A Pilot Trial of Dietary Therapy directed by the Esophageal Sponge in the Management of Eosinophilic Esophagitis

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A Pilot Trial of Dietary Therapy directed by the Esophageal Sponge in the Management of Eosinophilic Esophagitis

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Background

Dietary Therapy has been shown to be [1] successful in the treatment of adult and pediatric patients with eosinophilic esophagitis [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 elimination diet has been effective in about 70% of adult patients with EoE [3, 4]. In these adult studies skin prick testing was not helpful in predicting which foods would lead to a flare of disease when reintroduced into the diet. Therefore, the current standard of care requires multiple EGDs with esophageal biopsy during the dietary restriction and reintroduction phases of this study. Since we are making lifelong dietary decisions during this process of food reintroduction, it is imperative we be accurate. Unfortunately, these multiple EGDs have significant cost and are invasive procedures with some risk. Moreover, there is significant indirect costs with travel and time off work for the patients and drivers.

Recently, Katzka et al have found the esophageal sponge to be an accurate technique of accessing esophageal eosinophilia in EoE [6]. The sponge is swallowed as a 12 mm capsule on a string. The capsule rapidly dissolves upon entering the stomach and the sponge then expands and can be pulled out the mouth five minutes after ingestion. In this study, the procedure was very well tolerated and all patients preferred the sponge to endoscopy.In the event this cytosponge is unavailable we will use the CapNostics EsophaCap, which is very similar to the cytosponge and is FDA approved, in order for the subjects to complete the trial.Therefore the sponge is a well tolerated, inexpensive, very low risk procedure that would be an ideal option to replace EGD esophageal sampling in the evaluation of dietary treatment of EoE.

We perform a pilot study using the esophageal sponge to direct dietary therapy in adult patients with EoE.

Hypothesis: Esophageal sampling with the esophageal sponge can accurately direct dietary therapy in EoE.

Aims 1. Evaluate the effectiveness of the esophageal sponge to guide dietary therapy in adult patients with EoE.

Methods

Design: Prospective trial

Inclusion Criteria:

- 18 to 80 years of age
- Diagnosed with Eosinophilic Esophagitis > than 15 Eos phf
- Going through the six food elimination diet or have just completed elimination the six foods: fish, nuts, eggs, soy, wheat, and milk

Patients that have completed the six food elimination diet clinically and none of the foods were identified as being the food causing their EoEExclusion Criteria:

- Clinical evidence of infectious process potentially contributing to dysphagia (e.g. candidiasis, CMV, herpes)
- Other cause of dysphagia identified at endoscopy (e.g. reflux esophagitis, stricture, web, ring, achalasia, esophageal neoplasm)
- Esophageal minimal diameter < 13 mm on structured barium esophagram

Timeline:

Entry

- Patients will be recruited from the Esophageal Clinic.
- Meet with study investigator (JAA, DAK, KR). Vital signs and weight will be recorded; dysphagia (Appendix #1) and EEAI (Appendix #2) questionnaires will be evaluated.
- Patients will complete the food anaphylaxis questionnaire; any food positive will be restricted from the diet and not reintroduced. If a patient is avoiding one of the six foods for any reason, we will not reintroduce this food.
- Patients will meet with a dietician for an educational session

Study Period

- Patients will meet with an EoE dietician and go on the Mayo six food elimination diet (SFED) avoiding: fish, nuts, eggs, soy, wheat, and milk
- Study flow diagram Appendix #4
- Non responders to the SFED will be placed on the extended SFED avoiding the following: corn and legumes.
- Patients will undergo a repeat EGD with biopsies after dietary reintroduction is complete for histologic assessment.
- At the end of the dietary reintroduction patient will evaluate tolerance of the sponge and endoscopy by a standardized Lickert scale (Take from the Katzka study)
- Patients will complete a 3 day dietary log during the first 2 weeks of SFED. This will be reviewed by the dieticians and if noncompliant a dietician will talk to the patient and the diet will be extended 3 more weeks.

  . Significant dietary compliance issues or dietary questions will lead to direct conversation with a research dietician and the investigators continuation of the same treatment until dietary compliance is obtained. Inability to maintain reasonable dietary compliance will lead to study withdrawal.

