaluate growth. It shows an improvement in both groups, but there is not a control group (infants kept on CM diet)

aetiology. Thus, one study (28) considered eliminating cow's milk, egg and wheat in children with severe AEDS but only single-blinded provocation tests were carried out with these foods *after* the elimination diet. The two studies evaluating children with a challenge-confirmed diagnosis of food allergy (31,35) report clinical improvement in all children. An unconfirmed diagnosis but strong sensitization indices also characterized positive outcomes for diet therapy (22,33). That children with a confirmed food allergy diagnosis respond better to an elimination diet is suggestive that indication predicated on a precise food allergy work-up may have yielded better results elsewhere also. Five studies investigated the efficacy of single food elimination [egg (27,34) and cow's milk (31,32,35)] although this kind of intervention is relatively

easier to implement in a family setting but interest in this avenue of research seems to have waned (only one of such studies appeared during the last 5 years) while the attention of researchers regarding the diet therapy for AEDS has focused on treatments the biopathogenesis of which remains at the pure research biology level. Although metabolic alterations at the core of atopic dermatitis have been postulated (45,46), pathophysiological confirmation is still lagging behind empiric attempts to capitalize on the comparatively harmless effects of essential fatty acid supplements (47). There is, however, recent negative randomized controlled trial evidence against the efficacy of oil of borage in atopic dermatitis (48), a situation reminiscent of similar attempts using gamma-linolenic acid (49). Another dietary approach to

the treatment for AEDS predicated on basic research axiomatization (or lack thereof) is through a 'probiotic effect' conferred by viable bacteria supplementation. The rationale underpinning this empiric treatment is derived from the indirect evidence of epidemiological studies in turn predicated on the hygiene hypothesis (50) that reduced colonization by enterobacteria and intestinal mucosal alterations are involved in the pathogenesis of AEDS, a postulate that also awaits microbiological, pathophysiological and randomized clinical trial evidence confirmation. Furthermore, studies of probiotic bacteria supplements in AEDS are based on limited populations (32,51,52) and their authors rely on future research to clarify their mechanisms of action (53). Thus, sheer lack of scientific and clinical evidence of the efficacy of 'probiotic' bacteria in the treatment (54) or prevention (55) of AEDS argues against recommending these supplements. As an endnote, reviewing the literature on diet therapy for atopic dermatitis has revealed as wide a spectrum of opinion and advice as there is on its description. Denial of the role of food allergy in AEDS, evidence of which, avowedly, is not incontrovertible, has been put forward by some researchers who claim that 'although many patients with atopic dermatitis do have an allergic constitution (56), the contribution of allergy and IgE-mediated hypersensitivity reactions to the pathogenesis and the clinical severity of atopic dermatitis remains controversial' (51).

Conclusions

Previous reviews have been confined to particular aspects of the dietetic treatment of infants and children with atopic dermatitis, such as the effect of exclusion of egg

and milk from the diet of breast-feeding mothers of children suffering from eczema, the conclusions being that maternal avoidance of dietary antigen may reduce the severity of eczema but that larger trials are needed (57).

At the moment, however, no Cochrane review has been mounted into the effect of dietetic restrictions in children suffering from AEDS. Studies assessing the effect of an elemental or few-foods diet in atopic dermatitis report different types of interventions and are unable to support their use (14). There is little evidence to support an egg- and milk-free diet in unselected atopic eczema patients (14), but the use of specific food-free diets can be advocated on the grounds of the experience with an egg-free diet in infants with suspected egg allergy whose blood contains plasma egg-specific IgE (34).

Future studies on the efficacy of exclusion of specific food allergens in diet should be longer-term trials, focusing less on children than on infants who have dermatitis severe enough to require dietetic intervention and who are allergic to one or two foods. Food allergy must be demonstrated before the study and only specific triggers should be excluded from the diet. Objective parameters should be used in these studies, for instance the SCORAD (35), SASSAD (58), or ADASI (59) scoring system. The quality of life can now be estimated using specific scores as the Dermatology life quality index (60), developed for adults or specific paediatric questionnaires measuring the impact of the disease in children (61). As the evaluation should be performed blinded, children allergic to cow's milk form the ideal population for such trials but the blindedness is seriously hampered by ethical considerations. Finally, assessment of the magnitude of diet responsiveness requires infants from a general population of children with eczema, not selected populations of children sent to tertiary care, to be studied.

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