Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE

Overview

Mirna Chehade, MD, MPH, reviews long-term nutritional strategies and medical management for pediatric patients with Eosinophilic Esophagitis (EoE). Dr. Chehade specifically discusses the immunopathogenesis of EoE; identifies EoE clinical manifestations in pediatric patients; distinguishes EoE from other causes with similar symptoms, such as gastroesophageal reflux disease; reviews essential diagnosis criteria and histological features; and examines current standard of care and clinical recommendations.

Content Areas

- Recognize clinical presentation of EoE
- Identify common symptoms by age group
- Distinguish phenotypes
- Incorporate nutritional strategies
- Guide dietary therapy

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Section

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Recognize the clinical presentation of EoE in infants, toddlers, children and teenagers
- Explore various dietary and medical management options for pediatric patients with EoE

Faculty

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The estimated time to complete the activity is 1.0 hour.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE

This activity was released on November 9, 2020 and is eligible for credit through November 9, 2022.

Contact Information

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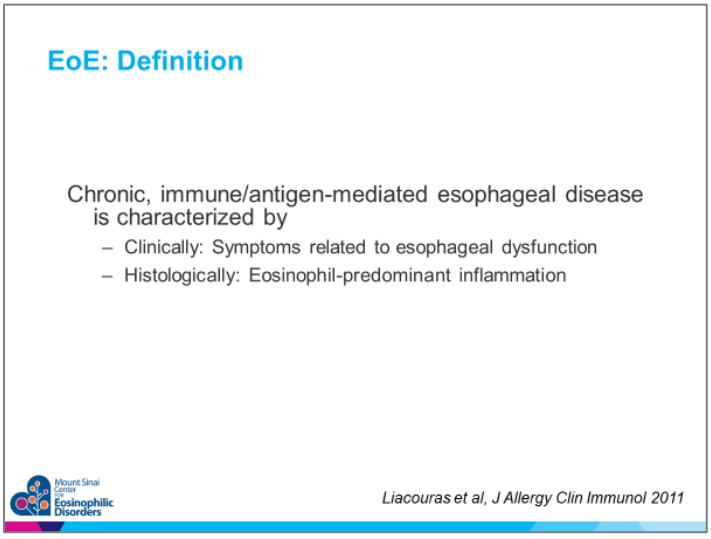
Module 1

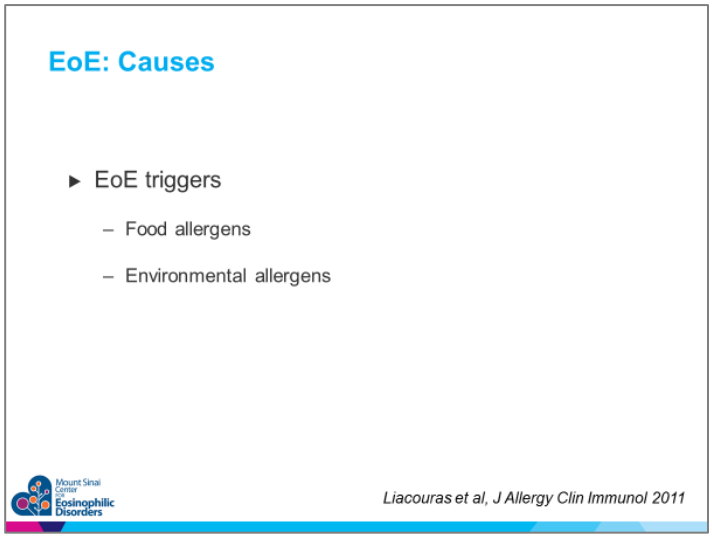
Dr. Mirna Chehade: I will be going over the practical diagnosis and management of pediatric patients with EoE. I'll be referring to eosinophilic esophagitis as EoE for the rest of my talk.

This talk will be divided into 3 modules. Module 1: what we will try to achieve in that module is to define EoE, discuss the etiology of EoE, and to review the immunopathogenesis of EoE.

First, let's start with the definition. EoE is a chronic immune or antigen-mediated esophageal disease that has 2 features. One is clinical symptoms related to esophageal dysfunction, and 2, the histological counterpart, which is an eosinophil-predominant inflammation of the esophagus.

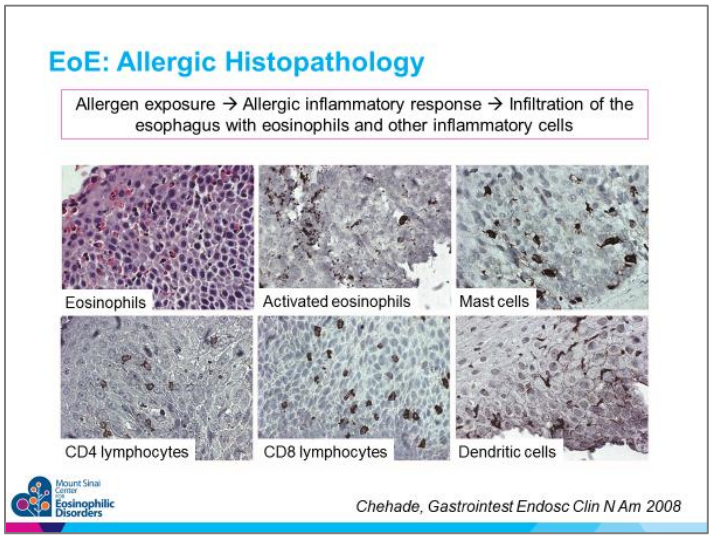


What causes EoE? There are 2 triggers we suspect for EoE. One is food allergens, and there's good evidence now for food allergens based on multiple patients who went on food elimination trials with a change in their EoE disease activity. The evidence for environmental allergens, though, is still debatable. It is so far based on observations of patients with EoE who have a flare-up of their disease during the pollen season.



If we look briefly at the allergic histopathology of EoE, we do find, of course, eosinophils, as you can see on the left upper part of your screen. **The eosinophils are the hallmark of the disease**, and they infiltrate esophageal mucosa. Not only do we see eosinophils, but we also see that the eosinophils are also activated, as you can see here on the slide showing degranulation of the eosinophils by a special stain that we did on the tissue.

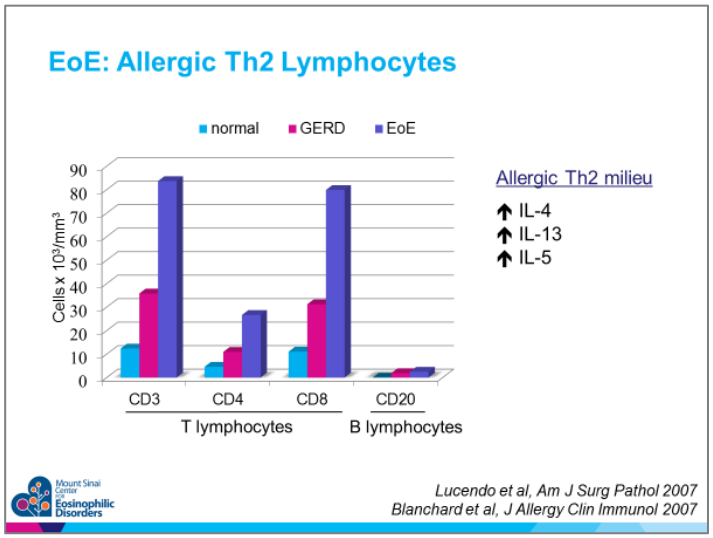
Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



Not only [do] we see eosinophils, but we also see other inflammatory cells, such as mast cells, different types of lymphocytes, the CD4 lymphocytes or the T helper lymphocytes. We have CD8 lymphocytes or T suppressor lymphocytes. We see dendritic cells in the esophagus, as well.

If we take this tissue and replace that epithelium with lung epithelium or skin epithelium, then this would look like the picture we see in other atopic diseases, such as asthma or atopic dermatitis. So far, the allergic, the immune cells do point to an allergic etiology.

What if we look at the lymphocytes now in more detail? This is a study done by Alfredo Lucendo and colleagues out of Spain,[1] where they counted the number of different lymphocytes and the tissue and esophageal tissue of patients with EoE. The light blue bars represent normal. The dark pink is acid-induced reflux disease, and the dark blue is EoE. These are all esophageal tissues of patients.

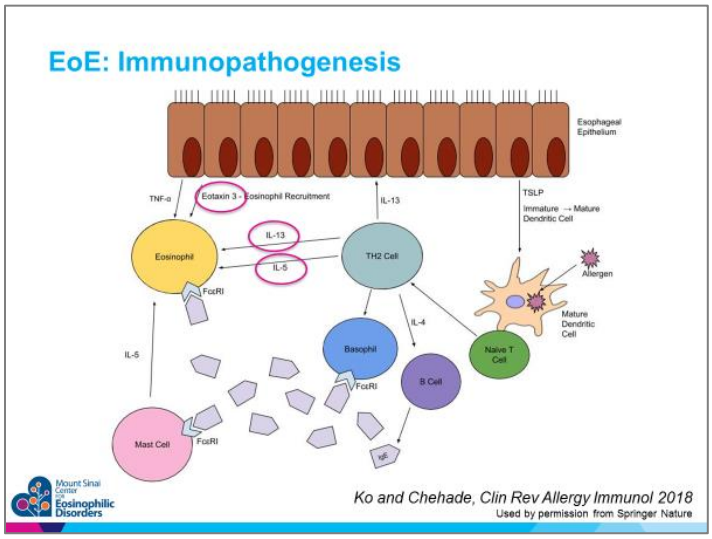


When we count the lymphocytes, we see that B lymphocytes are not that increased in EoE. In contrast to T lymphocytes, which are increased. CD3 represents all T lymphocytes. CD4 T cells represent the T helper lymphocytes, and CD8s are the T suppressor lymphocytes. You can see that the T lymphocytes are increased.

In addition, when we look at the different cytokines in the tissue, in the esophageal tissue of patients with EoE, we see an increase in IL-4, IL-13, and IL-5. All of these are known to be allergic T helper type 2 type of cytokines.

If we put all of this together, this is what we think could be going on. Upon exposure to the food trigger, now the food goes into the esophageal mucosa. It's taken up by dendritic cells that will transform the naïve T cells into a Th2 allergic type of lymphocyte.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



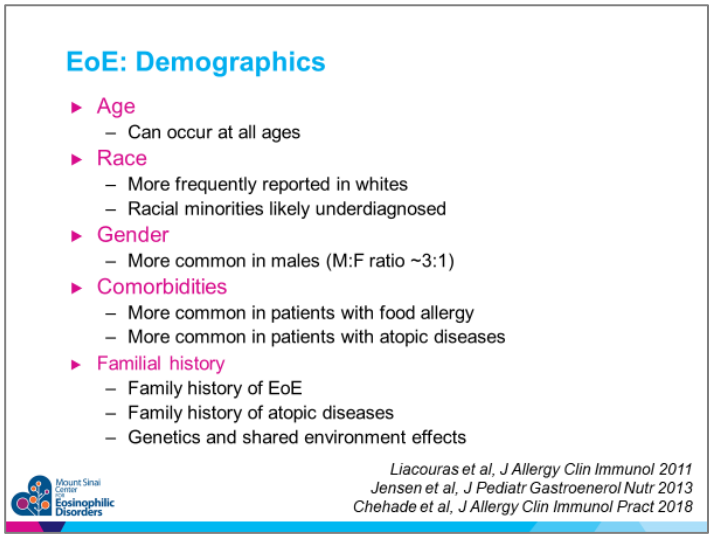
Now, this results in secretion of IL-4, an allergic cytokine, as well as IL-5. IL-5 is responsible for eosinophilic proliferation on migration to the esophagus. The Th2 cell also produces IL-13, which induces the esophageal epithelial cells to secrete eotaxin-3, which in turn also results in eosinophilic proliferation and chemotaxis to the esophagus.

Module 2

What about clinical, now that we understand the cause and the immunopathogenesis of EoE with established allergic disease caused by food triggers and potentially by environmental triggers? Who are the patients that develop EoE, and how [do we] diagnose it? In this module, Module 2, we will go over the demographics of EoE, how to diagnosis EoE, and we'll go over also the natural history of EoE if left untreated.

First demographics: Who are the patients that are likely to develop EoE? In terms of age, EoE can occur at all ages, anywhere from infancy, all the way to adulthood. In terms of race, EoE has been more frequently reported in whites, but racial minorities are likely underdiagnosed.

