



## Management Strategies for the Newly Diagnosed Patient with Eosinophilic Esophagitis: Diet, Medications, or Both?

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### Webinar Objectives



1. Understand the importance of using the current diagnostic criteria for eosinophilic esophagitis (EoE).
2. Acquire practical tips on how to inform patients/caregivers about 3 fundamental management options: pharmaceuticals, dietary elimination, or combination of diet and pharmaceuticals.
3. Recognize the role of amino acid-based formula in these patients.
4. Explore the development of an EoE management plan.

## Management Goals



- Symptomatic improvement
- Histologic remission
  - Symptoms do not always correlate with histology
- Prevention of complications
- Maintain a good quality of life
- Provide adequate nutrition

## Review of EoE



### Definition from 2011 consensus:

- “Eosinophilic Esophagitis (EoE) represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.”
  - Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of  $\geq 15$  eosinophils per high-power field (eos/hpf)
  - Mucosal eosinophilia is isolated to the esophagus **and persists after PPI trial**

**EoE is a lifelong chronic condition that is becoming one of the most common eosinophilic diseases of the gastrointestinal tract**

Dellon et al. *Am J Gastroenterol*, 2013.  
Liacouras et al. *J Allergy Clin Immunol*, 2011.  
Spergel et al. *J Pediatr Gastroenterol Nutr*, 2009.

## Poor Adherence to Diagnostic Guidelines



- Only **24%** of academic (n=37) and **3%** of community adult gastroenterologists (n=133) follow consensus guidelines to diagnose EoE.
  - **25%** required a PPI trial or negative pH study prior to diagnosis
  - **60%** did not use the recommended threshold of 15 eos/hpf to diagnose EoE


Peery, AF et al. *Aliment Pharm Ther*, 2010.

## Proton Pump Inhibitors



- Very effective acid blockers
  - Traditionally used to control reflux in patients with EoE to reduce ambiguity between reflux esophagitis and EoE
- Now recognized to have anti-inflammatory properties
- A significant proportion of patients diagnosed with EoE have resolution of disease when treated with high dose PPI
  - PPI responsive esophageal eosinophilia (PPI-REE)

## PPI-Responsive Esophageal Eosinophilia (REE)




|                                | Patient 1               | Patient 2               | Patient 3              |
|--------------------------------|-------------------------|-------------------------|------------------------|
| <b>Age (yr)/sex</b>            | 14/M                    | 25/M                    | 13/F                   |
| <b>Symptom Presentation</b>    | Pain                    | Food impaction          | Dysphagia              |
| <b>Environmental Allergies</b> | Yes                     | Yes                     | No                     |
| <b>Treatment</b>               | Omeprazole<br>10 mg BID | Omeprazole<br>20 mg BID | Omeprazole<br>20 mg QD |
| <b>Eosinophils/HPF</b>         |                         |                         |                        |
| <b>Before treatment</b>        | 37                      | 21                      | 59                     |
| <b>After treatment</b>         | 1                       | 3                       | 0                      |

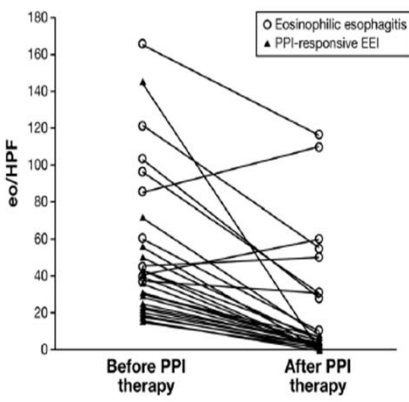
Many other publications since 2006 have corroborated results.

Ngo et al. *Am J Gastroenterol*, 2006.

