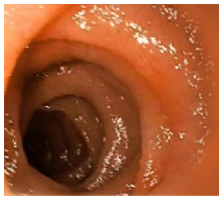

Targeting Pharmacotherapy to Effectively Manage Eosinophilic Esophagitis

Editor's Note: This is a transcript of a presentation on February 17, 2023. It has been edited and condensed for clarity. To obtain CE credit **click here.**

Module 1: Pathophysiology, Epidemiology, Diagnosis

Question 1
Which of the following statements regarding the epidemiology of eosinophilic esophagitis (EoE) is true?
A. The prevalence of EoE has remained stable over the past decade.
B. EoE affects only adults.
C. A diagnostic delay of several years after symptom onset, and thereby increasing disease burden, is common.
D. Females affected 3 to 4 times more often than males.

Correct answer is C

Answer rationale:
- Factors such as not considering EoE a separate disease entity and confusing symptoms with other disorders, eg, gastroesophageal reflux disease (GERD), have contributed to a large disease burden.
- Rising global incidence and prevalence due to improving disease recognition.
- Higher prevalence reported in Western, industrialized countries.
- Prevalence in males 3-4x more than females.
- Prevalence higher in Caucasians compared to other races.
- All age groups with peak incidences between ages 5 and 10 years and between ages 30 and 40 years.

References:
Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology*. 2018;154(2):319-332.e3.
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Faculty Discussion

Ikuo Hirano, MD: The correct answer is C, a diagnostic delay of several years after symptom onset, and thereby increasing disease burden, is common. For eosinophilic esophagitis (EoE), both in children and adults, diagnostic delay is unfortunately quite common, with longer delays in adults than in children. Quite interestingly, about this particular topic, is that the diagnostic delay is typically several years, between 3 to 5 or 6 years. And the other concerning fact is that diagnostic delay has not shortened over the past 20 years that EoE has been followed. The other answers here, the prevalence of EoE has remained stable over the past decade, answer A, is incorrect. The prevalence and instance of EoE has been rising around the globe over the past 20 years.

Answer B is also incorrect: that EoE affects only adults. EoE affects both children and adults. It's kind of an equal opportunity offender. It can affect infants and it can affect 90-year-olds, although the peak burden tends to be around 20 to 40 years of age, and the median is typically around 30 to 35 years of age. So, the majority of patients in a population are typically adults, but it absolutely affects children.

Answer D - that EoE predominately affects females – is also incorrect. It's actually the opposite. Every study around the globe has shown that this is a male predominant disease.

Mirna Chehade, MD: Incidence of EoE is increasing, and since this is a chronic disease, prevalence automatically increases over time. The incidence is increasing both due to increased recognition, since we're doing a better job at diagnosing these patients, but also there's a true increase in the incidence of EoE. The other thing I would like to add is that, in the pediatric population, it seems that there's a peak incidence between ages 5 and 10 years, however we should definitely keep in mind that EoE can occur in all age groups.

Ikuo Hirano, MD: Mirna, you wrote that nice paper that looked at diagnostic delays in pediatric and adults, I think it's from the Consortium for Food Allergy Researchers (CoFAR) population. You found a shorter delay in pediatrics than adults. Any thoughts on why children are getting diagnosed quicker than the adults? Are you guys just smarter than we are?

Mirna Chehade, MD: I don't think so. This difference was a little bit surprising. The paper was done by the CoFAR Researchers, so it was a multicenter study where we looked at all age groups with EoE across these centers. And it was surprising, in a way, that the diagnostic delay was shorter for children, especially that symptoms in adults typically tend to be mostly dysphagia and esophageal food impactions which almost always lead to an upper endoscopy with biopsies. In contrast, children, the younger they are, have nonspecific symptoms, such as abdominal pain, intermittent vomiting, and gastroesophageal reflux symptoms. This does not always lead to a quick endoscopic diagnosis. You would think that the diagnostic delay would be longer, but for some reason the kids are diagnosed sooner. It is possible that atopy, which tends to be a little more common in the pediatric population than in adults, is one reason. But there are multiple factors that could contribute.

Ikuo Hirano, MD: As a parent, if I saw my child vomiting or complaining about pain or having food aversion, I think that would drive me to bring my child to a pediatrician sooner. With the adults that I see, they have dysphagia typically for several years and they adapt their eating behaviors by chewing carefully, prolonging mealtimes, etc, so that they actually mitigate the symptoms and therefore do not seek medical attention. They don't get too panicked unless they aspirate. But for the most part, if something's slow going down, they adapt their eating, and I think that can delay their presentation. The other thing is kids routinely see a pediatrician. Adults sometimes don't have a primary care doctor and they often aren't plugged into a healthcare system so they're not going yearly to see a doctor. So, I wonder if that also is a factor.

Mirna Chehade, MD: Given EoE is more common in the younger adult population, between 30 and 40 years of age, as opposed to older adults who may start going to the doctor more regularly – this could also be a reason. On the other hand, with children, if they have intermittent symptoms, they can be missed or thought of as an acute viral illness. If they vomit, they've just got a stomach bug, and then it gets dismissed because the vomiting does not necessarily continue. For reflux, they get antacid therapy. So, these would be reasons why they might be missed or delayed. Now, failure to thrive prompts an endoscopy, and about a third of children with EoE have failure to thrive. Also, for EoE to be suspected, you have to look for history of atopy and history of food allergy. If they're having symptoms and they have this atopic comorbidity, then they are more likely to get an endoscopy. I wonder how much that contributes to the workup being done and the diagnosis being made. The difference could also be that this was a multicenter study which had a lot of the principal investigators [who] were very focused on the pediatric age groups, so maybe we were doing a little bit of a better job. But this was not a population-based study that would allow us to feel confident that this is a true difference in diagnostic delay between pediatrics and adults.

Question 2

CF is 16 years old and has been referred by his primary care clinician with a chief complaint of epigastric abdominal pain and several episodes of difficulty swallowing and food impactions over the past 6 months. Dietary changes, focused on reducing meal size and decreasing ingestion of "trigger" foods such as meats and breads, have not had much impact. CF's parent reports that he has grown anxious as these symptoms have progressed, causing CF to spend less time with friends.

Which one of the following symptoms is a common presenting symptom in older children and adults with EoE?

A. Dysphagia
B. Vomiting
C. Depression
D. Coughing after eating

The correct answer is: A

Answer rationale:

•Adults and adolescents with EoE commonly present with dysphagia, food impaction, substernal chest pain, and heartburn.
•Children with EoE commonly present with dysphagia, food impaction, abdominal pain, vomiting, failure to thrive, and anxiety.
•Patients often delay seeking care until symptoms have worsened.
•Diagnosis of EoE requires exclusion of other causes of esophageal dysfunction/irritation.