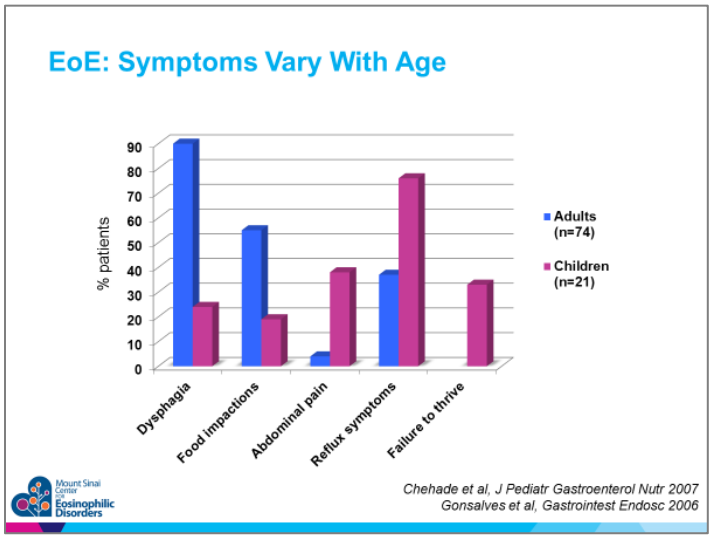
In terms of gender, EoE seems to be more common in males than females, with a male-to-female ratio of 3:1. EoE also tends to be more common in patients with atopy. EoE is more common in patients with food allergy. By food allergy, I mean IgE-mediated immediate type of food allergy. It's also more common in patients with atopic diseases, whether we're talking about asthma, allergic rhinitis, or atopic dermatitis.



Importantly, there's also familial history in some patients with EoE. In some patients with EoE, we'll find family history of EoE, or family history of atopic diseases, in general. We also think there's a genetic component to this familial history, as well as potentially shared environmental effects.

How to diagnose EoE. EoE in children is tricky. We have to be careful because the symptoms do vary with age. To illustrate this, I would like to refer you to this graph where under y axis, you see percentage of patients, and on the end x axis, you see the different symptoms. If we look at the blue bars, those represent adults and the dark pink bars represent children.

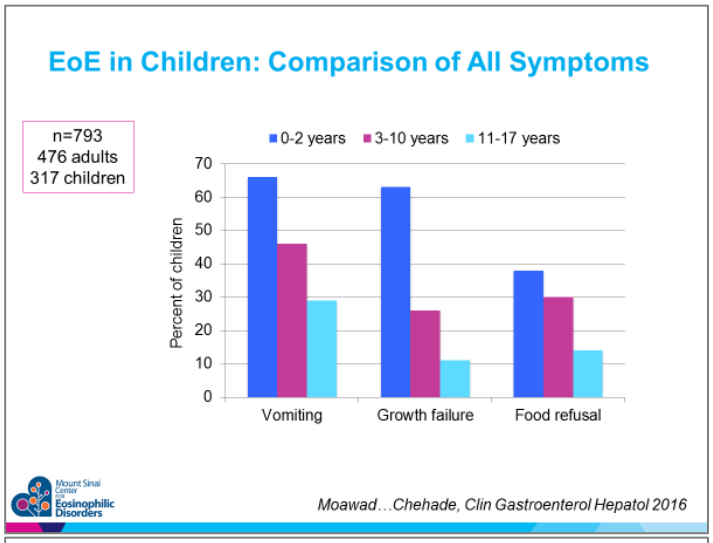
Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE

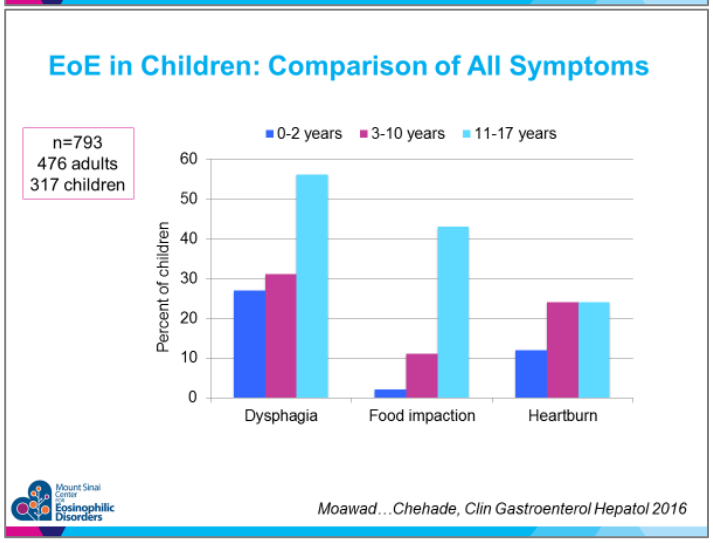


As you can see from the blue bars, adults present mostly with dysphagia, or trouble or difficulty swallowing the food, as well as esophageal food impactions, where the food gets stuck in the esophagus. Some of them also present with reflux symptoms.

Now, if we focus on the pink bars, representing children, you can see this is not the case. Most children present with abdominal pain, reflux symptoms, including vomiting, and less so with dysphagia and food impactions. Note that little bar to the right of your screen, which is very important, which is failure to thrive. Up to 30% of children with EoE present with failure to thrive. Luckily, this is reversible once you take care of this patient and treat adequately.

If we take those symptoms a little bit further and dissect this gradation, or this difference, which is important when we're talking about the age of the child, the answer [is] yes. We do have a difference as the child gets older. This is a multicenter study that we have conducted recently where the lead investigator was Fouad Moawad,[2] who was at the Walter Reed Army [Medical Center] at the time.





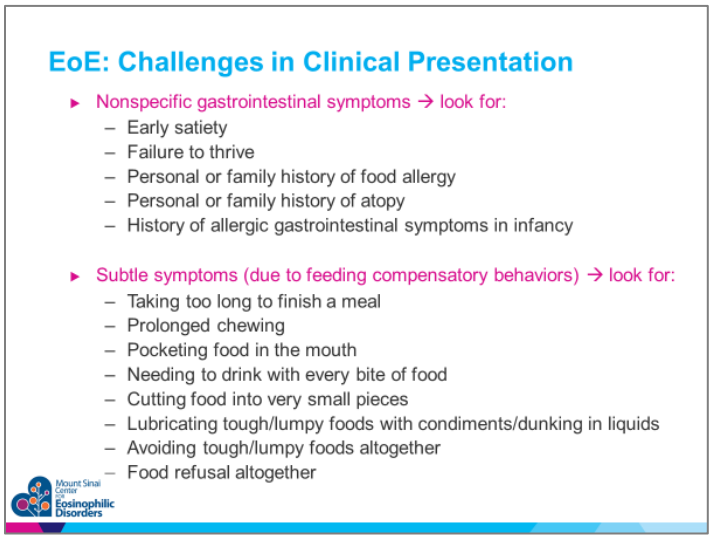
What we did here—we took 793 patients, and 317 of whom were children. Here again, we have y axis percent of children. On the x axis, you see the symptoms. Dark blue represents 0 to 2 years of age. The pink is 3 to 10, and the light blue is 11- to 17-year old patients.

As you can see, as we have older children, we had less of the vomiting, growth failure, and food refusal and more so of dysphagia, food impaction and heartburn. These are the symptoms, now, that look more and more like the adults.

This differentiation is very important, as the younger the patient you are facing, the more

nonspecific the GI symptoms are. This will pose some challenge for you in the office, or when you are facing a patient or a child with EoE. What are the challenges you will face, potentially, and what to look for so you do not miss a child with EoE?

I summarized 2 of them here in this slide. One is the fact that we have children, or most children, [who] have nonspecific gastrointestinal symptoms. To be able to differentiate EoE from a sea of different diseases presenting that way, look for the following: Early satiety, failure to thrive, personal or family history of food allergy, personal or family history of atopy, and history of allergic gastrointestinal symptoms in infancy.



What do I mean by that? For example, if the child had a history of blood in the stool when they were infants, and responded to a hypoallergenic formula instead of a cow's milk-based formula, that patient could have had an allergic GI manifestation in infancy. That patient, which is here [with] another red flag to suspect EoE.

The other problem, or challenge, in identifying children with EoE is that sometimes you have subtle symptoms due to feeding compensatory behaviors. Remember, EoE is a chronic disease, and it smolders very slowly where you have progression over time. Patients do develop compensatory feeding behaviors.

For example, we look for things. If you ask the patient or the parent, "Is there trouble swallowing?" They may say no. Next, you have to ask a few other questions. For example, taking too long to finish a meal. Does the child take too long to finish a meal? Does the child have prolonged chewing? Does the child pocket food in the mouth? Is there any need to drink with every bite of food? Does the child cut foods into very small pieces? Do they need to lubricate tough or lumpy foods with condiments or dunk them in liquids? Or do they avoid tough or lumpy foods altogether, or refuse certain foods all together?

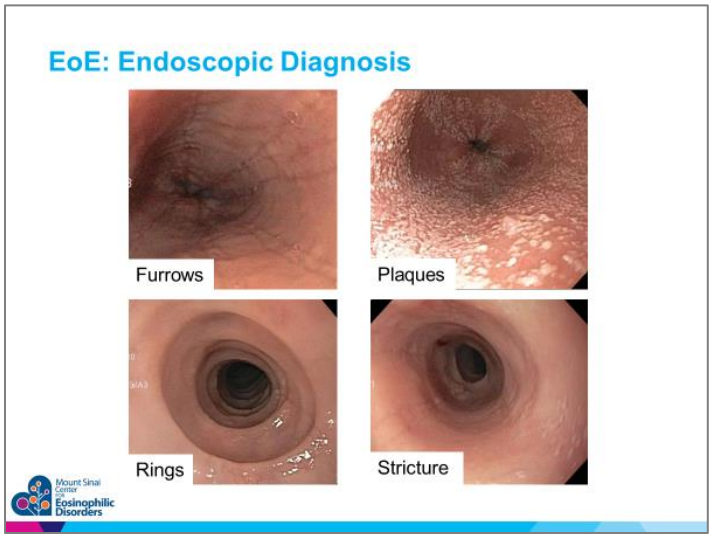
What happens is that with adults, they'll tell you. I may avoid meat, or I may avoid dense breads, if I have EoE. With a child, they may not be able to differentiate which foods are the problem, which ones are not. They may generalize and start avoiding foods across the board.

The other thing is that it's important to ask them, “What do you like to eat?” For example, I always ask, "Can you handle a bagel?" If they say yes, then do not stop there. Ask, "How do you eat it? Do you add any condiments? Do you always add some cream cheese?" This is just one out of many examples you could ask and adapt according to what your patient eats on a regular basis.

Now that we know what to ask in terms of symptoms, how do we diagnose it? The diagnosis still rests on an endoscopy with esophageal biopsies. These are examples here of what you could see on an endoscopy.

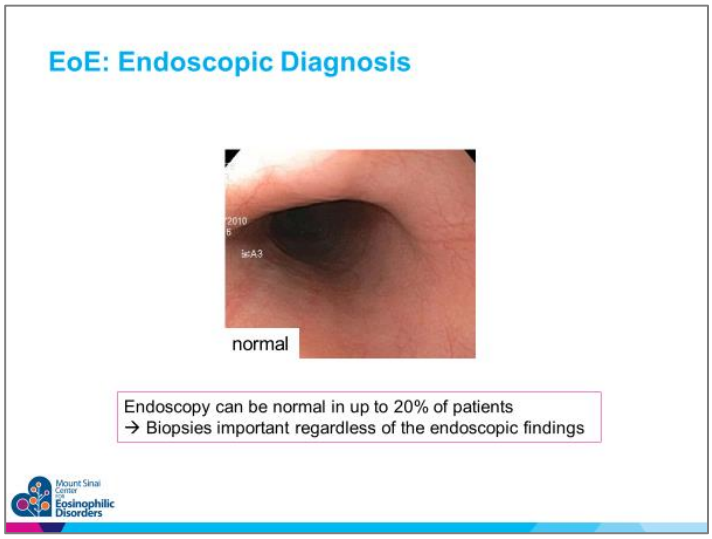
As you can see on the top left panel, there are furrows that go down the links of the esophagus. Or

you can have plaques. All of these white dots that you see here on the right top panel, and these are not due to a candida infection of the esophagus. These are a collection of eosinophils that go up to the surface lining causing this appearance.



Sometimes you could have rings, as you can see in the lower left panel. That is an appearance that's also referred to as trachealization of the esophagus. If you look at this esophagus, it does look like a trachea, doesn't it? Then you sometimes have patients with severe disease, who have a stricture, as seen here in the lower right panel, which is a rare problem in the pediatric population.

Now, an important thing to keep in mind is that endoscopy can be completely normal in 20% of patients. That emphasizes the importance of taking biopsies regardless of the endoscopic findings. If we see a normal mucosa, if you're suspecting EoE, biopsies are really important. It is a patchy disease; therefore, multiple biopsies are important so that the diagnosis [is] not missed.