## PPI-Responsive Esophageal Eosinophilia




- N=35 adults with esophageal eosinophilia (>15 eos/hpf)
- **75%** had improvement on PPI
  - Median eosinophil count 36 before, 3 after PPI
- pH monitoring poorly predictive of response
- Concluded EoE is “overestimated” in adult population

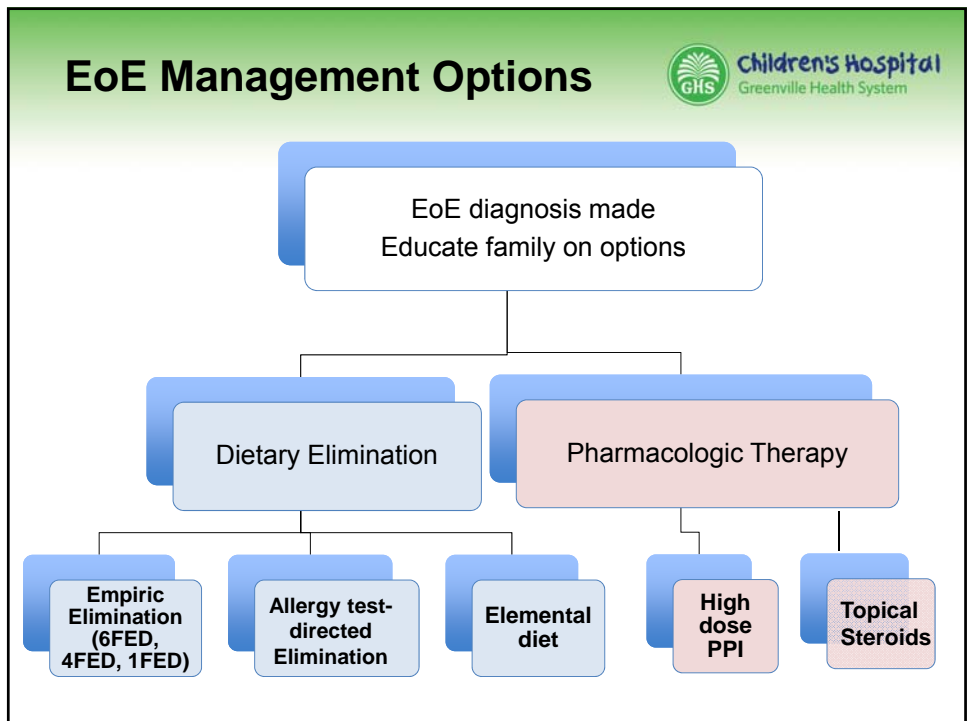


Molina-Infante, J et al. *Clin Gastroenterol Hepatol*, 2011.