References:

Hirano I, Furuta GT. Approaches and challenges to management of pediatric and adult patients with eosinophilic esophagitis. *Gastroenterology*. 2020;158(4): 840-851.
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Faculty Discussion

Mirna Chehade, MD: The correct answer is A: dysphagia. If we look at the common presenting symptoms across age groups, we see the following: adults and adolescents mostly present with dysphagia and food impactions although some of them also present with substernal chest pain or heartburn that is refractory to antacid therapy. Children, on the other hand, present with less specific symptoms. They can present with abdominal pain, vomiting, failure to thrive and, if we're dealing with older children, we also start having the dysphagia and the food impaction that you see with the adult population.

The toughest group here in terms of symptoms are the infants and toddlers since they are dealing with really nonspecific gastrointestinal (GI) symptoms, including feeding difficulties. So, possible symptoms could be gastroesophageal reflux symptoms, coughing or gagging with food intake, feeding difficulty, food refusal and/or failure to thrive. Failure to thrive is a big factor to consider in EoE diagnosis.

Going back to the options here, vomiting is obviously not the most common presenting symptom in older children and adults. Depression is a very nonspecific symptom and therefore it is not correct. Patients with EoE tend to have anxiety. Depression is not that well studied in terms of its prevalence in patients with EoE. Coughing after eating could be indicative of reflux. Now, that reflux could be due to EoE that's giving them reflux or regurgitation or it could be due to concurrent gastroesophageal reflux in patients with EoE.

Ikuo Hirano, MD: This case highlights some of the distinction between the pediatric and adult phenotypes or clinical presentations. It's very unusual, as an adult gastroenterologist, for me to see a patient with EoE who has concomitant complaints, in addition to dysphagia, of abdominal pain, nausea, vomiting, anorexia, food aversion. That's very distinctly unusual unless they've got some concomitant secondary disease, like ulcer disease or nonulcer dyspepsia. But, for the most part, it's dysphagia, dysphagia, dysphagia, and sometimes food impaction. But it is interesting—and I've never fully understood why—children have this more diffuse symptom complex compared to adults and why we don't see more adults with some of those symptoms overlapping. It's a phenotypic difference I don't think is fully explained.

Mirna Chehade, MD: Some of the patients could probably have dysphagia but some of them are too young to verbalize that. As a pediatric gastroenterologist, I see a lot of children with EoE and when they cough or gag with food or they refuse food, one wonders if they are having difficulty swallowing and they just don't know how to express that. It could be that there is some dysphagia and food impaction that we're not detecting because of the age of the patients. Also, why do they have abdominal pain even though the problem is limited to the esophagus? We don't know. And why do they vomit? That's another symptom that still needs to be studied.

This patient tried to decrease ingestion of trigger foods, such as meats and breads. This is important because many patients get confused. They think that the food triggers the EoE, which must mean that it is the allergen since those are the specific foods they're having trouble swallowing. It's important to know that these foods trigger the symptoms, not because of the specific protein in these foods, but because of the texture. Meats are tough to eat, therefore the esophagus has to work harder, if you will. Same thing with bready or doughy foods that can trigger dysphagia and/or food impaction and removing them from the patient's diet to treat EoE is not necessarily treating the inflammation. It's just helping to reduce the symptoms. That's an important distinction to make here.

Ikuo Hirano, MD: We see that this patient has become anxious about his symptoms, leading him to spend less time socially with friends, and that could lead to anxiety and depression. Even though depression is not the correct answer, there are studies showing significant detrimental psychosocial effects of EoE on quality of life and psychosocial aspects because so much of our society is based on eating. If you're a child, you're eating in a cafeteria with friends and if you start choking and you're embarrassed by vomiting during meals, you're probably not going to want to be around your friends. It's too embarrassing for a 16-year-old to vomit or spend an hour eating a sandwich. So, that has significant comorbidity for patients. Again, it wasn't the right answer, but it's something that we should be mindful of.

We can also bring up coughing with eating, which is certainly something to consider. They could have concomitant GERD, and reflux can certainly cause a vagal reflex that induces a vagally-mediated cough or microaspiration. But another thing to consider in the EoE context are very proximal strictures at the esophageal inlet. So, cervical strictures can produce transient food bolus impaction that occur very high in the neck that can lead to aspiration and coughing.

Mirna Chehade, MD: The other thing is if you have coughing after eating. We have to distinguish that from coughing during eating. Coughing during eating is what we see in children with EoE because they're having that difficulty swallowing, that potential transient food impaction. It's an important point if your patient is a child to really ask whether they're coughing, gagging, or choking during meals because that could indicate potential dysphagia and food impactions.

Question 3

CF is 16 years old and has been referred by his primary care clinician with a chief complaint of epigastric abdominal pain and several episodes of difficulty swallowing and food impactions over the past 6 months. Dietary changes, focused on reducing meal size and decreasing ingestion of "trigger" foods such as meats and breads, have not had much impact. CF's parent reports that he has grown anxious as these symptoms have progressed, causing CF to spend less time with friends.

Which one of the following findings is required to make a diagnosis of eosinophilic esophagitis in a child or adult with symptoms of esophageal dysfunction?

A. Exclusion of *Helicobacter pylori* infection.
B. Failure of acid-reducing therapy with a proton pump inhibitor (PPI) to reduce symptoms.
C. Esophageal biopsy specimen showing ≥ 15 eosinophils per high-power field (HPF).
D. The presence of environmental allergies.

The correct answer is: C

Answer rationale:

- Diagnostic criteria for EoE are:
  - Symptoms of esophageal dysfunction.
  - Histology showing ≥ 15 eosinophils per HPF.
  - Exclusion of other causes that may be contributing to esophageal esosinophilia.

- Typical endoscopic findings include:
  - Linear furrows
  - Circumferential rings
  - Attenuation of the vascular pattern
  - White exudate

- Exclusion of *H pylori* infection is not required for diagnosis of EoE.
- 8-wk trial of high-dose PPI demonstrating suppression of eosinophilia no longer required for diagnosis.

Reference

Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022-1033.