Now that we took biopsies, what do we see on those biopsies? This is what a section or a hematoxylin, eosin stain section from a biopsy of a healthy individual would look like, on the left side. You can see here the stratified squamous epithelium. The top part is the luminal part. The lower end of that biopsy is the deep end of the biopsy.

You can see it's all staining blue, and we don't have any eosinophils. That's because, normally, we should have zero eosinophils in the esophagus of a healthy individual without any esophageal disease. Now, on the right-hand side, in contrast, you can see a hematoxylin and eosin stain section from a biopsy of a patient with EoE. You can see all these pink-stained cells infiltrating the esophageal mucosa. By definition, if we have 15 or more eosinophils per high-power field, then this establishes the diagnosis, the histological diagnosis of EoE.

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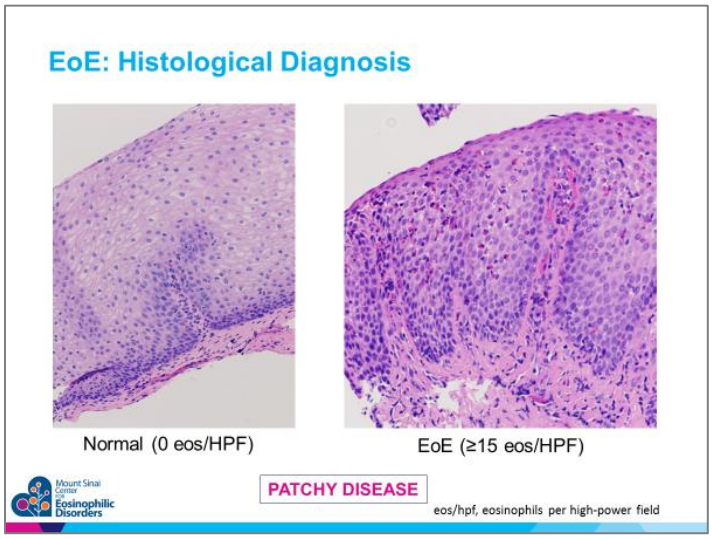
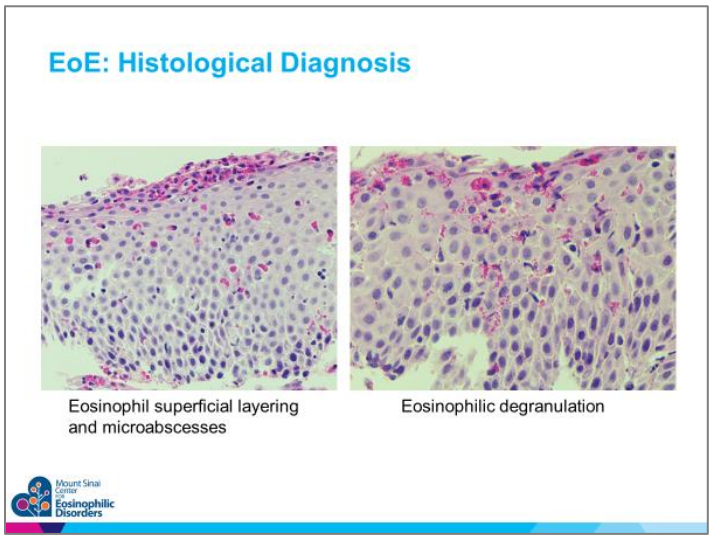
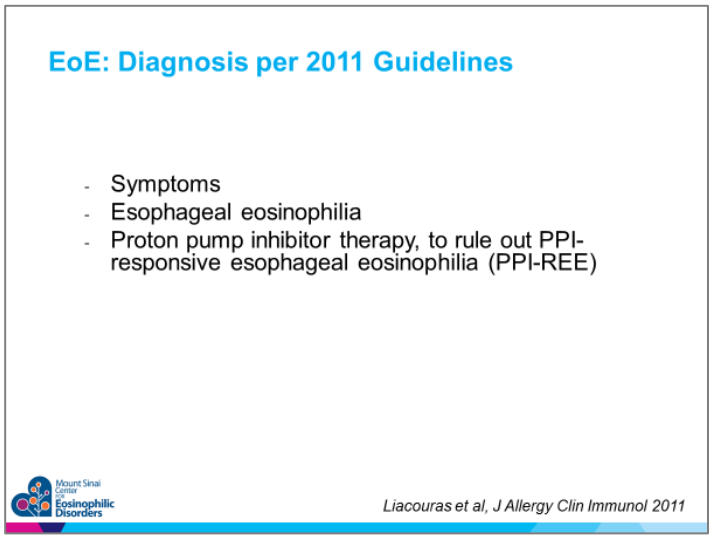


Now, what are those eosinophils doing? Sometimes they go all the way up to the surface layer. Again, I'm showing you here a hematoxylin-eosin stain section. The top part is the luminal part, which is the area where the food or the esophagus [is] exposed to food. The lower part is the deep end of the biopsy.



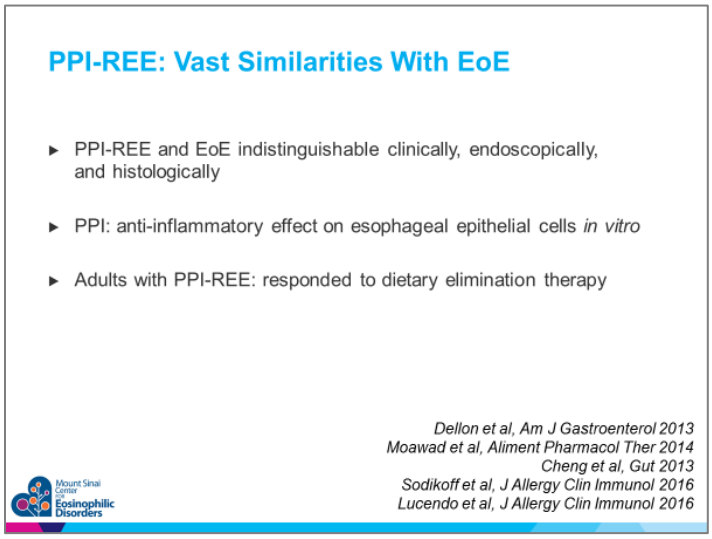
You could see the eosinophils all the way up there, accumulating and layering, causing a microabscess. This is what results in those white plaque appearances that I had shown you in the endoscopy earlier. Now, if you look at the right panel, you could see sometimes degranulation of these eosinophils. As you can see with these little dots right outside the cells, which you can demarcate by the eosin stain. That's another feature that could be present in EoE.

When we have symptoms and we have an endoscopy with a biopsy showing eosinophils, now, we have the diagnosis. Is this the full story? The answer is no. According to the 2011 guidelines,[3] what we needed to diagnose EoE are symptoms, esophageal eosinophilia, and a trial with proton pump inhibitor therapy—proton pump inhibitors being antacids, to rule out PPI-responsive esophageal eosinophilia or PPI-REE. This is because many patients who had symptoms of EoE and the histological features of EoE, interestingly, responded to proton pump inhibitors at high dose. These patients need to be ruled out to confirm the diagnosis of EoE.

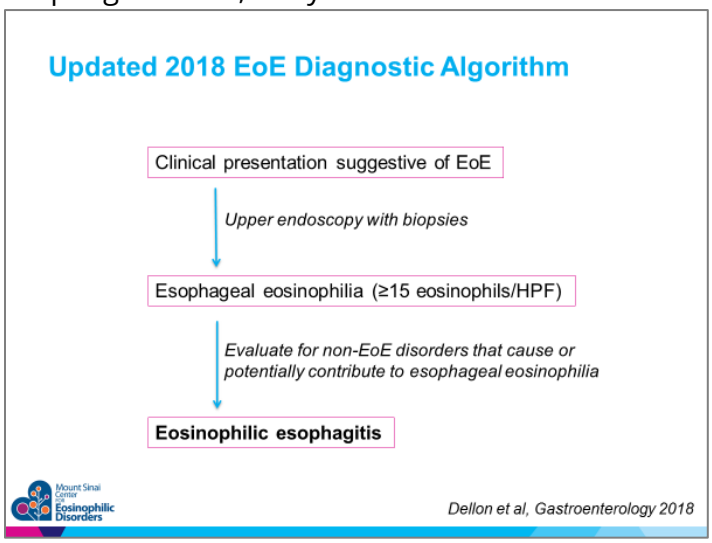


Then research was done since 2011 showing real vast similarities of PPI-REE and EoE. Many studies showed that PPI-REE and EoE were indistinguishable clinically, endoscopically as well as histologically.[4] In addition, Rhonda Souza's lab down in Texas, showed an anti-inflammatory effect of PPI on esophageal epithelial cells in vitro. Then at one report from Spain, another report from Chicago, had shown that adults with PPI-REE can

respond to a dietary elimination therapy that is targeted for EoE instead of a PPI.

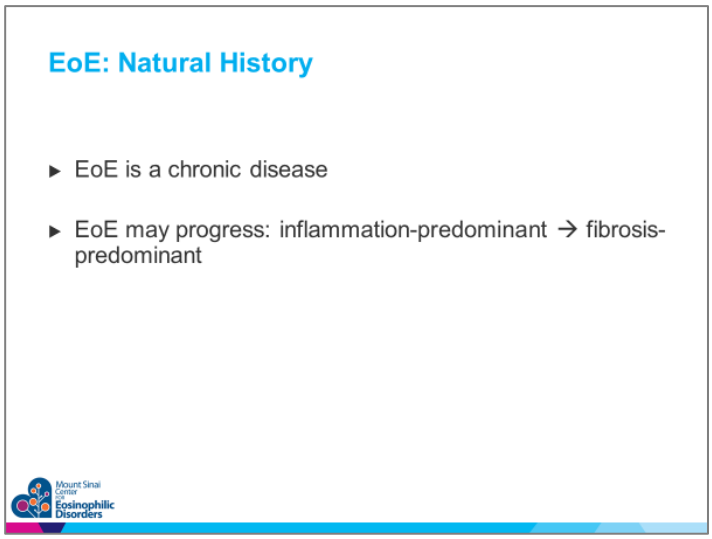


With all this evidence accumulating together, along with the evidence that EoE and reflux can concurrently exist, has led to a very recent update to the EoE diagnostic criteria. These are as follows: if you have a clinical presentation suggestive of EoE and you do an upper endoscopy with biopsies demonstrating esophageal eosinophilia—that's 15 or more eosinophils per high-power field in the esophagus—now, all you need to do is evaluate



for non-EoE disorders that can cause or potentially contribute to esophageal eosinophilia. If these are ruled out, now you have the diagnosis of EoE. In other words, you do not need to use a proton pump inhibitor therapy as an empiric trial to confirm the diagnosis of EoE. PPI is offered to the patient as a treatment option as opposed to a diagnostic test.

What about the natural history of EoE? If we leave it untreated, what happens? We know a little bit about that. We already know that EoE is a chronic disease. It can progress if left untreated from an inflammation-predominant to a fibrosis-predominant disease.



To illustrate this, I'd like to refer you to this study, which is a retrospective study done by Evan Dellon and colleagues, out of North Carolina in 2013, where they took 379 children and adults with EoE.[5] On the graph, you will see the x axis is age of the patient in years. The y axis shows the predicted probability of developing fibrostenosis.

