

Original Article

Liberalized Versus Strict Cow's Milk Elimination for the Treatment of Children with Eosinophilic Esophagitis

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Abstract

Objectives: Cow's milk is a commonly implicated trigger in eosinophilic esophagitis (EoE). Exclusive cow's milk avoidance has been reported previously, but the degree of elimination required for remission is unclear. Strict food avoidance may confer a risk of developing immunoglobulin E (IgE)-mediated allergy. The goal of this study was to evaluate the effectiveness of cow's milk elimination (CME) in children with EoE and compare responses of strict and liberalized CME diets.

Methods: Children (≤ 16 years) diagnosed with EoE who were treated with exclusive CME diets were evaluated clinically and histologically. Strict diets eliminated all milk products, including 'may-contain' and baked milk goods. Liberalized diets eliminated obvious sources including milk, cheese, yogurt, cream-based products but permitted foods with traces of milk and baked goods.

Results: Cow's milk elimination induced histological remission of <15 eosinophils per high-powered field in 18 of 31 children (58%) and complete remission in 23%. Overall, 77% had decreased eosinophils with this single intervention. Symptoms were improved in 90% of patients, regardless of histologic response. A liberalized ($n=7$) CME diet was associated with a nonsignificantly lower response compared with strict ($n=24$) elimination (29% versus 67%, $P=0.099$). Eight responders to strict elimination were transitioned to a liberalized diet; 63% maintained remission.

Conclusion: Cow's milk elimination induced clinicopathological remission in a majority of patients with EoE, supporting its use as a first-line intervention. Liberalized CME allows dietary freedom and may prevent subsequent development of anaphylactic milk allergy but may be inferior to strict CME for improving EoE.

Keywords: *Eosinophilic esophagitis; Food allergy; Food elimination diet*

Eosinophilic esophagitis (EoE) is an immune-mediated disease affecting the esophagus that is typically managed in children by either dietary or pharmacologic treatments. Dietary intervention often requires extensive lifestyle modification, and is dependent on tolerability and sustainability for both the patients and their families (1, 2).

Kelly et al. first described improved clinicopathological outcomes with complete replacement of intact dietary protein with elemental formula (3). Recurrence of esophageal eosinophilia following food reintroduction provides definitive evidence for

the role of food allergens in EoE (4–6). Current approaches to food elimination include the six-food elimination diet, targeting the common intact proteins associated with food allergies (cow's milk, soy, egg, wheat, peanut/tree nuts and seafood), and food elimination directed by skin prick and patch testing (7–9). Food elimination carries the burden of repeated invasive endoscopies for confirmation of biopsy upon food reintroduction. Several other factors impede successful elimination of multiple foods including compliance and the risk of iatrogenic nutritional deficiency (10). However, food elimination avoids side effects

associated with corticosteroid use, including the risk of oral candidiasis, growth problems or exogenous adrenal suppression (11–13).

Single-food elimination simplifies multiple-food elimination by removing just one of the most common foods associated with esophageal inflammation and requires only one endoscopy to confirm results. In particular, cow's milk has been identified to be one of the most common causative foods in EoE, with recurrence of the disease with the reintroduction of milk (5, 8, 9). Two previous studies have shown reasonable response rates of 65% and 64% to the elimination of milk alone (14, 15). Strict elimination requires avoidance of all sources of dairy including foods with traces of cow's milk or unlabeled products, and for some patients, this may be difficult due to the degree of vigilance required. The degree to which one must adhere to a strict elimination diet to maintain remission is unclear, and it has been argued that strict food avoidance may be a risk factor for developing anaphylactic immunoglobulin E (IgE)-mediated food allergy in a sensitized population (16). Extensively hydrolyzed cow's milk formula (eHF) has been shown to be tolerated in adults with milk-triggered EoE (17). In this retrospective study, we present the results of cow's milk elimination (CME) in a cohort of 31 pediatric EoE patients. Moreover, we are the first to compare the efficacy of strict versus liberalized avoidance of cow's milk.