## PPI as Treatment for EoE?

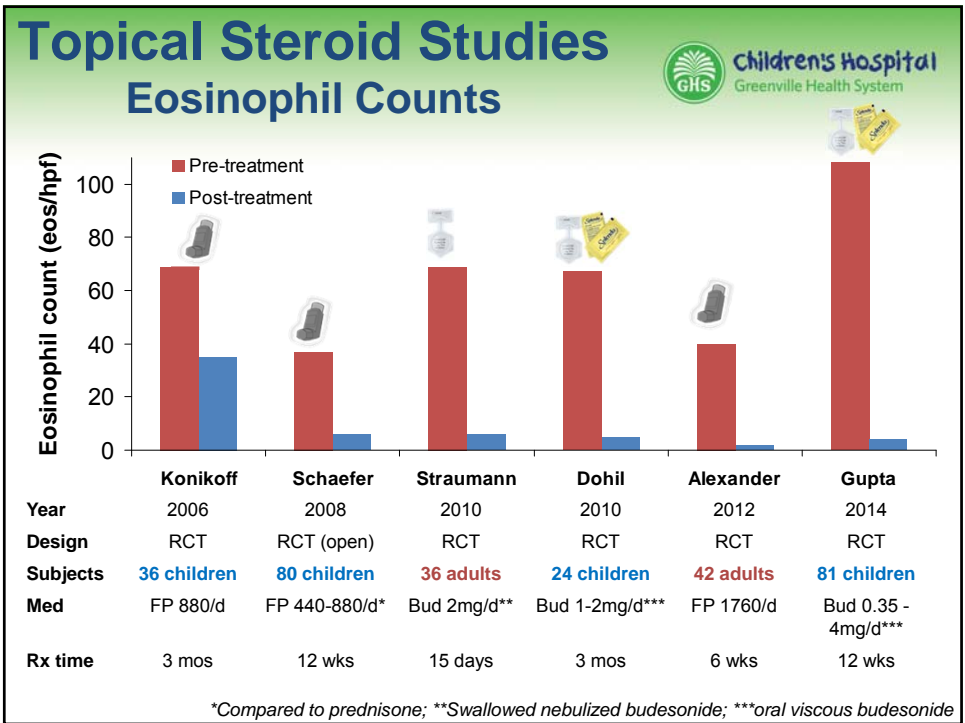


- All patients diagnosed with EoE need PPI trial
  - **Option A:**
    - Treat symptoms with PPI before EGD
    - Perform EGD if symptoms do not resolve
      - If findings are consistent with EoE, diagnosis is confirmed
      - Would not know whether PPI-REE is present
  - **Option B:**
    - Perform EGD before treatment
    - If findings suggest EoE, treat with PPI
      - High dose, 8 weeks
    - Repeat EGD at end of treatment
      - If still looks like EoE, diagnosis is confirmed
      - If findings resolve, PPI-REE is confirmed
- If PPI-REE is diagnosed, ongoing treatment with PPI is needed
  - Patients with PPI-REE should not be given corticosteroid or dietary therapy




## Topical Steroids for EoE


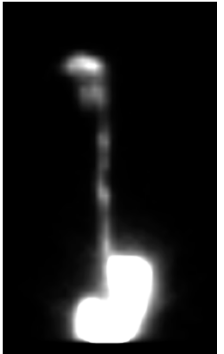
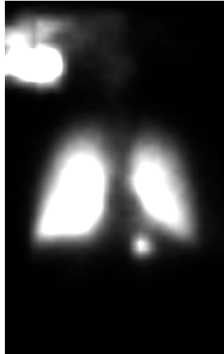
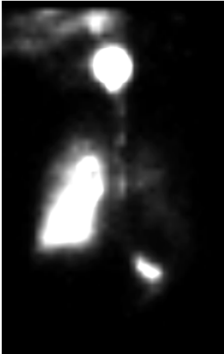
- Fluticasone from MDI  (swallowed, not inhaled)
- Budesonide in slurry form  (respule + “thickener”)
- Advantages:
  - Relatively easy to administer
  - Minimal systemic absorption
  - Minimal side effects:
    - Esophageal candidiasis (not necessarily candidal esophagitis) in up to 20%
    - Growth impairment, adrenal suppression remain concerns



## Viscous Budesonide: Prolonged Mucosal Contact

 **Children's Hospital**  
Greenville Health System


OVB static images                      NEB static images

|   |   |  |   |
|---|---|--|---|
| Patient 1:  | Patient 2:  | Patient 3:   | Patient 4:  |
|  |  |  |  |

OVB=Oral viscous budesonide  
NEB=nebulized (inhaled-aerosolized)

Dellon et al. *Gastroenterology*, 2012.

## Topical Steroids for EoE Summary

 **Children's Hospital**  
Greenville Health System

- Effective in most patients
- Viscous/slurry solutions may be more effective than aerosolized (from inhaler)
  - If parents dislike using Splenda® (sucralose), Neocate® Nutra is as effective as an alternative Rubenstein et al. *JPGN* 2014.
- Response may not be complete
  - EGD should be performed to confirm
- Steroids are only effective as long as they are taken
  - Disease relapses off of treatment

## Who Should Get Steroids As First-Line Therapy?



- Highly symptomatic (severe)
  - Significant dysphagia
  - Food impactions
  - Can be used as a bridge to dietary therapy
- Unwilling to consider dietary therapy