Post Therapy Period

- Patients will return for follow up at 6 months
- Sponge and EGD with biopsy will be performed if recurrent dysphagia develops as defined above (The EGD/biopsies will be part of the clinical care)
- If symptoms have not reoccured a sponge will be completed at the 6 months' visit

Time line (Appendix #4)

Methods:

Six esophageal biopsies will be obtained from the entire esophagus at EGD. Histology containing a peak level of $\leq$ 15 eosin / hpf on all biopsy specimens will be considered histologic remission. All biopsy specimens will be read by the same study investigator (TS). All EGD are clinically indicated in this protocol and will be performed in the clinical arena with clinical charges.

On sponge cytology remission will be defined as having no fragments of tissue containing < 15 eosin/hpf. All sponge studies will be read by the same study investigator (TS).

Analysis

Sample Size

100 patients.

Definitions of symptomatic remission:

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

Primary Analysis

We will determine 1) what % of patients are in histologic remission at the end the end of dietary therapy, 2) what % of those are in symptomatic remission as determined by EEAI PRO score.

Compare these histologic results to Mayo controls

Secondary Analyses

Compare cost of standard approach to sponge approach using last 20 standard patients

Compare final sponge result to EGD histology.

Compare patient tolerance of sponge to endoscopy.

Analysis of Safety

The sponge has been found to be very well tolerated in a previous study[6]. 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.

The dietician will meet with the patient at the study initiation, completion, and at any time in between if clinically indicated. Nutritional deficiencies are uncommon with a short term dietary study of EoE. After the food reintroduction phase, patients will be given dietary supplementation information depending on their dietary restrictions prior to the 6 month treatment period.

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

Feasibility / time frame

We see about 150 new patients with symptomatic eosinophilia, 30% have PPI-REE and 70% EoE, each year in the Esophageal Clinic. Dietary therapy is becoming increasingly more popular among our patient population. Currently, we have started 20 patients on dietary treatment over

the last year. Several patients interested in dietary therapy have been delaying initiating the program awaiting the clinical use of the sponge, preferring this over the cost, risk, and inconvenience of EGD. We would expect to recruit 35 patients over the next two years and expect a dropout rate of 15%. We expect to complete the study within 24 months time.

Addendum: We would like to increase our enrollment to 100 subjects. Many patients are interested in the cytosponge as it eliminates several EGDs during the six food elimination diet. We would like to offer the sponge trial to these patients as it helps them through completing the diet.

Strengths / limitations

The strength of the study is its simplicity and very high probability of being completed in 2 years' time. Many patients have chosen to be in this study over the traditional endoscopically directed dietary care. Therefore, there will be some inherent bias in their preferences of the sponge related to endoscopy.

Human Issues:

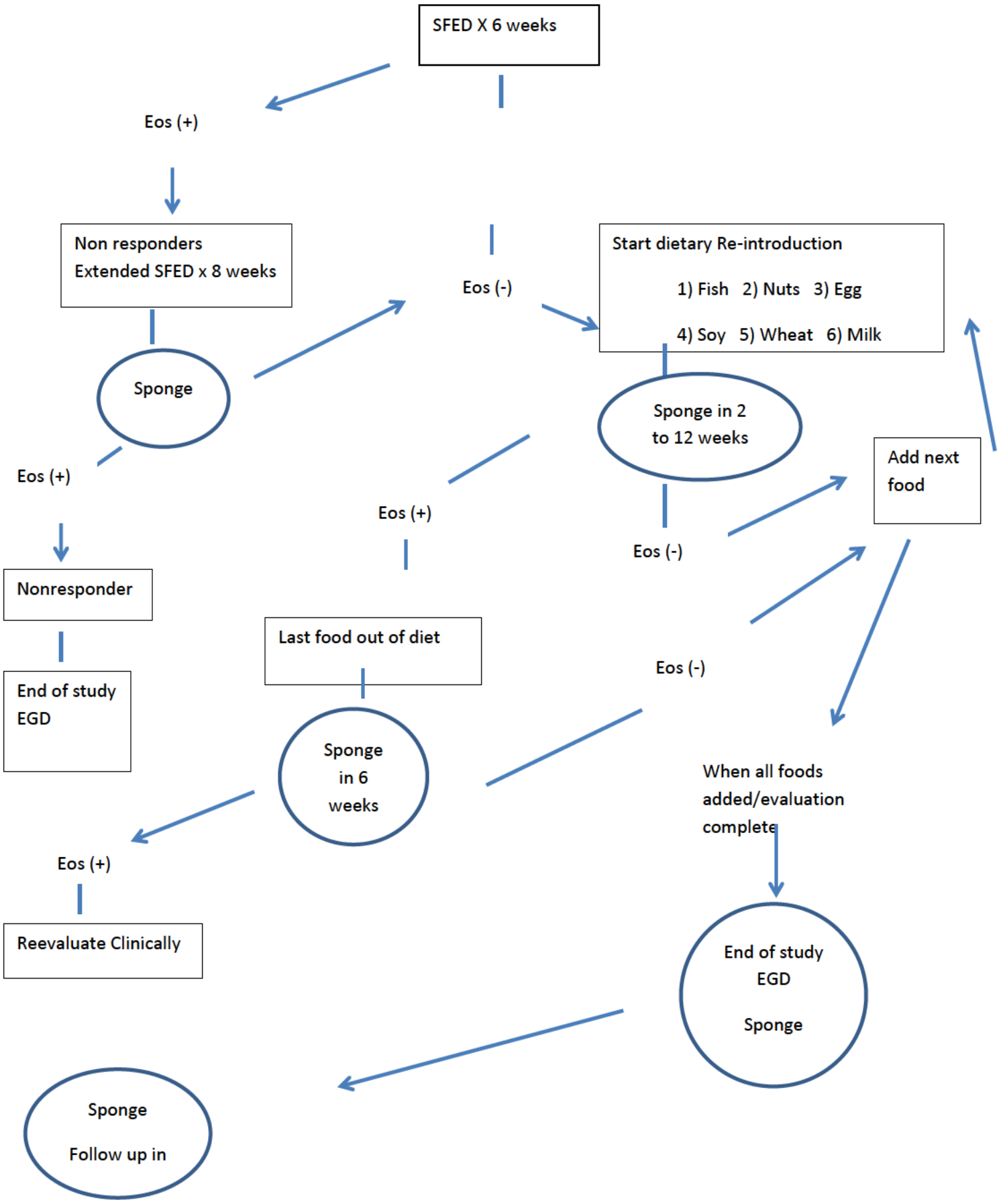
Treatment office visits and sponge costs will be covered by research funds. Standard medical care would be at least 5 endoscopies during the food reintroduction period, which are being replaced with the sponge. Upon publication, we will mail all participants a thank you note, with a copy of the manuscript, 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

The budget submitted to CURE foundation is enclosed. If this is not funded by CURE we have adequate funds in Dr Alexander's research account to complete the study.


SFED X 6 weeks
Eos (+)
Non responders
Extended SFED x 8 weeks
Sponge
Eos (+)
Nonresponder
End of study
EGD
Eos (-)
Start dietary Re-introduction
1) Fish 2) Nuts 3) Egg
4) Soy 5) Wheat 6) Milk
Sponge in 2
to 12 weeks
Eos (+)
Eos (-)
Add next
food
Last food out of diet
Sponge
in 6
weeks
Eos (+)
Reevaluate Clinically
Eos (-)
When all foods
added/evaluation
complete
End of study
EGD
Sponge
Sponge
Follow up in

Study Timeline:

Eligible patients meeting the diagnostic definition of EoE and are on or starting the eliminated the six foods for the SFED diet patients will meet with one of 3 investigators (JAA, DAK, KR) to discuss diagnosis and treatment

1. Meet with the study coordinator, explain study, either at the beginning of the diet or when patient returns after the eliminating the six foods, consent process completed.
2. Patients will complete the EEsAI questionnaire to assess symptoms
3. Patients will complete the anaphylaxis questionnaire: any food positive will be restricted from the diet and will not be reintroduced.
4. If patient meets criteria an appointment will be set up to meet with a dietitian to discuss the SFED diet. This is all part of the patients clinical care.
5. The clinical SFED protocol will be followed as below:

    - Meet with a dietitian
    - Patients will follow the SFED by excluding milk, wheat, eggs, soy, nuts, and fish for 6 weeks
    - Return for an upper endoscopy/biospsies (all part of their clinical care)