METHODS

Study Design

The University of British Columbia and the Children's and Women's Health Centre of British Columbia Research Ethics Board (UBC, C&W, REB) approved this study. British Columbia Children's Hospital (BCCH) is the only referral centre for children with EoE in the province. This is a retrospective study of patients in the multidisciplinary EoE clinic at BCCH. Patients consented to the EoE registry over a four-year period (2013–2016). Additional chart reviews were performed on nonregistry EoE patients seen in the gastroenterology clinic.

Inclusion criteria.

Patients 16 years old or younger at time of diagnosis who met diagnostic criteria for EoE according to consensus guidelines (1), including symptoms related to esophageal dysfunction, who had one or more biopsies showing eosinophilic-predominant inflammation with >15 eosinophils per high-powered field, and who had failed a six-week trial of PPI therapy were included in this study. Patients also had to be on exclusive CME and have had pretreatment and post-treatment upper endoscopy performed at BC Children's Hospital.

Exclusion criteria.

Patients were excluded if multiple foods were eliminated to treat EoE at the same time as cow's milk or if swallowed

corticosteroids were being used concurrently with CME. Patients with IgE-mediated food allergies continued on their strict avoidance of those foods.

Upper Gastrointestinal Endoscopy and Biopsy

All endoscopies were performed at BCCH. All patients underwent endoscopy under anesthetic. Pediatric gastroenterologists followed a biopsy protocol of three levels of the esophagus, two biopsies per site, regardless of macroscopic appearance. Olympus gastroscopes H190/190 series with disposable biopsy forceps were used. Samples were placed in formalin and sent for histopathological analysis. Histological findings were identified from pathology reports including eosinophil counts. Follow-up endoscopies were performed no sooner than eight weeks after making a change to the diet.

Liberalized milk elimination.

Patients in clinic were initially assigned to a strict cow's milk elimination diet. However, this was not always permissible given factors such as the child's age and family preferences. Patients who had refused strict CME were started on a 'liberalized' diet, which allowed foods with traces of milk, such as margarine, and baked goods with milk ingredients, such as cookies and muffins. This diet continued to avoid obvious sources of milk such as whole milk, cheese, ice cream, creams, and yogurt. Dietary counselling was provided in similar fashion to all families, and the same registered dietitian provided comprehensive education on milk ingredients to ensure adherence for both diets.

Definitions.

Remission from EoE was defined as a biopsy count of <15 eosinophils/hpf on repeat upper endoscopy. Complete remission was defined as zero eosinophils/hpf. Food allergies were defined as IgE-mediated with risk of anaphylaxis. Strict cow's milk elimination (CME) was defined as eliminating all sources of milk, including foods containing casein and whey, and products in which milk was identified as 'traces' or 'may contain' on the label. Liberalized CME was defined as only eliminating obvious sources of milk, including fluid milk, cheeses, yogurt, ice cream and cream-based products.

Statistical Methods and Analysis

All data were entered in Microsoft Excel and analyzed using R version 3.2.2 (18).

Mann-Whitney U tests, Wilcoxon signed-rank test (continuous variables), and Fisher exact test (noncontinuous variables) were performed.

RESULTS

Demographic Data

We identified 31 children to be exclusively on CME. The median age was nine years (IQR=7,14). The majority (84%) were male,

and 74% were Caucasian. Non-Caucasian patients consisted of South Asians (23%) and East Asians (3%). The median age of diagnosis was six years (IQR=3,9), and the median treatment duration on CME was three months (IQR=3,4), with a minimum of 9.7 weeks. Many participants were atopic (45%). Eczema was the most frequent atopic disease (57%), followed by asthma (50%) and allergic rhinitis (36%). IgE-mediated food allergies were present in 32% of patients. Skin-prick testing to cow's milk was performed in 65%, among which 85% tested negative. All patients, however, had tolerated milk products before the intervention and did not show signs or symptoms of milk anaphylaxis.

Clinical Data

Dysphagia (39%), vomiting (42%), and abdominal pain (16%) were the most commonly reported symptoms before treatment. Overall, 90% of patients reported symptom improvement regardless of their histological response, while 77% of patients who did not achieve remission on CME still reported an improvement in symptoms. Improvement was reported with dysphagia (39% pre-CME versus 3% post-CME, $P=0.0006$), vomiting (42% versus 3%, $P=0.0003$) and abdominal pain (16% versus 6%, $P=0.2$).