## Dietary Elimination



- 1. Empiric:** selecting the most likely antigenic triggers
  - **6FED**-eliminates the top allergens in U.S.--milk, soy, egg, wheat, peanut/tree nut, fish/shellfish
  - **4FED**-eliminates milk, soy, egg, wheat
  - **1FED**-eliminates milk
- 2. Allergy test-directed:** based on results of allergy testing
  - Requires specialized testing to increase accuracy
- 3. Elemental:** remove all foods and use just an amino acid-based formula
  - Most effective, most life-altering

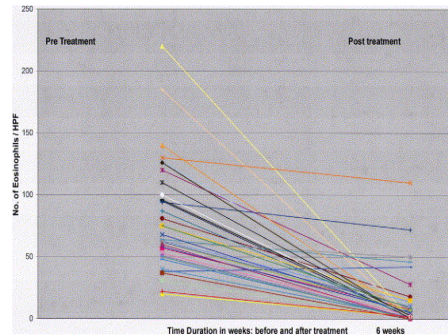


## Empiric Food Elimination is Effective in Children



### Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis

- 35 children on 6 weeks of SFED:
  - 74% histologic response (<10 eos/hpf)
  - Peak eosinophils dropped from 80.2 to 13.6 eos/hpf

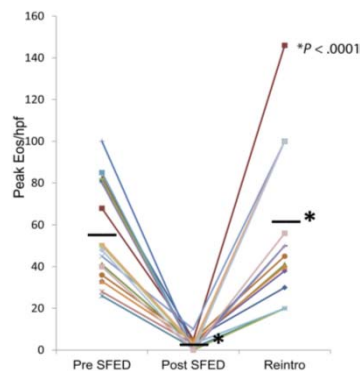


Kagalwalla, et al. *Clin Gastroenterol Hepatol*, 2006.

## Six Food Elimination Diet is Effective in Adults




### Diet effectively treats eosinophilic esophagitis in adults; Food reintroduction identifies causative factors



Gonsalves N et al. *Gastroenterol*, 2012.

- 50 adults with EoE managed with SFED
  - 70% histologic response (<10 eos/hpf)
  - 94% symptom response
  - Recurrence of symptoms with food reintroduction (n=20 patients)
- Most common foods: milk and wheat
- Skin prick testing not predictive

## Less restrictive options? 4 and 1 food elimination diet



**Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study**

Javier Molina-Infante, MD,<sup>a</sup> Angel Arias, MSc, BSc,<sup>b</sup> Jesus Barrio, MD,<sup>c</sup> Joaquin Rodriguez-Sánchez, MD,<sup>d</sup>  
Marta Sanchez-Cazalilla, MD,<sup>e</sup> and Alfredo J. Lucendo, MD, PhD<sup>e</sup> *Caceres, Ciudad Real, Valladolid, and Tomelloso, Spain*

- n=52 adults eliminated dairy, wheat, eggs, legumes
- **54%** response rate (< 15 eos/hpf)


**Cow's Milk Elimination: A Novel Dietary Approach to Treat Eosinophilic Esophagitis**

*\*Amir F. Kagalwalla, \*Katie Amsden, \*Ameesh Shah, \*Sally Ritz, \*Maria Manuel-Rubio, \*Katherine Dunne, †Suzanne P. Nelson, \*Barry K. Wershil, and †Hector Melin-Aldana*

- n=17 children eliminated cow's milk only
- **65%** response rate ( $\leq$  15 eos/hpf) with **41%** "complete remission" (0-1 eos/hpf)

Molina-Infante et al. *JACI*, 2014; Kagalwalla et al. *JPGN*, 2012.