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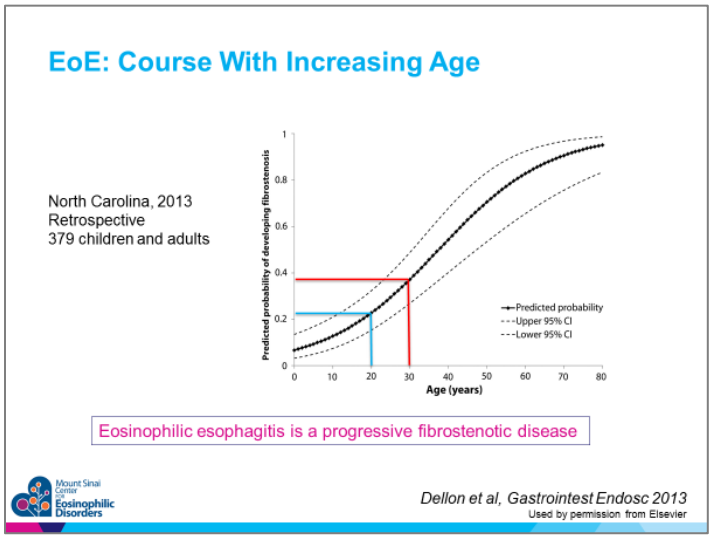
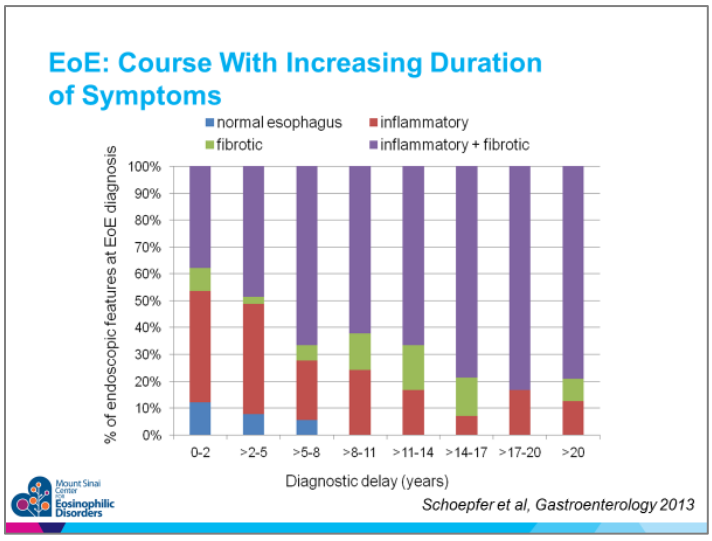


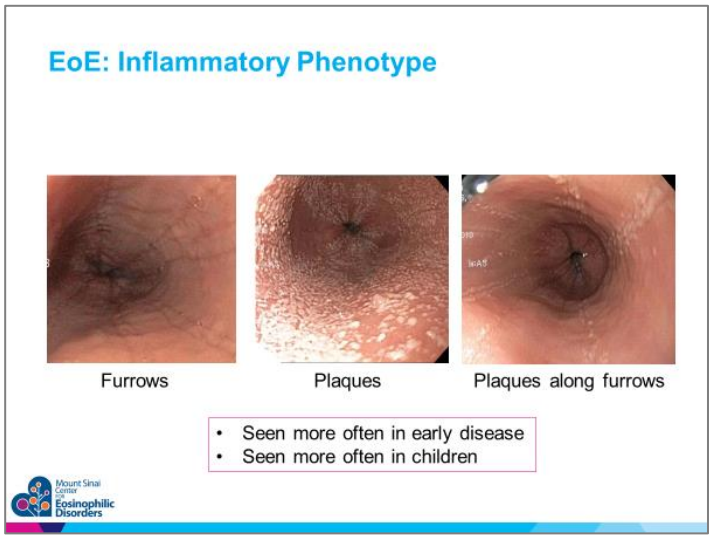
As you can see with the lines that I drew in blue and red, for a 10-year increase in age, the probability of developing fibrostenosis doubles. EoE is a progressive fibrostenotic disease.

To illustrate this even more accurately, I'd like to refer you to this adult study out of Switzerland done by Alain Schoepfer and colleagues[6] where on the x axis, you can see the diagnostic delay in years, which is in other words, a reflection of the number of years a patient had symptoms before they sought medical attention and therapy.



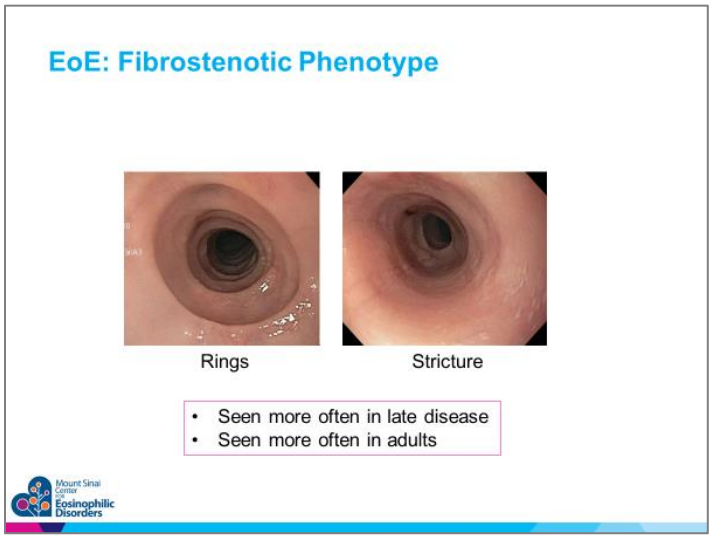
I'd like you to focus on 2 colors in particular: the red bars and the purple bars. The red bars represent inflammatory. The purple bars now represent inflammatory disease plus fibrostenotic disease. You can see that the longer the patients had symptoms before they got treated, the higher chance they had both inflammatory and fibrostenotic features.

What do they look like on endoscopy, those inflammatory and fibrostenotic phenotypes? This is what the inflammatory phenotype looks like. If we go back where we're looking now with the endoscope at the esophagus, furrows, white plaques, which I showed you earlier. Sometimes you can see the plaques lining up along the furrows. These are all representing the inflammatory phenotype, which is seen more often in early disease and seen more often in children.



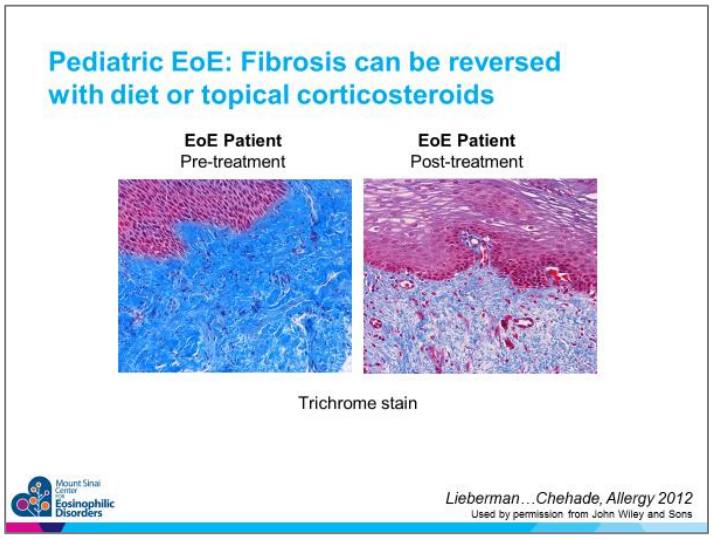
In contrast, the fibrostenotic phenotype is when we start seeing features of remodeling. Rings, which we described earlier, are an example of fibrostenotic phenotype, and a stricture, of course, is due to esophageal remodeling and fibrosis formation, so it falls in that category. These features are seen more often when we have a late disease and, therefore, see more often in the adults whose diagnoses have been missed, if they've had it for a while.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



Luckily in children, fibrosis can be reversed with diet or with topical corticosteroids. This was an impressive result that we did not expect when we did this study, which was published in 2012.[7] With only 3 months of therapy, we were able to see a reversal of the fibrosis.

Just to orient you on the slides, this is now a trichrome stain, as opposed to hematoxylin-eosin stain, of a section of biopsy from a patient with EoE. That's why the colors are completely the opposite of what you saw before. Now, the top part of the slide is the epithelium—the stratified squamous epithelium in red. The bottom part is the collagen, which sits right under the epithelium, and you can see on the left panel, these dense collagen strands forming the fibrosis.



Then literally after 3 months of treatment, you can see now the blue lacy appearance of the collagens after treatment. This emphasizes the importance of treating children with EoE, not only to reverse their symptoms but also potentially reverse long-term complications.

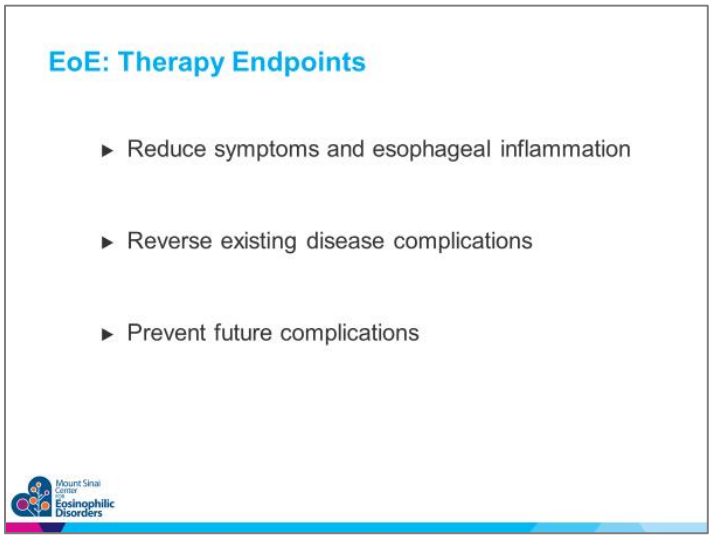
To conclude this module in terms of diagnosis and natural history of EoE, EoE diagnosis is based on clinical, endoscopic, and histological criteria. Symptoms can be nonspecific in children with EoE. That's why we have to learn today the red flags to look for, so you don't miss them. If left untreated, EoE can lead to fibrostenotic complications, hence the importance of treatments.

Module 3

That leads us to Module 3, which is treatment options for EoE. We will be discussing the various treatments, including different diets, as well as medications.

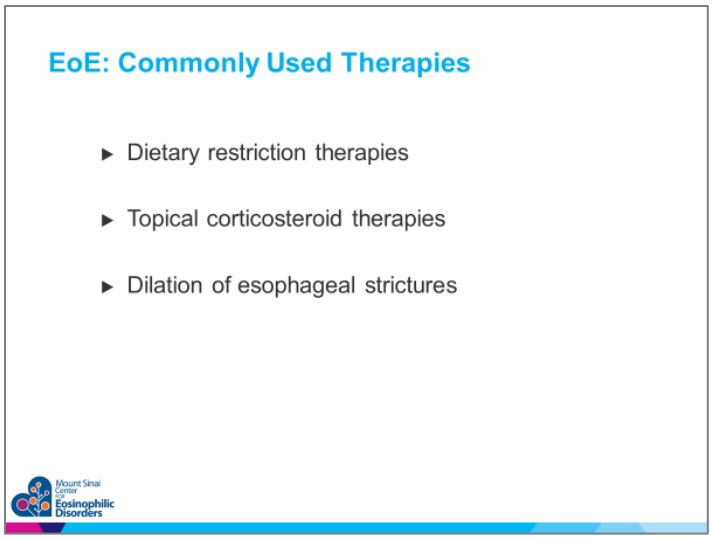
Back to the important part, which is therapy endpoints. What do we need to achieve when we treat? We want to reduce symptoms of esophageal inflammation, we want to reverse existing disease complications, and we want to prevent future complications of EoE.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



What are commonly used therapies? As I mentioned earlier, there's dietary restriction therapies. Topical corticosteroid therapies are commonly used, and another commonly used modality is dilation of the esophageal strictures.

I will not be discussing dilation of esophageal strictures in detail since strictures are not as common in children as in adults. Also, since dilation of esophageal stricture does not help you as an anti-inflammatory treatment; it only breaks down that fibrotic tissue and, therefore, works as a mechanical way to relieve symptoms.



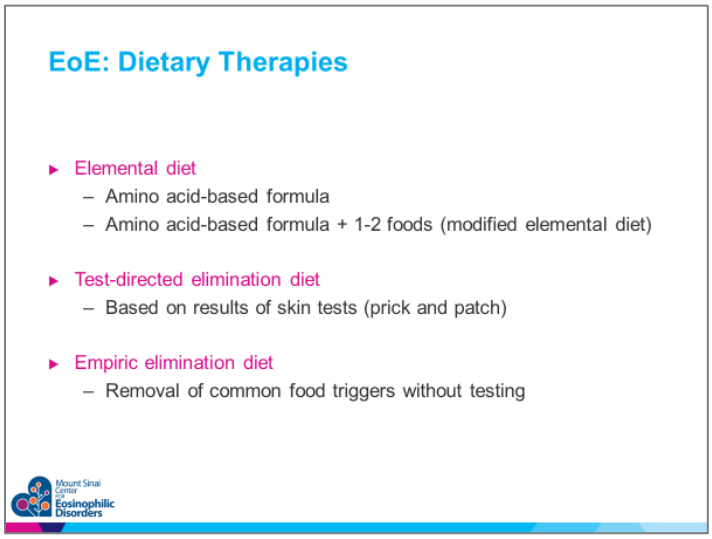
We'll be focusing more on diets and medications. Let's start with dietary therapies. Three different types of diets have been commonly reported, and so far [this] has been accepted as "standard of care." One is the elemental diet, which consists of exclusively feeding of a child with an amino acid-based formula.

There's also a modified elemental diet, which is an exclusive feeding with an amino acid-based formula, but also adding 1-2 foods to the child's diet. That's because if you have a child, and you don't give them any solid foods, after 2 or 3 weeks they will go crazy. So, hence the importance of a modified elemental diet in that case.

