

**Version #4 10/26/2023**

**A Pilot Trial of Baked Milk Introduction in Patients with  
Milk-triggered Eosinophilic Esophagitis**

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## **Background**

Dietary Therapy has been shown to be successful [1] in the treatment of adult and pediatric patients with eosinophilic esophagitis (EoE) [2-5]. Dietary studies were initially reported in children, but the results appear to be similar in adult patients. Elemental diets are successful in 70-95% of patients but are poorly tolerated [1, 2]. A six-food-group elimination diet (SFGED) has been effective in about 70% of adult patients with EoE [3, 4]. In these adults, skin prick testing was not helpful in predicting which foods would lead to flare of disease when reintroduced into the diet.

Both empiric and directed methods for antigen elimination show that milk is the most common food trigger for EoE in children, and it is also a common trigger in adults [4, 6]. Among adult patients, 43% respond to milk and wheat elimination diets and of these, 52% had only milk as a trigger [7]. Strict milk elimination may have negative effects on patient quality of life. Prior evidence has shown that some patients with milk-triggered EoE are able to tolerate milk in a baked form [8]. In patients with IgE-mediated cow's milk immediate hypersensitivity, the denaturing of the conformational epitopes of cow's milk due to extensive heating is suggested as the underlying mechanism of baked milk tolerance of a majority of these patients [9]. In addition, evidence shows that inclusion of extensively heated cow's milk regularly in the diet may accelerate the development of tolerance to unheated forms of cow's milk in patients with IgE-mediated hypersensitivity [10].

We will perform a pilot study to assess tolerance of baked milk introduction in patients with milk triggered EoE, followed by re-introduction of varying amounts of straight milk to see if there is a threshold amount of milk that is tolerable.

Hypothesis: Most patients with milk triggered EoE will be able to tolerate baked milk. In patients tolerate baked milk, there is a threshold amount of straight milk that is tolerated.

Aims:

1. Assess how many patients with milk triggered EoE can tolerate re-introduction of baked milk
2. Determine if there is a threshold amount of straight milk that is tolerated

## **Methods**

Design: Prospective trial

Patients previously referred to the Mayo Clinic Rochester with an establish diagnosis of EoE who were responsive to elimination diet with milk and up to one additional food trigger will be identified (as defined below).

Inclusion Criteria:

- 18 to 90 years of age
- Diagnosed with Eosinophilic esophagitis  $\geq 15$  eosinophils per HPF
- Going through or completed the six-food elimination diet, with milk only or milk plus one additional food identified as a trigger

Exclusion Criteria:

- Patients with conditions known to be associated with esophageal eosinophilia, including Crohn's disease, Churg-Strauss, achalasia, and hypereosinophilic syndrome
- Topical swallowed steroids within 8 weeks of study enrollment
- Inability to read due to: Blindness, cognitive dysfunction, or English language illiteracy

Timeline:

Entry

- Patients will be recruited from the Esophageal Clinic.
- Meet with study investigator (AAK, KR, DLS, JAA). Patients will complete the EEsAI (Appendix #1), EHAS-7 (Appendix #2) and EoE QOL A (Appendix #3).
- Patients will meet with a study team member for an educational session to review a standardized recipe for a muffin containing baked milk (Appendix #4).
- Patients will undergo baseline cytosponge to ensure they are in remission

Study Period

Baked Milk

- Patients will eat one baked milk muffin at least 5 days a week for a period of 6 weeks.
- Patients will log their baked milk intake in a diary.
- Patients will be contacted via phone call every 2 weeks for EEsAI questionnaire completion and to inquire about any issues with the baked milk diet
- At the end of the 6-week period, the following will be assessed:
  - Repeat cytosponge
  - EEsAI questionnaire
  - EHAS-7 questionnaire
  - EoE-QOL A questionnaire
  - Review of the patient's food diary to ensure compliance
    - If significant noncompliance is observed, the patient will be offered repeat consultation with dietitian and extension of baked milk for 6 weeks
- If a patient has clinical recurrence with baked milk, they will undergo an elimination period of 6 weeks, followed by cytosponge to confirm resolution. If symptoms have resolved and they have confirmed histologic resolution, they will proceed to straight milk intervention.