Faculty Discussion

Mirna Chehade, MD: The correct answer is C: esophageal biopsy specimen showing 15 or more eosinophils per high-power field (HPF). The diagnostic criteria for EoE, according to the most recent diagnostic guidelines, include the presence of symptoms of esophageal dysfunction, esophageal biopsy showing 15 or more eosinophils per HPF, and exclusion of other causes that may be contributing to esophageal eosinophilia. By that, we do not mean that you need to do a full workup looking for every potential disease that could mimic EoE and cause esophageal eosinophilia, but simply exercise your judgment given the patient's history. If there are other diseases to be ruled out,

then they should be ruled out accordingly. If there's no other disease mimicking EoE, and you have the symptoms, and you have the histology, the diagnosis of EoE is made. A PPI trial before making the diagnosis of EoE is no longer required. If you were taught at some point to try a PPI trial at high dose to confirm the diagnosis of EoE, you do not need to do that anymore. There is, however, still a role for PPIs in treating patients with EoE with a histologic response of about 30% to 50%.

Ikuo Hirano, MD: The diagnostic threshold of 15 or greater eosinophils per HPF on biopsy has stood the test of time. It was part of the initial diagnostic criteria back in 2007. I think that the distractors here are interesting. The majority of EoE patients, children and adults, do have concomitant atopic disease, including environmental and allergic rhinitis and history of asthma and/or atopic derm and IgE-mediated food allergy, but it's not required for the diagnosis. It is a clue. If you see a patient with symptoms suggestive of EoE and they've got a strong atopic history, it makes EoE more likely. But the allergies are not required for the diagnosis. Similarly, the *H pylori* is interesting because the majority of studies have shown an inverse association between *H pylori* infection and the detection of EoE. So, that begs the question: is there any protective role for *H pylori* or is *H pylori* a marker for the hygiene hypothesis? Countries where the *H pylori* burden is very high tend to have lower prevalence of EoE. In places where *H pylori* has been driven down through detection and antibiotic use, such as the United States and Western Europe, the EoE burden in higher. So it may not be that *H pylori* is directly causing or protecting against EoE, but it might just be a marker of the hygiene hypothesis.

Mirna Chehade, MD: It's important that we consider endoscopic findings in the diagnosis. It is not a requirement for diagnosis per the guidelines, however I think it's important. For example, if you have a patient who has any of the features of EoE, such as edema, furrows, white exudate, rings and/or stricture, those are more suspicious for EoE. However, if you find a patient with a large hiatal hernia with barely any of the EoE features, then this is a patient where you have to suspect, is this gastroesophageal reflux that's mimicking EoE? This is when you exercise your judgment. Three important factors always need to be considered: symptoms, endoscopic findings, and histology.

Ikuo Hirano, MD: I love endoscopy and I love inspecting the esophagus. The studies are pretty good, in both pediatric and adults, with a high degree of accuracy, sensitivity, specificity, for endoscopic detection of features of EoE. They are not required for the diagnosis, but they have such a high degree of sensitivity and specificity that they are a very valuable clue that you're dealing with an EoE patient. In the prospective studies where clinicians are asked to look for these features, the detection rates are over 95% in adults. It's a little bit lower in children, but even in children, when you're prospectively looking for the features, you can find them in the vast majority of patients.

Module 2: Diagnosis

Question 4

DG is a 65-year-old patient with a long history of dysphagia, including food sticking and occasional regurgitation. Since DG recently retired, and moved to the area, you are meeting him for the first time. He has been told his diagnosis is chronic GERD. DG has used a range of medications in the past and reports mixed success with diet modifications recommended by prior gastroenterologists. DG reports that symptoms are worse with heightened anxiety. Although his anxiety levels have decreased since retirement, his dysphagia has not, and most recently seems to be worsening. DG has been taking 20 mg daily of omeprazole for 15 years. He avoids known food triggers, such as bread and meat, is careful about thorough chewing, and uses liquids to help with swallowing. He is concerned about prolonged use of omeprazole.

Which of the following elements of the history suggests EoE might be causing DG's symptoms?

A. Symptoms have been relatively stable over time.
B. Worsening of dysphagia despite PPI therapy.
C. The lack of a clear relationship to his anxiety levels.
D. Nonadherence to diet modifications.

The correct answer is: B

Answer rationale

- EoE diagnostic criteria are based on symptoms, endoscopic appearance, and histologic findings.
- Characteristic symptoms are those of esophageal dysfunction but not food impaction specifically.
- PPI therapy is histologically effective in 40% of patients.
- An unclear cause/effect relationship between EoE and anxiety can confuse diagnosis.
- Histologic remission is achieved in 94% who follow an elemental diet and 51% who follow an allergy-testing based elimination diet.

Reference

Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022-1033.

Faculty Discussion

Ikuo Hirano, MD: The correct answer s B: worsening of dysphagia despite proton pump inhibitor (PPI) therapy. There is some overlap between symptom presentation for gastroesophageal reflux disease (GERD) and EoE. Both diseases can present with heartburn-like symptoms and both diseases can present with symptoms of dysphagia. The fact that this patient's symptoms of dysphagia were not improving with appropriate therapy with a PPI does increase the likelihood that you're dealing with EoE. Just the presence of dysphagia as a dominant symptom in this patient already would have made me suspect something like EoE. Chronic dysphagia that's getting worse regardless of the response to PPI therapy is an important clinical clue that should make EoE rise to the top of your differential diagnosis.

In terms of some of the incorrect answers, this patient did have a long period—we don't know exactly how long—but it sounds like many years, where symptoms were relatively stable. Then, when he retired and moved, he noticed some worsening of his symptoms. But that long interval of symptom stability is a little bit atypical for EoE. Many of my EoE patients notice that symptoms become a little bit more frequent over time. It's not uncommon for me to see a patient who tells me it started in grammar school or high school. They had maybe 1 episode a month or every few months and, over time, as they got older, it became more frequent, perhaps monthly, then weekly, and eventually they get a food impaction that brings them to the emergency room. That is the natural history of this disease being borne out in an individual patient, showing the progression over time of symptom severity or intensity.

Ikuo Hirano, MD: Other incorrect answers here: the lack of clear relationship to anxiety levels. There have now been studies that have shown that hypervigilant anxiety levels do correlate with symptom intensity. You could say it's a chicken and egg thing. If you have more symptoms, you're going to get more anxious, but more anxiety can also lead to an increased symptom burden. And patients often will attempt to modify their diet subconsciously and this is not diet modification to avoid food allergies. It's diet modification to avoid foods that worsen their symptoms, and that's typically very crusty bread and meat. Along with tablets or pills, these are the top things that tend to get stuck. It's very common for patients to modify their eating behavior to avoid foods that precipitate their symptoms.