Patients with symptomatic and histologic response (defined by <15 eos per HPF EGD/biospsies) will be defined as responders. Responders will then undergo food reintroduction via the following protocol:

a. Fish for up to 12 weeks
b. Return for cytosponge to monitor the patients eosinophilia histologically.
c. At any time if the histology is positive > 15 eosinphils phf we will wait 6 weeks prior to adding in a new food. If negative <15 eosinophils phf we will add in the next food.
d. Nuts for up to 12 weeks
e. Repeat cytosponge
f. Eggs for up to 12 weeks
g. Repeat cytosponge
h. Soy for up to 12 weeks
i. Repeat cytosponge
j. Wheat for up to 12 weeks
k. Repeat cytosponge
l. Milk for up to 12 weeks

m. Repeat cytosponge
n. If pathology shows ≥ 15 eos per HPF, eliminate milk and repeat cytosponge

When all foods added back, EGD and cytosponge at the end of the diet (EGD is part of the clinical care.

Follow up with the cytosponge/ histology in 6 months

We are further extending the in intervals returning for the cytosponge, scheduling is an issue. Also for patients that are having symptoms but had a negative cytosponge results we will continue them on the same foods and have them return in two weeks for a repeat cytosponge. We are also finding that some patients are not responding to a food group, so we would like to further extend each re-introduction to up to 12 weeks.

SFED nonresponders with symptomatic and histologic nonresponse (defined by >15 eos per HPF on cytosponge) will then undergo an expanded directed 8 food elimination diet including the six foods adding corn and legumes. After 8 weeks on this diet patients will return to repeat the cytosponge/ histology. If patients are still nonresponders this will be the end of the study for them. Reponders will undergo the food reintroduction following the same protocol as the reponders for the six food diet only excluding the additional foods corn and legumes.

When all foods added back, EGD and cytosponge at the end of the diet

Follow up with the cytosponge/ histology in 6 months

Patients that have completed the six food elimination diet clinically and no foods were identified as the food causing their swallowing issues, we will offer participation in the cytosponge trial. We will add foods back in up to 12 week intervals to see if the additional time between foods will help identiy the food they are reacting to.

Addendum:

We will senda limited data set with sample a portion of the primary cytosponge will be flash frozen in a dry eppie tube and shipped on dry ice., for extra-cellular RNA signature analysis with possible detection of EoE specific lumen protein products proposed to Dr. [redacted] lab at the Cincinnati Children's Hospital

Addendum (11/05/2019):

Revise inclusion criteria of “>/ 15eos/hpf and failed to respond to high dose PPI” to “>/ 15 eos/hpf found upon initial biopsy”. The general agreed consensus for diagnosing Eosinophilic Esophagitis has changed and PPI-responsive EoE is no longer being recognized as a separate diagnosis, rather, eosinophils found in the esophagus is EoE.

Bibliography

1. Liacouras, C.A., et al., *Eosinophilic esophagitis: a 10-year experience in 381 children.* Clin Gastroenterol Hepatol, 2005. **3**(12): p. 1198-206.
2. Peterson, K.A., et al., *Elemental diet induces histologic response in adult eosinophilic esophagitis.* The American journal of gastroenterology, 2013. **108**(5): p. 759-66.
3. Gonsalves, N., et al., *Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors.* Gastroenterology, 2012. **142**(7): p. 1451-9 e1; quiz e14-5.
4. Lucendo, A.J., et al., *Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease.* The Journal of allergy and clinical immunology, 2013. **131**(3): p. 797-804.
5. Kagalwalla, A.F., et al., *Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis.* Clin Gastroenterol Hepatol, 2006. **4**(9): p. 1097-102.
6. Katzka, D.A., et al., *Accuracy, Safety, and Tolerability of Tissue Collection by Cytosponge vs Endoscopy for Evaluation of Eosinophilic Esophagitis.* Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association, 2015. **13**(1): p. 77-83 e2.
7. Grudell, A.B., et al., *Validation of the Mayo Dysphagia Questionnaire.* Dis Esophagus, 2007. **20**(3): p. 202-5.
8. Schoepfer, A.M., et al., *Development and Validation of a Symptom-Based Activity Index for Adults With Eosinophilic Esophagitis.* Gastroenterology, 2014.