The second type of diet is the test-directed elimination diet. That's a diet where you remove the foods based on the results of skin tests to food. Those skin tests include both prick skin tests and patch tests. The third diet is empiric elimination diet, which means we're removing foods that are known to be common food allergens without any testing. Let's go over each and see the efficacy of each diet.

First, we'll look at the histological remission with the elemental diet, which, as I mentioned, means feeding the patient with an amino acid-based formula.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



This is a meta-analysis done by Arias and colleagues out of Spain, which shows you the histological remission that includes all adults in pediatric studies.[8] As you can see highlighted in the red box, the efficacy is 91%. This is not much different between children and adults, surprisingly. Children had a 90% chance of histological remission with the elemental diet.

As you can see, this diet is really effective. The only problem is that it's hard to achieve, even in the motivated patients. But also even in a motivated child or motivated family sometimes it's hard to push the large volumes of amino acid-based formula needed to meet the caloric requirements and, therefore, might result in the use of tube feeding.

Other less restrictive diets have come up as a result. One of them we mentioned is the test-based or test-directed elimination diet, which is again, the diet based on... Or where foods are removed based on the results of prick and patch skin testing.

You can see here a combined histological remission rate of 45% is highlighted in the red box. That's not much different, again, between children and adults. Children had 48% remission rate. Adults even slightly lower with a 32% histological remission rate.

How about the empiric diet where we are not doing any testing, but removing the foods that are known to be common food allergens in the general population? This is, again, the same meta-analysis showing you histological remission to a 6-food elimination diet. What do we mean by 6-food? Six-food means avoidance of milk, wheat, egg, soy, nuts—that's peanuts and all tree nuts—and seafoods—that's fish and shellfish.

We have a combined histological remission rate of 72%, so it did perform slightly better than a test-directed elimination diet. Again, we have results that are comparable, and children [are] having a 73% remission rate and adults 71% remission rate.[9]

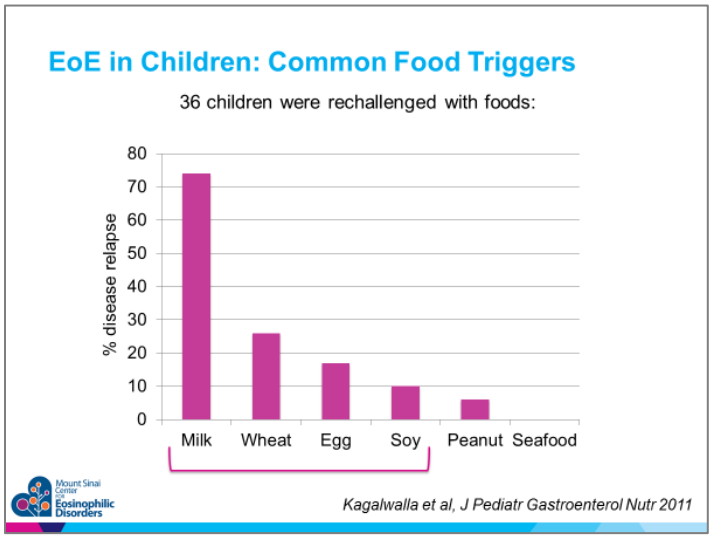
These diets are not easy, even when you are removing 6 foods. This is still very hard on families. We're removing, really, 6 food groups. An attempt was made to see [if] we can reduce the extent of this dietary restriction further. This resulted in the 4-food elimination diet.

How was this born? This was born by having patients that responded clinically and histologically to a 6-food elimination diet. Then we rechallenged to 1 food at a time to establish which are the most common foods among those removed.

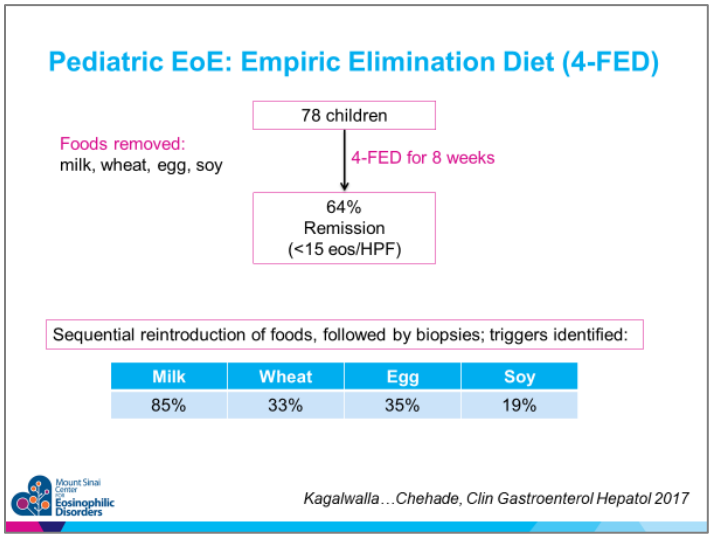
As you can see on this graph, from a study done by Kagalwalla and colleagues,[10] milk, wheat, egg and soy were the most common triggers among the 6 foods removed. This resulted in a prospective study—multicenter prospective study—removing literally those 4 foods from the diet, and the results are shown here.

This is a multicenter prospective study, where 78 children had undergone [a] 4-food elimination diet

for 8 weeks. Foods removed were milk, wheat, egg, and soy, and this resulted in a 64% remission rate.

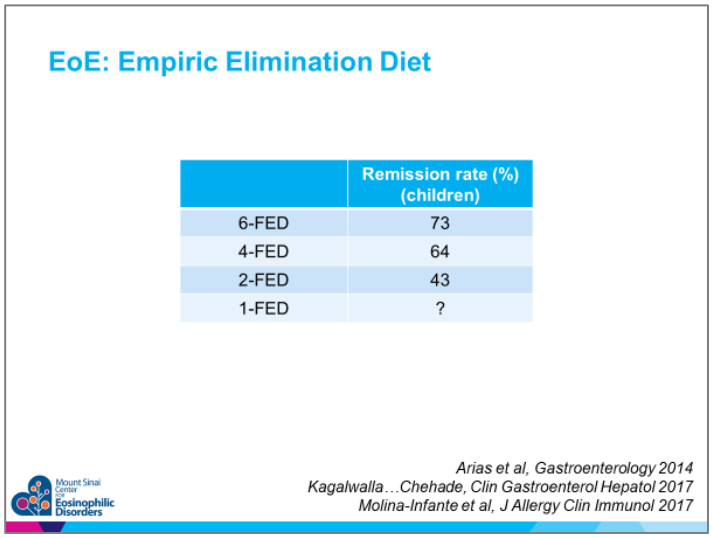


Then what was done with sequential reintroduction of foods, followed by biopsies, and therefore triggers were identified and rated according to which one is more common and which one is the least common. As you can see, milk was the most common food trigger, with 85% of patients having a problem with that food, followed by wheat and egg and then finally soy.



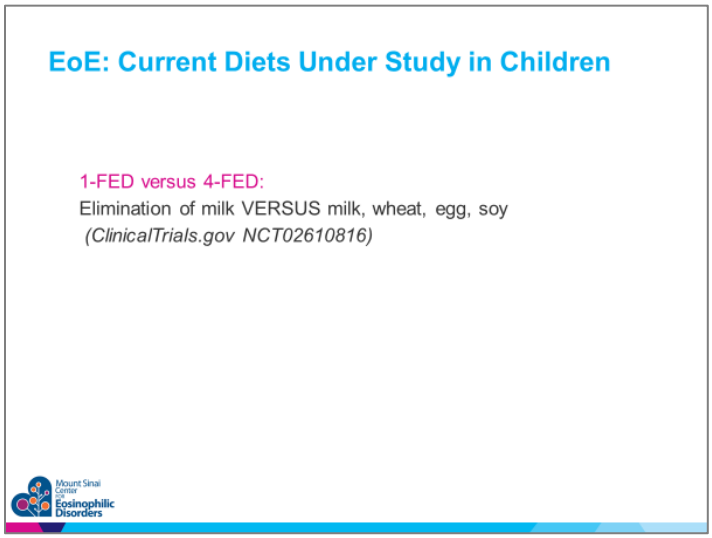
What are the different empiric elimination diets that are currently being used based on all these results in children? These are the 6-food elimination diet.

To recap, with a remission rate in children of 73%. Four-food elimination diet with 64% remission rate. Then we have the 2-food elimination diet. By that, I mean removal of milk and wheat, and that resulted in 43% remission rate.[11]



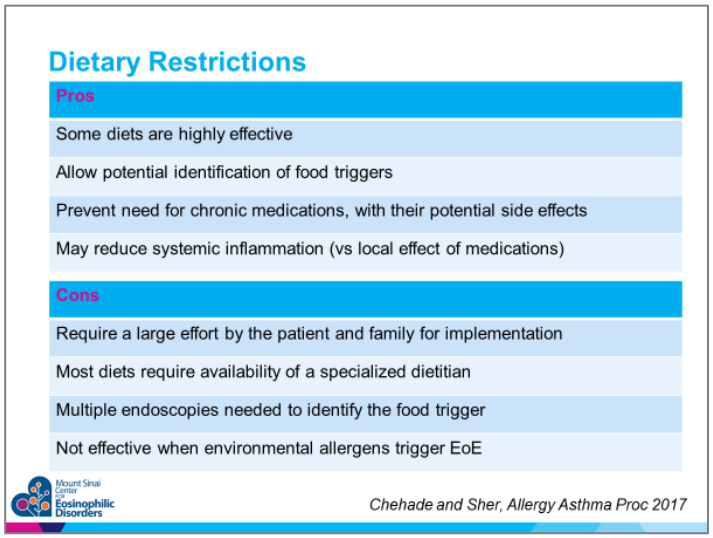
How about 1 food? If we just restrict this now to 1 food, which would be milk elimination only, the remission rate is not yet established. However, this is now a trial, results for which are to be determined, since diet that's currently under study in children is the 1-food vs 4-food elimination diet, which means elimination of milk vs elimination of milk, wheat, egg, and soy. What I listed here is the ClinicalTrials.gov identifier number if you'd like to look at it more.[12]

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



What are the pros and cons of dietary restrictions? A pro is that some diets are highly effective, as you saw earlier. They also allow potential identification of the food triggers in a patient. They also prevent the need for chronic medications with their potential side effects. They also may reduce the systemic inflammation vs local effect of the medication.

Cons: those diets require a large effort by both the patient and the family for their implementation. Most of these diets do require the availability of a specialized dietitian to help them. Also, multiple endoscopies are needed to identify the food triggers. And these diets are not effective when we are suspecting environmental allergens to trigger EoE on top of the food elimination.

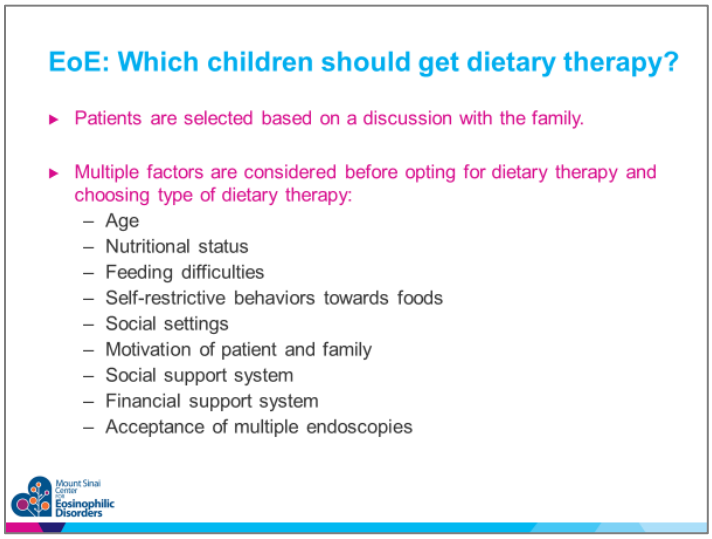


Then, which children should get dietary therapy? This is a very difficult question and the best way [to answer it] is to have a discussion with the family and to choose the patients who are right for this. Multiple factors need to be considered before opting for such dietary therapies, and for choosing which type of dietary therapy.