Mirna Chehade, MD: Two points I'd like to make. One is to reemphasize pill impaction. Pill impaction is really important. We need to keep track of it when we have a patient with EoE, especially if the patient has stricture secondary to EoE. We need to counsel them that any time a medication is prescribed to them, they should not feel shy about asking for chewables, liquid or, at the least, small pills. We've seen over and over patients getting prescribed very large pills and then they get the unfortunate event of a pill impaction just because they didn't realize to ask, or sometimes they are simply embarrassed. The other is the concurrent presentation of reflux vs EoE and how it can be confusing to the practitioner. What happens is that you can have patients with EoE who have concurrent and independent GERD, and for those, even when you attend to the EoE and you treat the inflammation, you still have to attend to their reflux symptoms, especially with younger patients that have reflux symptoms secondary to their active EoE. When you treat EoE, you will notice that some of the reflux symptoms will disappear. Those are the lucky ones. But if they have dysphagia that disappears but they still have some heartburn, it's important not to be alarmed since you could have concurrent reflux, in many patients, especially the adults.

Ikuo Hirano, MD: One positive note on pill impaction is that it can absolutely be corrected with treatment of the EoE. Whether with medical and/or diet therapy alone or the patient may require an esophageal dilation, but the expectation with adequate treatment of their disease, is that inability to swallow pills should go away. They may still have some anxiety about it, but you should be able to allow your patients to swallow normal-sized pills and tablets after successful therapy.

Mirna Chehade, MD: At the beginning when you diagnose them, advise them to avoid large pills, and tell them what to do if they have to eat something meaty or bready, so that they don't end up with a food impaction. Once you have successfully treated their eosinophilic inflammation, the peristalsis will return to normal and the caliber of the esophagus will allow it to work properly again.

Question 5

DG is a 65-year-old patient with a long history of dysphagia, including food sticking and occasional regurgitation. Since DG recently retired, and moved to the area, you are meeting him for the first time. He has been told his diagnosis is chronic GERD. DG has used a range of medications in the past and reports mixed success with diet modifications recommended by prior gastroenterologists. DG reports that symptoms are worse with heightened anxiety. Although his anxiety levels have decreased since retirement, his dysphagia has not, and most recently seems to be worsening. DG has been taking 20 mg daily of omeprazole for 15 years. He avoids known food triggers, such as bread and meat, is careful about thorough chewing, and uses liquids to help with swallowing. He is concerned about prolonged use of omeprazole.

Which of the following would be the best next step in this patient?
A. Conduct an ambulatory acid probe test.
B. Perform an esophagogastroduodenoscopy (EGD) with biopsy.
C. Reassure DG that omeprazole can be taken long-term.
D. Prescribe an anti-anxiety medication.

The correct answer is: B

Answer rationale
• DG's history suggests that a diagnosis of GERD should be reassessed.
• Conduct thorough history and physical examination.
• Esophagogastroduodenoscopy would allow visualization of the upper GI tract; biopsy would enable examination of tissue.
• Ambulatory acid probe test would be appropriate if endoscopy was suggestive of GERD.
• Modifying treatment is inappropriate until a firm diagnosis is established.

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Muir A, Falk FW. Eosinophilic esophagitis: A review. *JAMA*. 2021;326(13):1310-1318.

Faculty Discussion

Ikuo Hirano, MD: The correct answer is B: perform an esophagogastroduodenoscopy (EGD) with biopsy. Actually, I would argue that an EGD should have been done very early in the patient's presentation. Any patient, even if they've got concomitant GERD symptoms, if they have a symptom of dysphagia, should have an EGD. Conducting an acid reflux test with a pH probe or pH capsule device is not appropriate at this stage. You would do the EGD first. If the EGD did not show EoE, or does not detect a reason for the patient's dysphagia with a stricture, and the biopsies were clear, then you can consider whether this patient may indeed have refractory reflux and consider appropriate testing with an esophageal motility test combined with some sort of reflux test with a pH monitor.

Reassuring the patient that omeprazole can be taken long-term is absolutely true. PPIs are extremely safe, but that is not the appropriate part of the management for this particular patient who's not responding to the PPI since he is having ongoing symptoms of dysphagia. You can have a discussion about PPI safety, but recognize that the patient is having symptoms despite the PPI and likely needs to transition to a different form of therapy for EoE.

Prescribing an antianxiety medication may be appropriate if the patient has significant concomitant anxiety, but would not be the appropriate workup or evaluation management strategy for patients with dysphagia who have not had prior endoscopy.

Mirna Chehade, MD: It's important to take multiple biopsies to diagnose EoE. EoE is a patchy disease, so if an endoscopy is performed but only 1 or 2 biopsies are obtained, it may not be adequate for diagnosis. At least 6 to 8 biopsies from the esophagus are needed to make the diagnosis. I always get the question, where do I biopsy? Do I biopsy the distal esophagus, or proximal esophagus? Do I biopsy every 2 cm? My answer is go to where you see the problem is. For example, if you see white exudates in the esophagus, it indicates that there's a high likelihood of finding an aggregate of eosinophils right there. So, take biopsies in that area in addition to other areas of the esophagus.

Module 3: Initial Treatment

Question 6
TM is a 58-year-old patient whom you diagnosed with EoE based on EGD with biopsy. He indicated that he preferred to avoid pharmacologic therapy if possible, so you recommended an empiric elimination diet to decrease his exposure to potential food allergens. On follow-up, he has had minimal symptom relief and persistent esophageal eosinophilic inflammation with this approach. You review some options, including other dietary approaches, swallowed corticosteroids, and starting a PPI. He elects to start a PPI.

Which of the following points should you include in your patient education as he starts treatment?
A. When his symptoms resolve, it indicates that his EoE is being successfully controlled.
B. PPI therapy for EoE is effective when taken on an as- needed basis.
C. Avoiding suspected food allergens is unlikely to be helpful once PPI therapy has been initiated.
D. Histologic response rate with PPI therapy is 30%-50%.

The correct answer is: D

Answer rationale
• Treatment guidelines for EoE are evolving.
• An option for first-line pharmacologic treatment is daily PPI therapy.
• Advantages of PPI therapy include low cost, wide availability, and ease of use.
• A trial of PPI therapy with evaluation of symptomatic response at 8 weeks is recommended.
• Repeat EGD with biopsy can then be considered based on symptoms to establish histologic response to treatment.
• Avoidance of known allergens in addition to PPI therapy can be useful in managing EoE.