## Allergy Test-Directed Dietary Elimination



- An alternative approach to empiric elimination and elemental diets
- Based on identification of specific food antigens responsible for EoE
  - Involves both **IgE-** and **non-IgE-mediated** allergies
  - Utilizing multiple types of allergy testing that may offer improved results
    - Combination of **skin prick testing (SPT)** and **atopy patch testing (APT)** necessary to get reasonable remission rates

## Atopy Patch Testing (ATP) Children's Hospital Greenville Health System

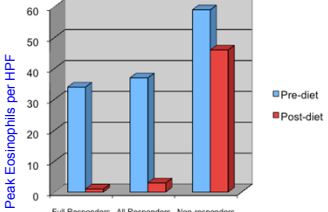
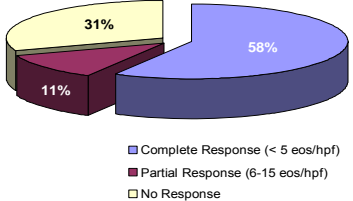


Finn Chambers




## Using Allergy Testing to Guide Dietary Elimination Children's Hospital Greenville Health System


- 64 pediatric patients with EoE underwent SPT and ATP testing
  - Repeat EGD 6 weeks after starting restrictions
- 58%** partial remission
- 11%** complete remission
- Results comparable to empiric elimination diets



Markowitz JE. *J Pediatr Gastroenterol Nutr.* 53(S1) 2011.

## Limitations to Elimination Diets






"Oh boy! ... It's dog food AGAIN!"

- Difficult to implement
  - Patients need instruction on reading labels, avoiding inadvertent exposure & creating nutritionally adequate diet with allowable foods
- Difficult to maintain long-term
  - Process of identifying food antigens can be long
  - Restrictive diets may be tedious
- May be overly restrictive or not restrictive enough
- May place at risk of nutritional deficiencies
  - Should monitor nutritional status
  - Co-manage with dietitian
  - May need supplemental amino acid-based formula to fill nutritional gaps


## Elemental Diet: Amino acid-based formula



- Exclusive feeding of amino acid-based formula (AAF)
- Up to 97% response rate\*
- Advantages:
  - Most effective of any published therapy
- Disadvantages:
  - Most life-altering
  - May require NG or gastrostomy feeds
  - Cost (if paid out of pocket)
    - Increasing state legislative mandates for AAF coverage

\*Markowitz J et al. *Am J Gastroenterol*, 2003.  
\*Liacouras C et al. *Clin Gastroenterol Hepatol*, 2005.


## Elemental Diet for Pediatric EoE

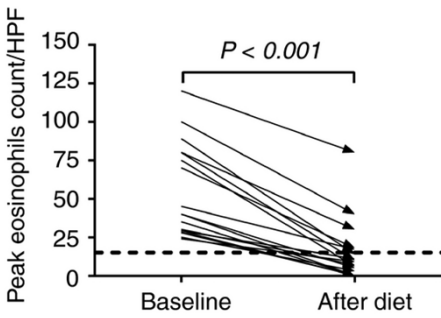


|                            | Pre-diet  | Post-diet | P-value |
|----------------------------|-----------|-----------|---------|
| <b>Eosinophils per HPF</b> | 33.7±10.3 | 1.0±0.6   | < 0.001 |
| <b>Abdominal Pain</b>      | 40        | 2         | < 0.01  |
| <b>Vomiting</b>            | 36        | 1         | < 0.01  |
| <b>GER Symptoms</b>        | 51        | 2         | < 0.01  |

Markowitz et al. *Am J Gastroenterol*, 2003.

## AAF Diet is Effective in Adult EoE





- **94%** (16 of 17) showed response to diet
  - **71%** (12 of 17) adult patients had complete remission
- **88%** (15 of 17) had complete symptom response
  - Symptoms improved in **all** patients

Warners, MJ et al., *Alimen Pharmacol Therapeutics*, 2017.  
<http://onlinelibrary.wiley.com/doi/10.1111/apt.13953/full#apt13953-fig-0002>