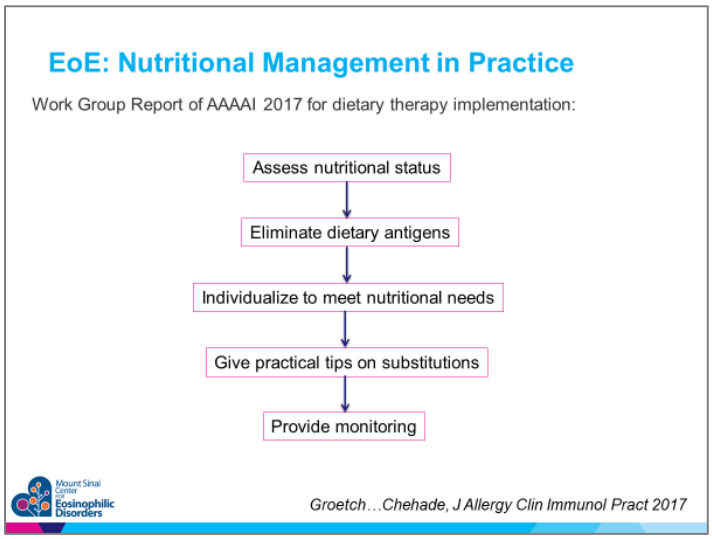
These include age, nutritional status of the child, feeding difficulties, if they are present; [as well as,] self-restrictive behaviors towards foods. If you have a kid who has a lot of feeding difficulties and would not accept new foods, when you have to remove some foods, you have to find ways to substitute. If there's resistance, those diets become difficult.

Social settings are important. The motivation of the patient, as well as the family, is important. Then the support system is important, whether we're talking about the social support system or the financial support system. Some specialized diets become expensive. The acceptance for multiple endoscopies, eventually to figure out the minimum number of foods to be removed, is also to be taken into consideration.

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients With EoE



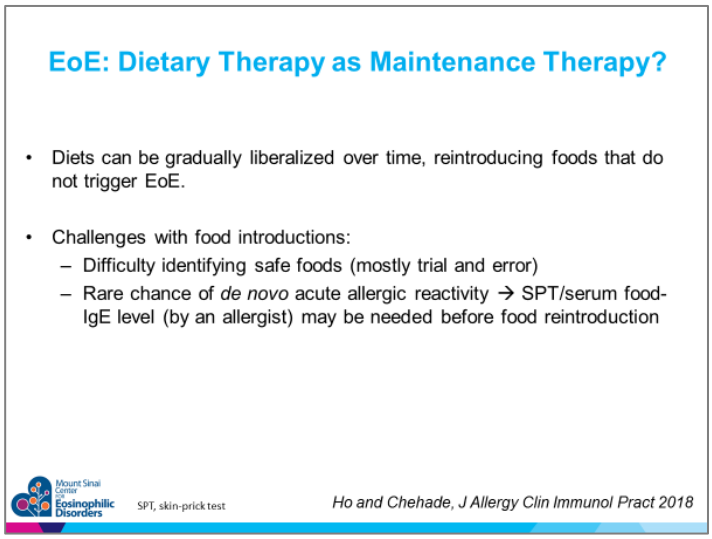
If a diet is selected for a child with EoE, I would like to point you to a great work group report that was supported by the American Academy of Allergy Asthma and Immunology. It was published in 2017 in the *Journal of Allergy and Clinical Immunology in Practice,* where 5 steps in implementing the diets are outlined.[13]



First, assist the nutritional status, then eliminate dietary antigens. The third step is to individualize to meet nutritional needs. The fourth step is to give practical tips on substitutions, and the fifth is to provide monitoring.

Now, in this report, lots of details are outlined and described for each step. I also would like to refer you to the online version of this report that has a lot of different handouts that would help a dietitian who doesn't have, yet, too much experience in food allergy, or the physician who does not have access to a dietitian, easily, to help with managing these patients.[14]

Can dietary therapy be used as a maintenance therapy? The answer is, definitely. Diets can be gradually liberalized over time, reintroducing foods that do not trigger EoE so the fewest number of foods are removed over time.

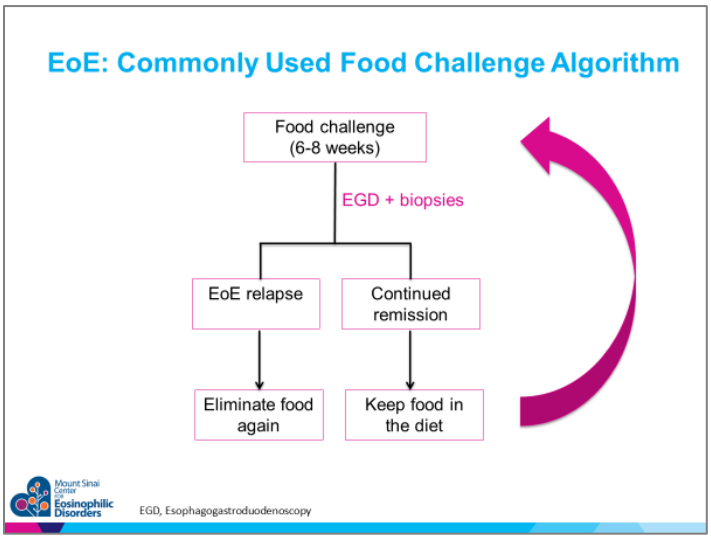


Now, the problem is there are challenges with these food introductions. One is difficulty identifying safe foods since the fasting is not that helpful. A lot of these additions are done by trial and error. The other thing, which is very important to watch for, is the rare chance of *de novo* acute allergic reactivity to a food that has been removed for a long time for EoE.

In here, the role of the allergist becomes very important to clear that food medically for food reintroduction, after its avoidance for a long time,

by doing skin prick testing, serum food-specific IgE levels, or other criteria.

What's commonly used in a food challenge algorithm? What happened is a food is challenged for 6 to 8 weeks, where the patient is eating that food at home after clearance is obtained from the allergist, which means no acute reaction will occur while eating it at home. Now, the patient is watching—or the family is watching—for any symptoms with that food. Then at least 8 weeks later, an endoscopy with biopsy is done.



If the biopsy shows eosinophilic esophagitis relapse, then we know that food is a trigger, and the food is eliminated from the diet. Again, if, on the other hand, after adding that food the biopsy shows the EoE is in continued remission—which means that food was never a trigger for EoE—that food can be kept in the diet, and then we move on to the next food, and the next food. Each added, individually, until the minimum number of food is avoided over the long run.

To conclude dietary therapy for EoE: dietary therapy, as you saw, can be effective in children with EoE. It is an optimal choice for eligible patients and for motivated families, but ongoing support is needed for its success.

What about medical therapy? What I'd like to do is mention a little bit of the role of PPIs, or proton pump inhibitors, as a treatment, knowing the changes in the guidelines I mentioned in the earlier modules.

This is the rate of histological remission using proton pump inhibitor. As you can see on the slide, it's a combined remission rate of 50%. Again, children and adults are not much different. Fifty-four percent remission rate in children and [in] adults it is 50%.[15]

Now, the dose of PPI that is used is 1-2 mg per kg per day in children, up to a maximum dose equivalent to an adult dose. What about other medications? Topical corticosteroids are commonly used in children with EoE. The 2 commonly used formulations are fluticasone to swallow and oral, viscous budesonide to swallow. Note that none of the corticosteroids or even other medications for EoE are approved for EoE, yet, by the FDA.

How effective are topical corticosteroids? In this slide, I'm referring to the very first randomized controlled trials, where topical corticosteroids were used in children. I'd like to draw your attention to the drug here in dark pink, so you can see budesonide and fluticasone were used in different studies.

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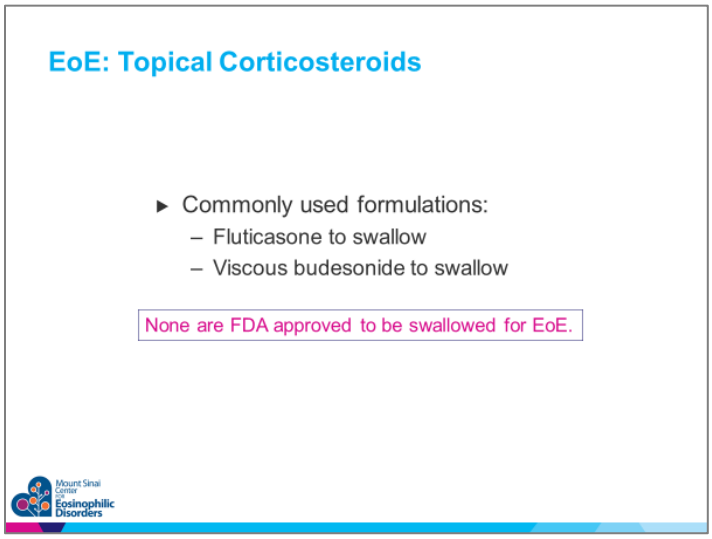
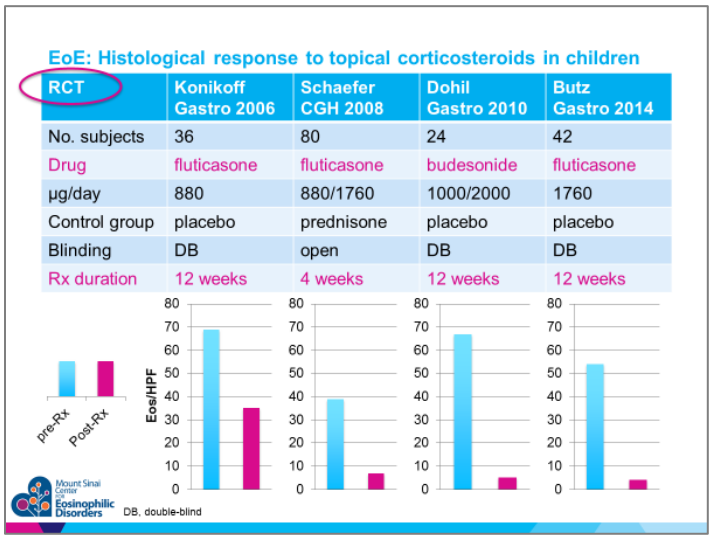
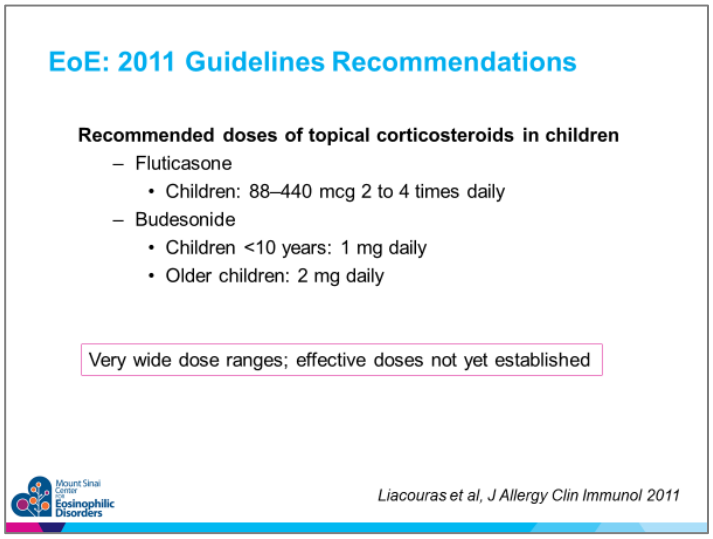


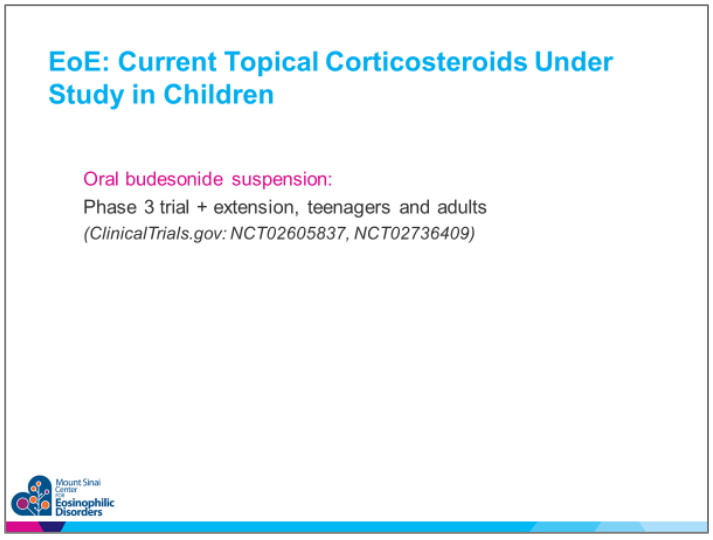
If you look at the treatment duration, again in pink, the duration was anywhere between 4 and 12 weeks. Now, if you look at the corresponding graphs at the bottom, the blue bars represent pre-treatment with steroids, topical steroids, and the pink bars are post-therapy. The y axis is eosinophils per high-power field in the esophagus. As you can see, some of the formulations, depending on the dose used and the drug used, were very effective.



The 2011 guideline recommendations tell us that for fluticasone, the recommended dose for children is 88 to 440 mcg, 2 to 4 times daily. For budesonide, for children less than 10 years, the dose is 1 mg daily. For older children, it's 2 mg daily. You can see here [the] very wide dose ranges. That's because effective doses have not yet been established.