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Faculty Discussion

Mirna Chehade, MD: The correct answer is D. When symptoms resolve, it does not necessarily indicate that his EoE is being successfully controlled because of the disconnect that there may be between esophageal symptoms and esophageal histology in patients with EoE. Let me give you an example so that it becomes a little bit clearer. If you have a patient with EoE who has an esophageal stricture and you treat them with a PPI, as in this case, and the patient still has dysphagia, you don't know if the PPI actually reduced the inflammation or not. It would be important to go ahead and perform an EGD to know if the PPI reduced the inflammation. If so, the residual dysphagia is not because of the persistent inflammation, but because of a stricture that now needs to be dilated. The disconnect can also happen the other way around. The patient's symptoms could also resolve, but they might still have esophageal inflammation. If you're evaluating a patient to see if a treatment is working, including a PPI as in this case, it's important to look for symptoms as well as for histology, since you could reduce the inflammation just enough to reduce this dysphagia but not enough to eliminate the esophageal eosinophilic inflammation. You could still have subclinical inflammation which could lead to long-term complications. It's always recommended that you reevaluate patients after therapy, both clinically as well as histologically.

Ikuo Hirano, MD: I caution clinicians not to use symptom-based management for EoE because of that disconnect. A stricture can drive symptoms independent of inflammation. Just as importantly, there's a high placebo response rate that's been shown in multiple trials where patients with a high degree of symptom burden were given a placebo and a substantial proportion of them feel better. Part of that may be reduced anxiety, but also they can modify their eating behavior by

doing these adaptive eating strategies that we've talked about, like using liquids during meals, taking a longer time to have meals, cutting food into smaller pieces, or avoidance of certain hard texture foods, like meat and breads. By doing this, they can mitigate symptoms, and you might think that they're actually better, but they may not have any objective evidence of improvement. Symptoms are important, but they shouldn't be used as a marker for success. Look for objective evidence of improvement in terms of endoscopic outcomes, stricture outcomes, and histologic outcomes.

Mirna Chehade, MD: When we see these patients early on and they have symptoms, we counsel them to be careful until we treat their EoE. So they take precautions and they feel better. I also notice that the disconnect between symptoms and histology, even though it's bidirectional, if histology clears or symptoms clear, but you have persistent inflammation. I see it more often in 1 direction in the pediatric population vs the other direction in the adults. For example, in the adult population, we see more persistent dysphagia even though the esophageal inflammation is clear, whereas in the pediatric population, often we see that the symptoms disappear but there's still significant subclinical esophageal inflammation. So, it's important that we reemphasize having both clinical as well as histological follow-up on all these patients.

Ikuo Hirano, MD: I wonder if it ties in with the fact that the adults have more strictures. That may explain some of that difference that you're seeing between children and adults.

Mirna Chehade, MD: I think strictures as well as some element of dysmotility come from long-term fibrosis formation in adults. But what's still a mystery is why they have persistent subclinical esophageal inflammation even though the symptoms go away. Sometimes we're dealing with what I call the hard symptoms, such as vomiting, which disappears. Sometimes vomiting can turn into just regurgitation. Other times both vomiting and regurgitation completely disappear, but you still have a lot of eosinophils. Eosinophils may not be the one and only inflammatory cell that we have to track in EoE. But that's probably a discussion for another session.

Module 4: Follow-Up Treatment

Question 7

JD is a 29-year-old male with complaints of heartburn and dysphagia on whom you performed an EGD 6 months ago and diagnosed with EoE. EGD findings included linear furrows, circumferential rings, and an attenuated vascular pattern, and LA grade B esophagitis. The esophageal biopsy showed 65 eosinophils per HPF. You recommended twice-daily PPI therapy and an EoE diet (6 food elimination diet) during the 3 months since diagnosis. On follow-up 3 months later, his heartburn has improved, but dysphagia has persisted. You perform another EGD which reveals that the esophagitis has resolved but linear furrows, circumferential rings, and attenuated vascular pattern are still present. Esophageal biopsy shows 50 eosinophils per HPF.

Which one of the following would be the most appropriate next step in the management of JD's EoE?

A. Stop the PPI; start a swallowed topical corticosteroid.
B. Stop the PPI; start a more aggressive diet modification regimen.
C. Continue the PPI; start swallowed topical corticosteroid.
D. Continue the PPI; start diet reintroduction.

The correct answer is: C

Answer rationale:

- The relationship between GERD and EoE is poorly understood but comorbid disease is possible.
- Dilation is not indicated given no complaints of dysphagia.
- Histologic response to swallowed topical corticosteroids occurs in about two-thirds.
- Likelihood of recurrent symptoms over time.
- Comanagement with an allergist can be useful in identification of specific allergens and managing atopic comorbidity.

References

Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102(6):1301 1306.

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Faculty Discussion

Ikuo Hirano, MD: The correct answer is C: continue the PPI and start swallowed topical corticosteroids. Here we have a young adult with EoE and concomitant GERD. GERD is defined by heartburn as well as the endoscopic detection of erosive esophagitis. The patient also has symptoms and endoscopic features and histopathology consistent with EoE. It would be very appropriate in this particular circumstance to continue the PPI, not for the EoE, but for the objective evidence of GERD as well as symptoms of heartburn that have resolved on PPI therapy. I would therefore not discontinue the PPI. But this patient was put on dietary therapy with a 6-food elimination diet and has had persistent symptoms, histopathology, and endoscopic changes of active EoE. So it would be appropriate to now consider alternative therapeutic approaches for the EoE, which could include a change in diet therapy or consideration of a biologic. I think it would be very appropriate to discuss options with the patient and to consider use of a swallowed topical corticosteroid, in which case you would stop the diet, continue the PPI, start topical corticosteroids, and then repeat an EGD 2 to 3 months down the road.

Stopping the PPI would be inappropriate both in the setting of resolved heartburn as well as the objective finding of erosive esophagitis. If it were LA-grade A, you could argue that that's not that much consequence. But here we've got LA-grade B esophagitis. What makes answer B wrong is not the consideration for a more aggressive diet therapy, which could be an alternative if you have a very diet-

motivated patient. It's that you would not stop the PPI. In answer D, continuing the PPI is appropriate, but dietary reintroduction would be inappropriate. You would not reintroduce food allergy triggers if you haven't induced remission. Before starting diet reintroduction, you have to get that patient into clinical remission, which means symptom improvement, histologic improvement, and endoscopic improvement. In this case, the biopsies show persistent high-grade eosinophilia at 50 eosinophils per HPF on a 6-food elimination diet.