## Reintroduction of Food After Elemental Diet



- Once remission is achieved, foods can be reintroduced
  - If symptoms develop, food is discontinued
    - Once symptoms resolve, move on to different food(s)
  - If no symptoms develop, repeat EGD to exclude histologic relapse
    - Can introduce multiple foods per trial (usually introduce one food sequentially about every ~2 weeks)
    - Usually wait 6-8 weeks for EGD after last food introduced
      - Must balance risk of abnormal EGD with risk of performing more endoscopies

## Limitations of Elemental Diet




- Most life altering
- No other foods for duration of the trial—usually 4 to 6 weeks
  - Sometimes allow non-antigenic foods (simple sugars, artificial flavors)
- While palatability of AAFs has improved significantly, must take significant volume to maintain adequate caloric intake
- While AAFs are nutritionally complete, micronutrient deficiencies should be considered
  - Monitor height, weight, lab work
- It can take many months or longer before enough food trials to significantly reduce AAF volume

## Steroids vs. Dietary Therapy


**Steroids**

- Relatively easy
- Relatively few side effects
- No allergy testing needed
- Incomplete remission
- Requires long-term medication
- “Band-aid” approach



**Diet**

- Can be difficult
- No “side effects”
- May require allergy testing
- Complete remission
- No need for medications
- Addresses the underlying “root cause” of the disease



## Long-Term Cost of Steroids vs. Diet



- Initial cost of steroids may be cheaper than dietary elimination (6FED)
- After ~1 year, elimination diet becomes more cost-effective than steroids
- For elemental diet, initial costs are marginally higher than steroids
- Over time, cost of steroids does not decrease considerably
  - Cost of diet therapy tends to reduce as foods are successfully reintroduced to diet


Cotton et al. *Gastroenterology*. 2015 Apr; 148(4)S1:S-2.  
Manuel-Rubio et al. *JPGN* Sept 2015; 61(S-2).



## Empiric vs. Directed Dietary Therapy


**Empiric**

- No allergy testing needed
- Multiple options: (6FED, 4FED, 1FED)
  - The more restrictive, the better the likelihood of response
- Each option restricts dietary “staples”
  - Still lots of kid-friendly foods (meats, fruits, vegetables) are allowable




**Directed**

- Relies on allergy testing
  - Highly dependent on allergist
- May bypass elimination of some dietary “staples”
  - Although almost always includes milk restriction



## EoE Management Choices Vary By Center

- Comparison of initial management choices in pediatric patients across academic and community allergy and gastroenterology practices in the Carolinas
  - Steroids as initial management choice varied from **86% to 1%**
  - Diet as initial management choice varied from **2% to 81%**
  - Elemental diet as initial management choice varied from **0% to 6%**



Huang et al. *Gastroenterol.* 150(4):S1:S669.



## Who Should Get Dietary Therapy as First-Line Management?



- Any patient with EoE
  - Must be willing to restrict their diet
- When highly symptomatic, may need additional initial management option
- Type of dietary elimination will depend on resources available to the patient and to their health provider
  - If no dietitian available, provider should be comfortable monitoring nutritional status
  - If allergist not comfortable with APT (patch) testing, empiric elimination may be better option

## Efficacy of Initial Management Options



- Topical steroids:
  - ~75% histologic response (may be dependent on dose and delivery method)
  - Does not necessarily mean no dietary restrictions
- Empiric diet elimination:
  - Up to 75% histologic response (SFED)
  - Less restrictive diets with lesser response
- Allergy testing-directed elimination:
  - Up to 70% histologic response
  - Requires combination SPT/APT
    - Response maximized by empirically including milk restriction
- Elemental diet:
  - Up to 98% histologic response

## How I Approach Initial Management



- Confirm diagnosis
  - Try not to perform EGD until adequate trial of PPI (high dose)
  - If has not had adequate PPI trial, start PPI and plan on repeat EGD to confirm eosinophilia persists

## How I Approach Initial Management



- Once diagnosis is confirmed, start treatment
  - If **severe** symptoms (dysphagia, weight loss, food impactions), consider temporary topical steroid use
  - If mild symptoms, refer to allergist for testing to assist in directing elimination diet
    - Often suggest restriction of milk +/- wheat pending allergy testing