Histologic Data

Of the 31 patients, 18 (58%) achieved histological remission and improved symptoms with CME. Of the patients achieving histological remission, seven (23%) achieved complete remission. Overall, 24 patients (77%) were found to have some degree of decreased esophageal eosinophils in response to CME. Twenty-eight patients (90%) reported symptom improvement regardless of histological response. We defined 'symptom improvement' as either an improvement in symptoms (e.g., less dysphagia) or a total resolution of symptoms evaluated subjectively in follow-up shortly after post-CME endoscopy.

Demographic data of patients achieving histological remission and nonresponders to CME are summarized in [Table 1](#). There was a significant difference between median pretreatment

biopsy counts and median post-treatment biopsy counts. This observation was unchanged when stratified by the presence or absence of atopy ($P=0.01$) or food allergy ($P=0.04$). There was no association between the results of skin-prick testing and response to CME ($P=0.22$).

Strict Versus Liberalized Elimination

Of the 31 patients, 24 patients underwent strict CME as their initial treatment, while seven patients underwent liberalized CME. Remission was seen in 16 patients (67%) of the strict elimination group, compared with two patients (29%) in the liberal elimination group. The difference in remission rates between the strict and liberal groups was nonsignificant ($P=0.10$). Demographic and histological data of patients following a strict and liberal CME are summarized in [Table 2](#).

After Cow's Milk Elimination

Among the 16 patients who achieved remission on strict CME, eight remained on strict CME, while eight opted to try a liberalized elimination. Histological remission was maintained in five patients (63%) of this latter group.

In this study, 13 patients did not achieve histological remission on CME: six patients responded to CME but did not meet remission criteria of <15 eos/hpf, while seven patients had increasing biopsy counts on repeat endoscopy. The 13 patients were offered dietary management, including the elimination of multiple foods, or medical therapy. Five patients achieved remission with the addition of swallowed topical corticosteroid, and one patient displayed no response to further dietary or medical therapy. One patient was lost to follow-up. We note that six patients declined further intervention and were likely satisfied with their improvements despite not achieving histological remission. At the end of follow-up, 24 of 31 had continued with CME (strict or liberal) as their primary treatment.

DISCUSSION

The elimination of cow's milk holds discrete advantages over dietary interventions involving multiple foods, including a

Table 1. Demographic and histological data of responders and nonresponders to CME

	All (n=31)	Histological Remission (<15 eos/hpf) (n=18)	Non-responders (≥ 15 eos/hpf) (n=13)	P
Gender (% males)	26 (84%)	16 (89%)	10 (77%)	0.4
Food allergy (%)	10 (32%)	4 (22%)	6 (46%)	0.2
Age (years)	9 (IQR=7,13)	9 (IQR=14,7)	8 (IQR=5,9)	0.2
Age at diagnosis (years)	6 (IQR=3,9)	6 (IQR=3,9)	5 (IQR=3,8)	0.7
Treatment duration (months)	3 (IQR=3,4)	3 (IQR=3,3)	3 (IQR=3,4)	0.3
Pre-tx (eos/hpf)	37 (IQR=28,61)	38 (IQR=26,59)	37 (IQR=28,63)	0.7
Post-tx (eos/hpf)	7.2 (IQR=2,33)	2 (IQR=0,6)	37 (IQR=29,57)	$<.00001$

Table 2. Demographic and histological data of patients undergoing strict and liberal CME diets

	Strict (n=24)	Liberal (n=7)	P
Ethnicity (% South Asians)	3 (13%)	5 (71%)	0.002
Gender (% male)	21 (88%)	5 (71%)	0.3
Food allergy	8 (33%)	2 (29%)	0.8
Age (years)	9 (IQR=7,12)	9 (IQR=8,11)	0.9
Age at diagnosis	6 (IQR=4,8)	2 (IQR=2,9)	0.3
Treatment duration (months)	3 (IQR=3,3)	3 (IQR=3,5)	1.0
Pre-tx (eos/hpf)	34.5 (IQR=28,58)	57.3 (IQR=32,77)	-
Post-tx (eos/hpf)	6 (IQR=2,17)	33.7 (IQR=20,44)	-

smaller impact on lifestyle and nutrition and a need for fewer repeat endoscopies, overall facilitating long-term adherence. Participants in our study required only one scope to verify response within a short treatment duration of two to three months. In our clinic, CME is offered as first-line management for EoE to families who prefer a dietary approach. Other foods are avoided concurrently only if there is a concern of anaphylactic food allergy.