Mirna Chehade, MD: By starting diet reintroduction while continuing the PPI, you would just be addressing the reflux but you're not addressing the EoE. So, you need to move on to a second therapy if the first one is not working, in this case the 6-food elimination diet. EoE is a chronic disease, so anything that we do we need to do long-term, and this is a discussion that has to happen with the patient. Patients tend to be very motivated to go above and beyond what they can tolerate as a treatment if their symptoms are severe. We have to have a discussion that includes different options for treatment in a shared decision-making way, where we would say diet is not working for you, here are the different treatments. Is this something that you wish to consider? Would you like a more restricted diet? Can you do a more restricted diet? This is where you would go over the pros and cons of a more restricted diet and do they have the motivation and the setting to be able to do more restrictive diets or should we go to medications? In that case, topical corticosteroids are a very good option. In fact, if we look at the American Gastroenterological Association/Allergy Joint Task Force guidelines, topical steroids were given a good recommendation, so that's an option. The 1 biologic, dupilumab, was just approved by the Food and Drug Administration (FDA), so that's another consideration for some patients with EoE.

Ikuo Hirano, MD: One other discussion point would be the concomitant use of PPI therapy and diet therapy up-front. In my own practice, I would have started PPI monotherapy before adding diet therapy, steroids, or dupilumab because a significant proportion of patients - as high as 40%, 50%, respond to PPI monotherapy. In this patient who has GERD and EoE, I would probably start PPI monotherapy first and then repeat the EGD. If he did not respond to PPI monotherapy, then I would've added the diet or steroid or considered dupilumab.

Mirna Chehade, MD: Another advantage of monotherapy, even though it might take longer to get into remission, [is that] it is a single therapy. If they get combination therapy, they pay for it in the long run because if they have had multiple treatments and their disease goes into remission, the question becomes, what fixed it? Now you're doing the workup in reverse, trying to remove 1 treatment and see if they're still in remission, which is just as intense in terms of EGDs as starting from the beginning. You also expose the patient to potential side effects of combination therapies when another treatment is layered on, or the inconvenience of a restrictive diet.

Ikuo Hirano, MD: Of course it turns out in this case that combination therapy was appropriate because the patient had both and did not respond to the PPI alone. But we'd still argue to try the PPI first.

Question 8

JD is a 29-year-old male with complaints of heartburn and dysphagia on whom you performed an EGD 6 months ago and diagnosed with EoE. EGD findings included linear furrows, circumferential rings, and an attenuated vascular pattern, and LA grade B esophagitis. The esophageal biopsy showed 65 eosinophils per HPF. You recommended twice-daily PPI therapy and an EoE diet (6 food elimination diet) during the 3 months since diagnosis. On follow-up 3 months later, his heartburn has improved, but dysphagia has persisted. You perform another EGD which reveals that the esophagitis has resolved but linear furrows, circumferential rings, and attenuated vascular pattern are still present. Esophageal biopsy shows 50 eosinophils per HPF.

Which of the following patients with histologically confirmed EoE would be the best candidate for dupilumab?

A. A newly diagnosed patient.
B. A patient who had failed both PPI and swallowed topical corticosteroids.
C. A patient without esophageal strictures.
D. A patient who responded to PPI therapy.

The correct answer is: B

Answer rationale

• Dupilumab was recently approved in the US for treatment of EoE in adult and pediatric patients aged 12 years and older, weighing at least 40 kg.
• Dupilumab, a fully human monoclonal antibody, blocks interleukin-4 and interleukin-13 signaling, which have key roles in eosinophilic esophagitis.
• Long-term safety of dupilumab is still being established.
• Use of dupilumab in relation to other treatment options is not yet clearly established.
• Society guidelines are in process of being updated.
• In phase 3 clinical trials, approximately 60% of patients who received dupilumab achieved histologic remission.
• High cost and subcutaneous administration could be barriers to adherence.
• Use of dupilumab can be beneficial in patients with atopic comorbidity or those who have been refractory to established therapies.

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Dupilumab. Prescribing information. sanofi-aventis U.S. LLC and Regeneron Pharmaceuticals, Inc. Accessed February 27, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s046lbl.pdf

Faculty Discussion

Ikuo Hirano, MD: The correct answer is B: patients who have failed both PPI and swallowed topical corticosteroids. I think that's kind of low-hanging fruit for using dupilumab for EoE. Interestingly, the FDA approval doesn't stipulate failure of any therapy for using dupilumab. It just states approval for EoE, patients aged 12 years and older who weigh at least 40 kg. So, answer A is actually technically not incorrect; it's just relatively not the right answer. Any newly diagnosed EoE patient can be considered for dupilumab, but I think in clinical practice we typically would start some other form of therapy. In my own practice, I always start PPI therapy first, before I consider alternative therapies, like steroids, diet, and now dupilumab.

For answer C, patients without esophageal stricture, there is no evidence of a lower or higher response rate for EoE to dupilumab in the presence or absence of esophageal strictures. In fact, many patients that went into the dupilumab phase 3 clinical trials had esophageal strictures, and many of them had had prior esophageal dilations, so the presence of a stricture would not be a reason to consider or dissuade you from using dupilumab.

For answer D, prior response to PPI therapy, if the patient responded to PPI therapy, I would just continue the PPI therapy. I wouldn't then switch to a biologic, and similarly I wouldn't switch to steroid or dietary therapy. If they respond to initial treatment with a PPI, I would just continue the PPI.

Mirna Chehade, MD: There are other indications though to go ahead with dupilumab use. For example, those that have side effects to these standard-of-care therapies, such as a patient who's having recurrent *Candida* esophagitis, not just a simple *Candida* colonization, but *Candida* esophagitis where we need to give them repeated fluconazole courses. This is a patient who should not get a topical corticosteroid and should be considered for dupilumab. A patient who needs high doses of topical corticosteroids to be controlled and therefore risking adrenal insufficiency should also be considered for dupilumab. This is rare, but this is another potential indication. Patients that do not want steroids at all and are exhausted from a reduced quality of life or the restrictions that a diet can cause for their day-to-day life are also potential candidates for dupilumab.

As we know, 60% to 70% of patients with EoE have concurrent atopic comorbidities, such as asthma, allergic rhinitis and/or atopic dermatitis, and some of them also have immunoglobulin E (IgE)-mediated food allergy. Patients who have 2 atopic comorbidities may be on other topical corticosteroids for those comorbidities, for example, a nasal steroid for their allergic rhinitis and/or an inhaled steroid for their asthma. In those patients, adding another topical corticosteroid for the esophagus may not be a great idea. This could be a patient where dupilumab could be used as first line, since it will address all their atopic comorbidities at the same time, including EoE.

Ikuo Hirano, MD: I have to say that, in my practice, many of those patients with moderate to severe atopic dermatitis or asthma were already being considered for biologic therapies before the FDA approval of dupilumab for EoE. But many of those, unfortunately, have already been taken out of the equation because they were started on dupilumab for the other comorbidities. I think there's a question about the patients with mild symptoms with concomitant mild atopic dermatitis or mild asthma. How do you factor in using dupilumab in those types of patients which I would say is the majority of my EoE patients?