- If a patient has evidence of subclinical histologic recurrence, defined as  $\geq 15$  eos per HPF, a washout period of 6 weeks will be pursued, followed by repeat sponge to ensure histologic remission. They will be deemed a failure and not proceed with intervention of straight milk.
- If a patient has histologic recurrence after baked milk, they will have elimination of baked milk for 6 weeks followed by cytosponge to confirm resolution. They will be deemed a failure and not proceed with straight milk.

### Straight Milk

Patients with confirmation of histologic remission ( $< 15$  eos per HPF) after the baked milk trial will move onto introduction of straight cow's milk.

- Patients will drink one glass (8 oz) of cow's milk a week for 4 weeks
- Patients will log a food diary for compliance
- Following the 4-week period, patients will complete the EEsAI and EoE-QOL A questionnaires and be evaluated with sponge. If still in histologic remission, then the amount of milk will be sequentially increased to 3 glasses, 5 glasses, 7 glasses and 10 glasses a week every 4 weeks (8 oz per serving) until patient develops symptoms or  $\geq 15$  eos per HPF when assessed with sponge. During this time period, we will have patients come into the office every 4 weeks for repeat sponge and questionnaire completion prior to proceeding to the higher amounts of milk.
- If patients have histologic recurrence at any point during the straight milk intervention, they will eliminate straight milk for 6 weeks, followed by cytosponge to confirm resolution.
- If patients have subclinical histologic recurrence at any point during the straight milk intervention, they will eliminate straight milk for 6 weeks, followed by cytosponge to confirm resolution.
- If a patient has clinical recurrence without histologic recurrence, they will not proceed further with straight milk.

### Analysis

## Sample Size

20 patients.

## Definitions of histologic remission:

- <15 eos per HPF on cytosponge

## Definitions of symptomatic remission:

- Symptoms: A complete response will be defined by
  - EEsAI PRO score of <20

## Primary Endpoint:

- 1) The proportion of patients in histologic remission at the end of a 6 week trial of baked milk

## Secondary Endpoints:

- 1) The proportion of patients in symptomatic remission after a 6 week trial of baked milk
- 2) The proportion of patients who remain in histologic remission after 1, 3 5, 7 and 10 glasses of milk a week
- 3) The proportion of patients who remain in symptomatic remission after 1, 3 5, 7 and 10 glasses of milk a week
- 4) The numerical improvement of quality of life after baked milk and sequential addition of straight milk
- 5) Correlation of symptomatic and histologic disease activity

## Analysis of Safety

The sponge has been found to be very well tolerated [11]. Any symptoms post sponge study will be evaluated by the MD investigator as clinically indicated. All sponge studies will be performed by the MD investigator.

We do not feel a safety board is needed for this study.

## **Remuneration**

Participants will be provided with remuneration of up to \$200 for their time and travel to and from the clinic. Participants will be eligible to receive \$100 for completing the baked milk portion of the study (must complete the 6-week visit). Participants will then be eligible to receive an additional \$20 per visit during the straight milk portion of the study, for up to 5 visits. Participants will be paid at the completion of the study in a manner compliant with Mayo Clinic's research participant remuneration policy.

## **Feasibility/ Time frame**

A total of 26 EoE patients meeting inclusion criteria (responsive to dietary therapy with milk and up to one additional trigger) have been identified from a prospectively maintained clinical database. In addition, each year approximately 150 new EoE patients are seen in the Esophageal Clinic at Mayo Clinic Rochester. We therefore anticipate a time frame of 6 to 12 months for study completion.

## **Strengths/ Limitations**

The strength of this study is its simplicity and very high probability of being completed within a 40 week (10 month) time frame. It is limited by its small sample size and lack of control group, however this is acceptable given its novel design as a pilot study.

## **Human Issues:**

Treatment office visits and sponge costs will be covered by research funds. Upon publication, we will mail all participants a thank you note, with a copy of the manuscript, explaining the results in layman terminology, as a way of providing feedback for their participation.

## **Gender/ Minority Mix**

All patients meeting criteria will be offered enrollment in this study. We expect the gender/minority mix of the subjects to reflect that of the Rochester community adjusted for the increased prevalence of eosinophilic esophagitis in males. We therefore anticipate approximately 70% male and 30% female with 85% Caucasian and 15% minority origin (Black, Hispanic, and Asian).

## **Budget**

Funding will be provided by the Mayo Clinic benefactor funds and CCaTS Small Grant Program.

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