Are there studies that are ongoing to establish this? The answer is yes. There's currently one oral budesonide suspension that's under phase 3, multicenter trial with an extension in teenagers and adults.[16] Again here, I'm referring you to the ClinicalTrials.gov identifier numbers, if you would like to look it up further.



What are the pros and cons of topical corticosteroids therapy? The pros: some formulations are highly effective, as you saw. If we do steroids, now we don't have to remove foods.

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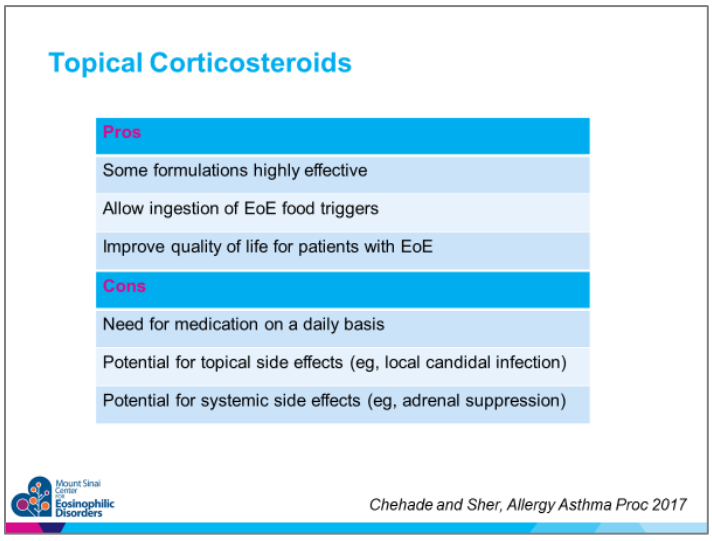
Then these treatments will allow ingestion of the EoE food triggers and, therefore, improve the quality of life for patients with EoE.

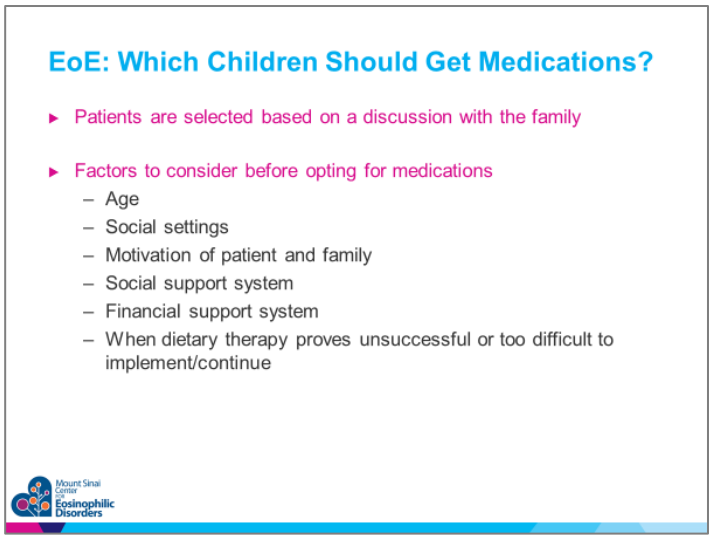
The cons of these medications [there are also a few here] is that you need to take that medication on a daily basis. In most occasions, twice a day. The other thing is you have to watch for side effects. These side effects can be topical, such as local candidal infection. The candidal infection can be oropharyngeal and/or esophageal. That may require treatment if it causes symptoms.



Then you have the systemic side effects that you have to watch for. For example, adrenal suppression. If you have, for example, a patient who has concurrent allergic rhinitis and, therefore, on a nasal steroid or concurrent asthma; and, therefore, on an inhaled steroid or even concurrent atopic dermatitis, is on a topical steroid or a combination of the above. If you have a little bit of absorption from each of these steroids, now you may have a problem.

This is a problem I see when we have multiple steroids on board. Some patients are just more sensitive, or if we're using higher doses of these steroids, we have to watch out for potential adrenal suppression.

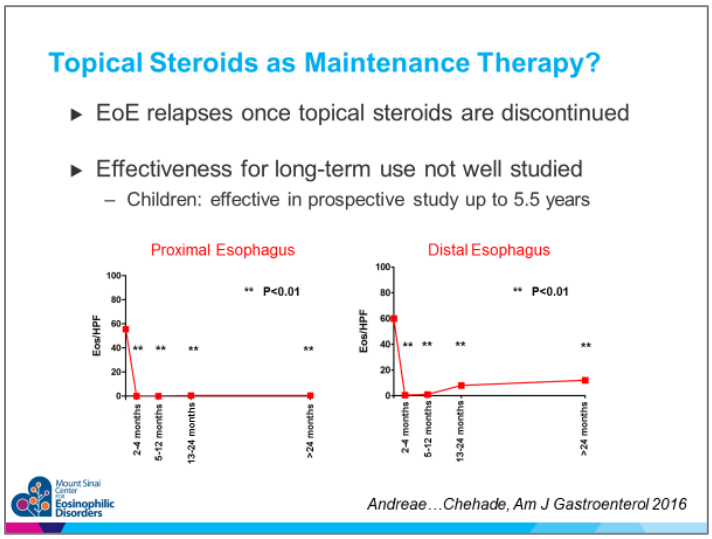
Which children should get topical steroids as opposed to a diet? Again, just like with diets, patients are selected based on a discussion with the family. Factors to consider here before opting for medications are almost similar to diet: age, social settings, the motivation of the patient, and the family, social, and financial support system, and also when dietary therapy proves to be unsuccessful or too difficult to implement or continue in a child with EoE.



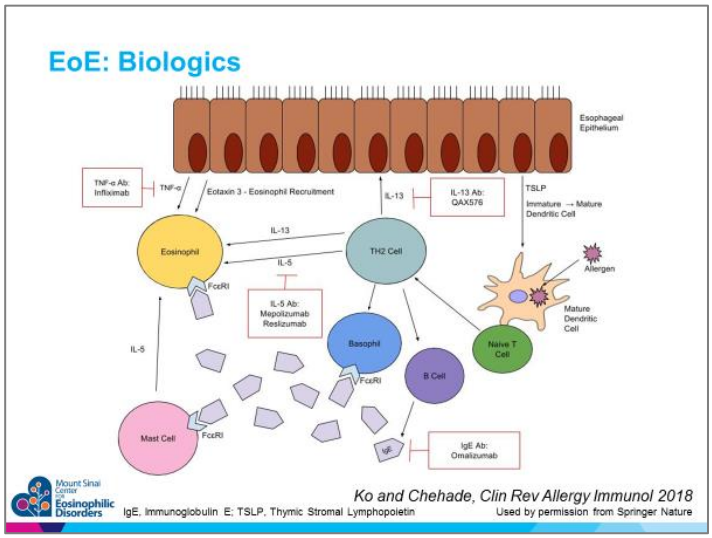
Can we use topical steroids as a maintenance therapy? The answer is most likely, yes. What we have seen is that EoE relapses once topical corticosteroids are discontinued. Remember how we talked about EoE as a chronic disease? If topical steroids are controlling the disease, if you stop them, and you don't have a plan B, then EoE will relapse. Hence the need for long term use of those topical steroids.

Now, the effectiveness of this long-term use has not been well studied. There's one study we performed locally, in particular, where we prospectively gave fluticasone to swallow for children with EoE, up to

5.5 years. We noticed, as you can see here on the graph, the left one, representing eosinophils per high-power field in the proximal esophagus, and the right one representing the eosinophil counts in the distal esophagus, showed prolonged efficacy.[17] At the doses we used and the method of administration we used, we did not have major side effects. These are things to watch out for and study, if you are using topical corticosteroids.



What about other medications? No talk can be complete without mentioning biologics, like with many other chronic diseases. If you remember that slide where we discussed the immunopathology. If we look at all these cytokines here on the graph or on the slide, you can see there are multiple ways where cytokines could be targeted. Indeed historically, multiple ones have been targeted so far.



An antibody to interleukin-5 (or IL-5) has been used in 2 different trials. One using mepolizumab, the other one using reslizumab[18]. Both resulted in histological improvement, but not much clinical improvement to warrant FDA approval.

Now, the antibody to TNF-alpha or infliximab, as well as the antibody to IgE, which was omalizumab in that case, were tried in a single-center, investigator-initiated study, and, unfortunately, did not result in any improvement. Now, anti-IL-13 was used—in particular, the antibody QAX576—in a multicenter study in adults, and it showed histological improvement and a trend towards clinical improvement.[19]

What's currently going on in terms of biologics for EoE? Unfortunately, none are currently under study for children, but we have 2 potential antibodies that are currently being studied in adults. One is an IL-13 inhibitor, which is RPC4046, which is according to preliminary data showing possible histological and clinical improvement in steroid refractory patients.[20] This is the ClinicalTrials.gov identifier number.

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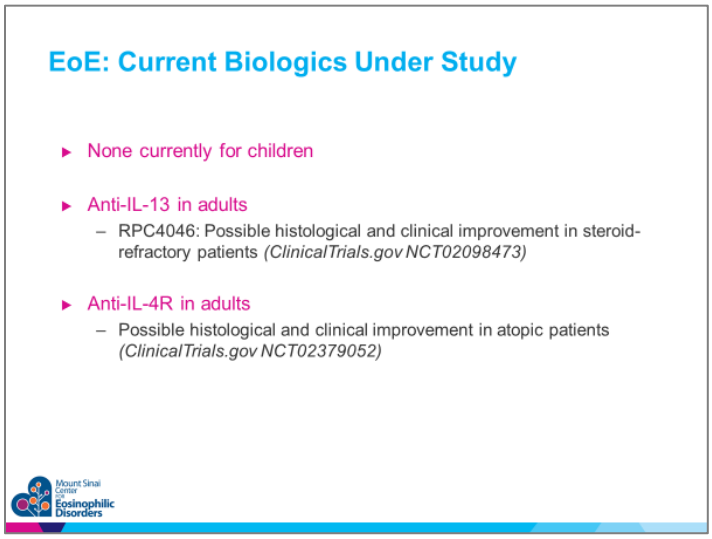

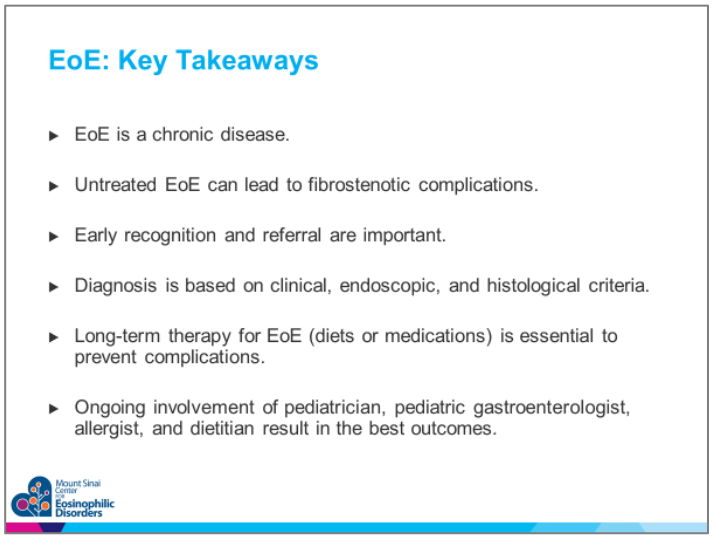

Also, we have another antibody again in adults which targets the IL-4 receptor. That will decrease IL-4 and IL-13 secretion by the cells and that's dupilumab, also showing in preliminary data possible histological and clinical improvement in atopic patients.[21] Again, here's the clinical trial identifier number.

To conclude this part on medication for EoE, none of the medications for EoE are FDA approved, to date. Chronic therapy is needed. But I'll tell you that it looks like the future is promising, given the multiple studies that are currently being conducted in adults, and hopefully, if they show results, then potentially they will be studied in children as the next step.

Key takeaways from this talk: EoE is a chronic disease. Untreated EoE can lead to fibrostenotic complications. Hence, the need for early recognition and referral. Diagnosis is based on clinical, endoscopic, and histological criteria. Long-term treatment for EoE, whether it is by diets or medications, is essential to prevent complications. Ongoing involvement of pediatrician, pediatric gastroenterologist, allergist, and dietitian often result in the best outcomes for these children. Thank you for your attention.

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Chehade's responses from the November 6 and 8, 2018, audio webcasts.

What tests should we run if we see a patient with potential EoE?

Dr. Chehade: This is an important question. If you have a child with EoE, and you're taking a history, there is really no one good test you could do before referring to the gastroenterologist for investigation.

What I would like to focus on is a good history. As you saw from the talk, the younger the child is, the more nonspecific the GI symptoms. A very thorough history is important to see the chronicity of the symptoms. Look for vomiting. Look for reflux symptoms. Look for abdominal pain.