Mirna Chehade, MD: Those are the tough ones. If you need an inhaled steroid for 2 weeks out of the year during the bad spring season, for example, then is this really a concurrent comorbidity that needs to be addressed with a biologic? Most likely not. So, I think it's important to know how bad the comorbidities are and what medications will be needed. If someone needs 2, 3 courses of oral prednisone for their asthma, that's a no-brainer. In that case the asthma is not under control and they could benefit from a biologic such as dupilumab. With the milder ones, on the other hand, it's more debatable. There are also adherence issues. PPIs need to be taken once or twice a day, every single day, even though it's just a pill, and usually a smaller pill so it doesn't get stuck in the event the EoE's active. Topical corticosteroids, if you're prescribing an off-label fluticasone to swallow, then it's just a puffer they carry around. If it's a thickened budesonide and they do not have access to a compounding pharmacy, they're actually doing their own compounding at home, and that's labor-intensive and they often have to take it twice a day. So, many patients are interested in dupilumab because it is given as a shot once a week.

Module 5: Dupilumab

Question 9
A 35-year-old woman is evaluated in follow-up after an emergent EGD for food impaction of the esophagus. A diagnosis of EoE is made after histologic examination of an esophageal biopsy specimen showed 45 eosinophils per high-power field. On examination, she appears well. Dupilumab 300 mg once weekly is prescribed. The patient is shown how to self-inject.

For which of the following sometimes severe adverse reactions to dupilumab should this patient be advised to contact you right away?
A. Diarrhea
B. Injection site reaction
C. Hypersensitivity
D. Arthralgias

The correct answer is: C

Answer rationale
• Hypersensitivity reactions are rare and usually occur within 1 hour of injection.
• Reactions have occurred as much as 1 month after starting.

• Most common hypersensitivity reactions are urticaria, angioedema.
• Ocular surface disorders such as conjunctivitis and blepharitis are also rare, mostly mild to moderate and in most cases resolve without discontinuation of dupilumab.
• Local injection site reactions occur relatively frequently; most are minor and can be treated topically.
• Allergic reactions, including joint pain, skin rash, breathing problems, dizziness, can be severe.

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Faculty Discussion

Ikuo Hirano, MD: The correct answer is C: hypersensitivity reactions. Hypersensitivity reactions are certainly a concern for any biologic therapy, but fortunately they were uncommon in the trials for dupilumab. Generally, under 1% of patients have been reported to have such hypersensitivity reactions. But if that occurred, you would stop the dupilumab. Diarrhea was not something that was significantly reported in the phase 3 clinical trial program for EoE with dupilumab. Injection site reactions are, in fact, the most common side effect that was reported. Over one-third of patients had injection site reactions, but there were a comparable number of patients who had injection site reactions to placebo as well as to dupilumab. The other distractor here was answer D: arthralgias. That was a side effect that was reported in the trials for EoE with dupilumab. The rate was about 2% for dupilumab and about 1% with placebo.

Mirna Chehade, MD: I think it was reported for EoE that there was a slight increase in the rate of upper respiratory infections or herpes virus infections. I'm not impressed with this data so far based on my clinical experience as well as having been an investigator on the trials. This doesn't seem to be a major concern. I do counsel my patients on the rare occurrence of eye problems, namely conjunctivitis or keratitis. If they get ocular symptoms or if they have any history of any eye problems, we investigate that with an ophthalmologist before we start just because, even though it's rare, it is more serious than those other side effects.

It seems like dupilumab is very specific against the type 2 immunity and doesn't affect the type 1 immune system as much. That's why we are not seeing significantly increased rates of upper respiratory infections or even situations where you're immunocompromised for certain infections where you get a more severe course following a viral infection or a bacterial infection. We have not seen that. It's not even in the package insert for EoE. We were all concerned about this during COVID while we were running the trials, but taking dupilumab did not seem to cause increased severity of COVID-19 infection.

Ikuo Hirano, MD: As you said, herpes infections are rare. I think it was 2% in the phase 3 trial for dupilumab and 1% for placebo, and those were not zoster. It was oral herpes infections that were reported. Dupilumab has been out for several years, approved for other type 2 inflammatory diseases. So we have a much more robust safety data set from its use for other atopic diseases that goes beyond the safety reporting during the most recent approval for EoE. It's generally, a very well-tolerated medication.

Module 6: Investigational Agents and Comanagement

Question 10
RK is a 10-year-old female who was diagnosed with EoE following intermittent random episodes of vomiting over 5 months, dysphagia with meats and breads, and 1 episode of food impaction requiring endoscopic food removal in the emergency department. After a 10-week course of PPI therapy her vomiting has lessened but she continued to experience moderate dysphagia. She was then treated with a swallowed topical corticosteroid, but experienced oral candidiasis despite good oral hygiene. You explain that this is not necessarily an indication to stop treatment, but her parents are asking about alternatives. Given her age, she is not a candidate for treatment with dupilumab. Her parents ask if any other medications might soon become available or if she would be a candidate for a clinical trial. She is allergic to peanuts and tree nuts. She also has allergic rhinitis and asthma that worsen in the spring and fall, resulting in throat clearing and cough with posttussive vomiting.

Which of the following agents that have been studied for treatment of EoE targets immunoglobulin E (IgE)?
A. Mepolizumab
B. Infliximab
C. Losartan
D. Omalizumab

The correct answer is: D

Answer rationale
• Several promising new therapies are at various stages of development.
• Agents in development target various pathophysiologic mechanisms:
    •Losartan targets transforming growth factor beta (TGF-β).
    •Mepolizumab targets interleukin 5 (IL 5).
    •Infliximab targets tumor necrosis factor alpha (TNF-α).
    •Omalizumab targets immunoglobulin E (IgE).

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ClinicalTrials.gov. Testing effectiveness of losartan in patients with EoE with or without a CTD. Updated September 24, 2020. https://www.clinicaltrials.gov/ct2/show/NCT01808196

Faculty Discussion

Mirna Chehade, MD: The correct answer is D, omalizumab. If we match each biologic with its mechanism of action, mepolizumab is an antibody target against interleukin-five (IL-5). Infliximab is ant-tumor necrosis factor alpha (TNF-α) biologic. Losartan targets transforming growth factor-beta (TGF-β) and omalizumab is a biologic that targets immunoglobulin E (IgE). However, an investigator-initiated study conducted by Kathryn Peterson's group at the University of Utah found no clinical or histologic improvement of patients with EoE when using omalizumab.