## How I Approach Initial Management



- Working with allergist, identify foods to target for elimination
  - Experience of allergist is important
    - False positives and false negatives are common
    - Reading tests, in particular patch tests, can be subjective
  - Usually eliminate milk regardless of results of testing
    - Allergy testing for milk in EoE is notoriously inaccurate
    - Milk is most common food trigger
  - Arrange for visit with dietitian to review diet and assess nutritional needs in detail
    - If extensive food allergies identified, recommend supplementation with amino acid based-formula to maintain adequate nutritional intake
    - Younger children commonly need supplemental formula

## How I Approach Initial Management

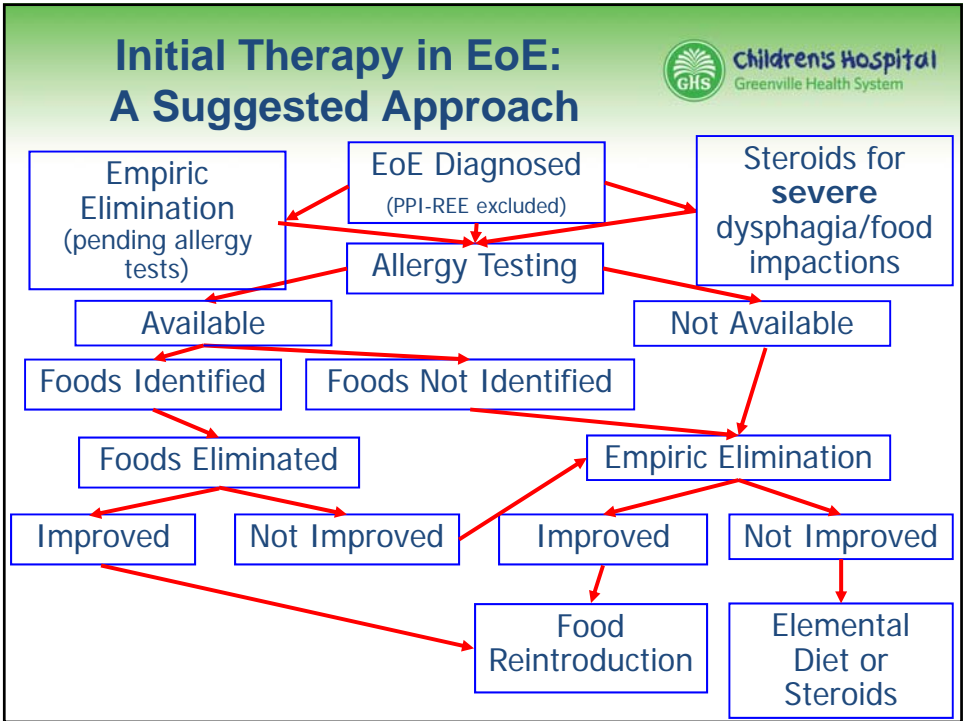



- If allergy testing is negative, start empiric therapy
  - Usually 4 or 6 food elimination diet
  - Meet with dietitian; assess AAF need
- Once dietary therapy is started, discontinue use of steroids (if started)
- Schedule repeat EGD approximately 6 weeks after starting dietary therapy
  - If in remission, can attempt food reintroduction
  - If not in remission, adjust diet further

## How I Approach Dietary Management




- If unable to achieve remission:
  - Consider elemental diet
  - Consider steroids
- Once new treatment started, schedule repeat EGD to confirm remission
- Once in remission:
  - Start food reintroductions
    - EGD to follow





## QUESTIONS



**Registered Dietitians and Nurses interested in obtaining a  
Certificate of Attendance for 1 CEU credit please visit:**  
<http://www.NutriciaLearningCenter.com>

**Information needed:**  
Event code = GWSEOE2  
Event date = 2.23.17