Typically, with vomiting, you will see that the patient is the "happy vomiter," where they would vomit and go back to play. This is not similar to what you see with a viral illness, for example. Look at the growth curve and see if you have issues with the growth.

Also, look for those subtle symptoms in feeding. Again, the younger the child we're dealing with, the more we have feeding difficulties. For those, we

outlined what to ask for. These questions don't take too long. Two, 3, extra minutes in your office would help to identify these. If you have a high index of suspicion, along with a history of atopy, a history of atopy becomes a red flag, then I would send those patients for a referral.

How prevalent are environmental allergens, such as pollen, as potential carriers for EoE?

Dr. Chehade: In my opinion, the problem is that the role of pollen as an environmental trigger in EoE is not well studied, as I pointed out earlier. It's always gleaned from studies looking at flare-up of patient's symptoms. Sometimes esophageal histology with eosinophilia during the pollen season. Also, there were many studies looking to see how often we are diagnosing EoE in the pollen season vs the non-pollen season.

The data are indirect in terms of implicating pollen. In my opinion, it is a bit over estimated at this point, where many patients who do not respond to dietary elimination would say, "Oh gosh, it must be the pollen causing my EoE."

It may be that the foods were not properly identified and removed, therefore, the diet didn't work because there are many other foods that need to be removed. This is difficult to get right because you don't know what are the food triggers, by any testing. What happens is that [this] also leads to over estimation of the pollen as a cause. In my opinion again, it's probably about 10%, not more, especially in the pediatric population.

When do you normally perform an endoscopy?

Dr. Chehade: That brings us back to the answer of the first question. If you have a history that's highly suspicious, I would not wait; again, if we have symptoms, plus failure to thrive or atopic history. Anything that's pointing to more than just a simple acid reflux or a simple viral illness, or a different etiology altogether, like inflammatory bowel disease, etc. If EoE is suspected, then I would rather perform an endoscopy immediately.

Is there an age where the child is too young, when you would not perform an endoscopy or a biopsy?

Dr. Chehade: That's an interesting question. If you're dealing with a young infant, where you're seeing some GI symptoms, and they're barely eating a variety of foods now, they're relying mostly on cow's milk formula, for example—those are the times when we tend not to scope and rather try to switch the formula. This is something pediatricians can do, by switching formula to see if the patient's symptoms respond and the failure to thrive improves, if it's present.

Since this is in the guidelines for the management of infants, then we don't end up scoping these very little ones. But, if we have someone a little older and the simple management, such as switching the cow's milk sources, is not working, then I don't see a reason not to scope this patient and make the proper diagnosis.

Can you tell us what are the clinical symptoms of dysphagia in children?

Dr. Chehade: Good question. Dysphagia is very hard to elicit. I agree with the person who asked this question. Kids will not tell you, "I'm having trouble swallowing," or, "It's difficult for the food to go down!" You have to be creative in terms of asking the question.

Basically, "When you eat, does the food feel sticky on the way down?" "Does it go down slowly?" I ask all these different questions you wouldn't ask an adult. Also, for both children and adults, I would not simply limit it to dysphagia. I would ask about how they eat, do they avoid certain foods? Do they have to chew too long? Are they the last ones to finish

dinner? Not because they are distracted watching a movie or something, but because they are chewing their food too long. If they're eating and the liquid next to them, the glass of water or any other liquid is empty, would they dare to continue? Or do they need to fill it before they continue? This would be for the older children. They'll be able to answer that.

If you have a very young one who cannot communicate with you, a lot of times, you ask the parents if they're coughing while they're eating, if they're "choking" while they're eating, or if they're gagging while they're eating. A lot of times, they tell you, "My kid coughs." “Eats the food and then cough, cough, cough,” to the extent that they don't even dare to go to a restaurant because it becomes embarrassing. Then you know that this could be a symptom of dysphagia. I would use all these various ways to determine dysphagia when you have a very young one.

How do you determine which elimination diet, elemental, test-directed or the empiric elimination is most appropriate for your patient?

Dr. Chehade: Well, that's a question where the answer has to be a long discussion with the family, and has to take many, many different historical parts into consideration. If, for example, you have a patient who has multiple IgE-mediated anaphylactic type of food allergies, including many of the foods you would have removed in an empiric diet, then that patient cannot get an empiric diet now. It has to be a little more restricted. An elemental diet or a modified elemental diet would be more appropriate.

If you have a patient who is eating a full diet, and the family is not ready or doesn't have the full setup to do a more extensive diet, then a less extensive diet, maybe 1-food or 2-food elimination diet would be more appropriate.

I think this is a discussion with a family who has to take into consideration all those little factors we discussed on one of the slides. Then, at the same time, outlining to the family the pros and cons of each diet and the expected success rate, as well as the potential implications on the patient's life and potential side effects, side effects here being nutritional quality of life, etc, and then make the proper decision on the diet.

What are the pros and cons of an elemental diet consisting exclusively of the amino acid-based formula?

Dr. Chehade: The pro is that it's super effective. You're removing all the foods. Basically, if you're using a modified elemental diet, and I prefer the modified, typically. A modified, just to remind everyone in the audience, is the one where you would do an amino acid-based formula with one or two foods. That's because it's human nature.

If I give you only liquids, after 2-3 weeks, you're going to go crazy. You need to chew on something. We prefer to do a modified elemental diet where we choose 1 or 2 foods that are not known to be common triggers. Of course, if you're not eating too many foods, then the chance of healing EoE is high.

The problem is you can do that over 3 months. Then you have a very long road of food introductions, followed by endoscopies, to be able to pinpoint the minimum number of foods you have to avoid in the long run, and maintain a safe diet.

That's a major drawback of this type of diet. The other problem, sometimes, that we see with this diet is that if you're dealing with a very small child who is also young, and we calculate the caloric requirement for that child, sometimes it's very hard to push that large volume of formula to meet the caloric needs. That child may need a feeding tube. A

tube placed, whether nasogastric or gastric tube, to be able to manage the entire caloric requirement.

It's best to always try to avoid these kinds of interventions if one can help it, so we can provide patients with EoE with the best quality of life possible as they go through this.

Are there any other causes for esophageal stenosis in a patient with dysphagia, if endoscopy does not note EoE?

Dr. Chehade: Yes. Well, the differential is really high. Any inflammation of the esophagus, by definition, can lead to a complication, such as stenosis. Acid reflux would be the most common in the pediatric population. In the pediatric population, in particular, I would like to point out that strictures are not that common. If you see a stricture, I would start the full workup to look for a cause, if you don't see EoE.

The other question, is there no EoE because it's been missed? There are multiple technical issues that could get in the way of diagnosing EoE. We mentioned that EoE is patchy, so several biopsies are needed. If, by eye, you see nothing endoscopically, then it's very important to verify that multiple biopsies were taken, not to miss it. If, indeed, EoE is not there, then I would start looking for other etiologies, chronic acid reflux being one of them.

Have you seen any EoE relapses to a given food after the 6-to-8-week challenge was normal for that food?

Dr. Chehade: No. So far, if the biopsies are done properly, if enough of the food was consumed after … I usually wait a little longer. The minimum we talked about was about 8 weeks. I wait even 12 weeks or so, because I do not want to start the food immediately. I'd like them to get used it, figure out brands they like, and eat as much as they can.

If you have a patient who is eating a good amount of that food, more than what they would usually eat, if they did not have EoE, you really challenge that esophagus. Two, 3 months later, if you look and you don't see EoE, and you did a proper job of getting all the biopsies you need, if you don't see EoE, it's less likely that food becomes a problem later on. Now, is this 100% observation? There are always exceptions in life and medicine, but typically no.

How do you decide between an elemental amino acid-based formula diet vs a modified elemental diet of amino acid-based formula plus 1-2 foods?

Dr. Chehade: Well, I would always go for the modified elemental diet, and that's what I would recommend because if you just do the pure amino acid-based formula, now you are giving the patient a liquid diet for at least 2 months, [and] you are inviting more feeding problems. It's human nature; they need to chew on something. After 2, 3 weeks, they would start to eat, randomly, foods that they're supposed to avoid, or even the younger, younger children would start eating other things like dirt, etc.

What happens is that we need to chew on something. Therefore, I always choose 1 or 2 solid foods to go along with the formula so we don't lose the feeding skills in case you are dealing with a younger child, and also to provide the satisfaction of chewing and swallowing food. Also, the food, not only would I choose the 1 or 2 foods to be very low potential triggers for EoE, and that's, by the way, individualized to each patient, because we don't know what they're triggers are. I would do the statistically less common triggers, in that case, but, also, I would choose a food that has a high versatility in terms of texture. If you choose a food, you want a crunchy food. For example, let me give an example, which is always the best.

So, if, let's say, you choose corn, then you can have corn on the cob. You can have corn in the form of

polenta, where you're just adding water, so you don't have another ingredient, or you could have popcorn. You could have corn chips, and now you're working with different textures with the same exact food. A young child may not realize this is 1 food, but, also, you're providing with a sweet, salty, higher texture, softer texture so they don't lose those feeding skills—in case you're dealing with a young child—so you don't put them back there. At the same time, if this is an older person or a young person, they could enjoy having a solid.

How can I best manage my pediatric patients with EoE during long referral wait times to pediatric GI specialists?

Dr. Chehade: Well, this is a tough one because, unfortunately, without a diagnosis of EoE that is confirmed by endoscopy and biopsies, it is simply a suspicion at this stage. What can be done is try to see if, nutritionally, you could supplement with, say, formula only if needed. But, also, what can be done if you're not sure if this is EoE or not in the child, and you're differential is this, an acid-related problem? Sometimes it helps to start a PPI in the interim while you are referring to the gastroenterologist.

Why would removal of a test-directed allergen be less effective overall than the removal of the common 6 allergens? For example, why would a child who has been tested to not have a milk allergy, respond well to removing milk from the diet. The person who posed this question said they've seen this occur.

Dr. Chehade: This is an excellent question. Why is the test-directed elimination, why did it not work? Basically, the tests that are performed historically for this type of diet consisted of skin prick testing and atopy patch testing.

The skin prick test is designed to identify foods to which you could have an IgE-mediated anaphylactic-type potential reaction. Since this disease falls into the chronic non-IgE-mediated category, where repetitive exposure to a food eventually causes chronic inflammation, as opposed to a 1-time exposure with immediate acute reactivity, the way it is with IgE-mediated allergic reaction, then the skin prick test is not that helpful to identify these foods, since the mechanism is not purely IgE mediated the way it is with anaphylactic food allergy.

So, then the other test that was also used to devise the test-reacted elimination diet was the atopy patch test. So, [with] the patch test, what you do is put the food in a little disc, metallic disc, called a Finn Chamber, and place it on the back of a patient for 2 days. Theoretically, what you are looking for ideally, is a cell-mediated allergic reaction. Theoretically, this would have been a great test to identify those slow cell-mediated non-IgE-mediated food allergies, which are suspected to be the culprits in EoE. But what happened, unfortunately, these skin tests did not perform well to identify the food triggers for EoE patients.

As a result, a combination of skin prick and patch testing did not do well, in terms of identifying these foods, and that's why you saw in the meta-analysis I showed you, a success rate in the 30% to 40%, as opposed to the empiric diet, which, luckily, showed a good response.

If you have a patient that has a skin prick test to milk that is negative, they could still respond to milk elimination, only because that test was not meant to come back positive, because that patient is not having [a] history of an acute allergy to that food.

In regard to the food elimination diet treatment, how many patients had more than 1 food trigger?

Dr. Chehade: Well that's the larger proportion of patients, so we look again at that table I showed you

in terms of empiric diets. For example, in children the 6-food elimination diet was effective in 73% of children, 4-food elimination: 64%, 2-food elimination diet: 43%. If we remove only 1, the 1-food elimination diet, it must be somewhere lower than 43%. Studies are ongoing now. We know that the chance of 1 food being the cause, typically the most common being milk, is somewhere below 40%.

Would that make us rule out the idea of trying milk elimination only? Not at all. It's not a small percentage, and if you have a patient where they really want to try the diet, they're not sure, they want to start slow, try with 1 food, and the disease is not that severe, there's not too much failure to thrive; you have a dietitian with you who can follow, this is not a bad option to think about.

Do you recommend avoiding soybean oil, soy lecithin with patients avoiding soy EoE (thinking minimal protein in them)?

Dr. Chehade: Soy oil is highly refined oil, so indeed you don't get much of the protein in there at all, almost. Soy lecithin, that's the fat part of soy, and they don't put much protein in there either. When I typically tell a patient to avoid soy, I'm concerned about the protein, so, yes, we do allow the soy lecithin and the soy oil because that soy oil in particular, is a highly refined oil.

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