In this study, 58% of patients responded to the exclusive elimination of cow's milk, a reasonable response compared with more aggressive forms of dietary elimination, such as the six-food elimination diet (73.1%) (9). These remission rates corroborate with previous studies of CME in smaller cohorts of 17 (65%) and 20 (64%) pediatric patients (14, 15). Responders and nonresponders to CME were statistically similar with regards to demographic features (i.e., age and age at diagnosis), histologic features (pretreatment mean eos/hpf) and treatment duration. There was no correlation between allergic features (presence of atopy and food allergy) and histological remission while on CME. A majority of patients that underwent skin-prick testing to cow's milk tested negative (85%), but no correlation between skin testing results and response to CME was observed. Overall, these results advocate for empiric application of CME, as strong clinical phenotypes or convincing testing have not yet been identified.

Symptoms were improved or eliminated in a majority (90%) of patients undergoing CME, in agreement with previous studies (15). Incidentally, 10 of 13 (77%) of patients who did not achieve remission on CME still reported an improvement in symptoms. Clinicopathological dissociation between symptoms and histology has been described in EoE, and guidelines indicate that neither should be interpreted in isolation (1, 2, 19). In this study, symptoms were assessed subjectively in follow-up visits in clinic.

As expected, the liberalized diet was associated with a lower rate of remission (29%) compared with strict elimination. This difference was nonsignificant, likely due to small sample size and subsequent low power of the study. Indeed, histological improvement may be dependent on the amount of milk

ingested. Tolerance to baked milk has been demonstrated in cow's milk-mediated EoE (20). Higher baking temperatures may destroy conformational epitopes targeted by milk-specific IgE antibodies (21).

Elucidating a patient's histological tolerance for milk is important because a liberalized diet allows dietary freedom (i.e., only avoiding obvious sources of milk without having to read labels). In addition, ethnic differences in milk consumption may inform patient preferences, as South Asian patients in this study were more likely to refuse strict elimination initially compared with Caucasians. Liberalized milk elimination also provides a certain degree of beneficial exposure to milk. Studies in food-triggered atopic dermatitis and eosinophilic gastrointestinal disease have reported an association of strict food elimination with the development of new IgE-mediated allergy and—in some cases—anaphylaxis in children with no previous history of allergy to the food (22, 23, 24). This may be due to a loss of oral tolerance or lack of opportunity to develop tolerance (23). Thus, a liberalized diet maintaining tolerable levels of milk allergens (e.g., baked goods) may mitigate this risk.

We noted some limitations in our study. Small sample size resulted in decreased statistical power, and future studies on larger sample sizes are needed. Symptom improvement is a difficult parameter to measure aside from information gathered on history, and as with all dietary treatments, it was difficult to measure the degree of compliance. Validated scoring systems such as the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS™ v2.0) may be able to more objectively determine CME efficacy on symptom reduction (25).

This studies' nonrandomized approach to strict and liberal milk avoidance, with patients opting for the latter when strict avoidance was less acceptable, may indicate issues with nonadherence to the diet. However, adherence is invariably a difficult factor to control with food elimination, and varied adherence may simply reflect the reality of this diet. Future studies comparing the tolerability of CME with other elimination options and validated tracking tools measuring adherence are needed.

In summary, 77% of patients were found to have some degree of decreased esophageal eosinophils in response to CME, with

58% achieving histological remission and an even higher proportion (90%) reporting symptom improvement, confirming previous observations that it is an effective dietary intervention for EoE. A liberalized approach to cow's milk avoidance allows for dietary freedom and may prevent subsequent development of anaphylactic milk allergy but may be inferior to strict elimination in achieving histologic remission. However, it is likely that there is a spectrum of histologic responses to milk avoidance, and practitioners may benefit from tailoring the degree of milk elimination to their patients' preferences and biopsy results after a discussion of risks and benefits.

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