Ikuo Hirano, MD: I think it's good to note that, even though there has been a randomized trial of omalizumab for EoE, there was a 2020 task force on allergy/immunology practice parameters for EoE that did not recommend the use of anti-IgE therapy. There's trial data but it does not support its use. Among the other therapeutic agents here that were studied, mepolizumab, infliximab, and losartan, were all given no recommendation in the 2020 guidelines because there was insufficient evidence to support or refute their use. We will be seeing data from a phase 2 clinical trial in adults with mepolizumab being presented at a GI meeting in 2023. The initial pediatric studies, however, were not very impressive.

Mirna Chehade, MD: Keep in mind that EoE is a type 2 immune disease, so you would not expect any of these antibodies that work against the type 1 immune phenotype, such as infliximab, to be effective. Many of the drugs given for Crohn's disease, for example, target the type 1 mechanism. If you are targeting a type 1 mechanism, then it is less likely to work for EoE.

Ikuo Hirano, MD: One agent that's not on this list here which has been studied and had a successful outcome from a phase 2 clinical trial is cendakimab, which is a monoclonal directed against interleukin 13 (IL-13). The success of cendakimab in the phase 2 trial has led to an ongoing phase 3 clinical trial for EoE. Hopefully we'll have other therapeutic agents in the future.

Mirna Chehade, MD: With EoE, there are a lot of eosinophils in the esophagus. In fact 1 diagnostic criteria is 15 or more eosinophils per HPF in the esophagus. So you would think that targeting eosinophils with an antibody would be very successful. But so far those anti-eosinophilic biologics have not shown promising results. According to preliminary data, it is possible that the eosinophil is not the only immune cell in the esophagus that is responsible for disease pathophysiology. We'll have to stay tuned while we are working early in the chain of events, such as the type 2 immune pathway with dupilumab, which got good results, and now cendakimab, the anti-IL-13 that also works along the type 2 immune pathway and has shown good preliminary results from the phase 2 trial. It seems that if we work early on in the chain of the immune pathway, there's a higher chance of success.

Question 11

RK is a 10-year-old female who was diagnosed with EoE following intermittent random episodes of vomiting over 5 months, dysphagia with meats and breads, and 1 episode of food impaction requiring endoscopic food removal in the emergency department. After a 10-week course of PPI therapy her vomiting has lessened but she continued to experience moderate dysphagia. She was then treated with a swallowed topical corticosteroid, but experienced oral candidiasis despite good oral hygiene. You explain that this is not necessarily an indication to stop treatment, but her parents are asking about alternatives. Given her age, she is not a candidate for treatment with dupilumab. Her parents ask if any other medications might soon become available or if she would be a candidate for a clinical trial. She is allergic to peanuts and tree nuts. She also has allergic rhinitis and asthma that worsen in the spring and fall, resulting in throat clearing and cough with posttussive vomiting.

Comanagement of RK by a gastroenterologist and allergist is recommended because
A.The underlying mechanism of EoE is believed to be functional.
B. Endoscopic findings in EoE can sometimes be unrevealing.
C. There is an association between EoE and allergies.
D. Once diagnosed and under treatment, intervention by a gastroenterologist is no longer needed in EoE.

The correct answer is: C

Answer rationale
• Allergic etiology of EoE.
• Allergic comorbidity, advantages of treatment when multiple allergic conditions require treatment.
• Overall care enhanced with both allergy and gastroenterology knowledge/intervention.
• Others can assist in important ways (adherence, care planning, treating comorbidity): Primary care provider, dietitian, behavioral health provider.
• Burden of disease and quality of life can both be enhanced with optimized/individualized therapies.

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Hirano I, Furuta GT. Approaches and challenges to management of pediatric and adult patients with eosinophilic esophagitis. *Gastroenterology.* 2020;158(4):840-851.

Faculty Discussion

Mirna Chehade, MD: The correct answer is C. There's an association between EoE and allergies. In fact, 60% to 70% of patients with EoE have an allergic comorbidity, and this includes asthma, allergic rhinitis, atopic dermatitis, and/or IgE-mediated food allergy. So, it is important to have a collaborative management approach between a gastroenterologist and allergist in many patients with EoE. This patient, for example, has EoE but also has food allergy. She's allergic to peanuts and tree nuts. She also has allergic rhinitis and asthma that worsen in 2 seasons - spring and fall - that result in throat clearing and cough with posttussive vomiting.

All of these symptoms overlap. Is this patient sometimes throat clearing because she has EoE with secondary reflux? She's only 10 years old, so this is a possibility. Is she coughing because of reflux? Or is it asthma? Asthma or allergic rhinitis could be making her do a lot of throat clearing, and coughing, and the intensity of the cough could be causing her to vomit afterwards. You would need to differentiate these symptoms and try to see what is secondary to which comorbidity and address them accordingly so that you can get to the proper management of EoE without overdoing your management of the comorbidities. That's when an open discussion and communication with this patient's allergist and/or pulmonologist, if applicable, is really important.

Ikuo Hirano, MD: EoE is a great example of a multidisciplinary disease and, in this particular case, I think there'd be comanagement by a gastroenterologist and allergist. In some practice settings, the allergist plays the primary role managing EoE, and the gastroenterologist plays the secondary role in performing diagnostic testing. So, more of a technician and the allergist is directing therapy with dietary therapy, steroids, or biologic therapy. Certainly allergists are more experienced using biologic therapy for allergic diseases. In other practice settings, the gastroenterologist is the primary person managing the disease and will collaborate with the allergist for specific questions about concomitant atopic disease, food allergy problems, or for advice on using biologic therapy.

Mirna Chehade, MD: Comanagement does not only have to be where a biologic, such as dupilumab, is needed that will address comorbidities, but can also be helpful in just simple EoE management. Patients can have flare-ups of their allergic rhinitis and asthma causing GI symptoms, for example, and management needs to be with standard-of-care therapies so that we can isolate which comorbidity is causing which symptom so that we can address the true symptoms of each comorbidity, including EoE. A gastroenterologist is needed to evaluate symptoms with endoscopy. This is not about just obtaining biopsies. The endoscopic findings need to be monitored by a gastroenterologist, especially if you have concurrent problems such as a hiatal hernia, esophageal stricture, or esophageal narrowing. Even with current noninvasive techniques to diagnose EoE, a full endoscopy is still an important part of care. It's an important diagnostic tool in the diagnostic phase, and also in monitoring patients, especially those who have complications from EoE or findings concurrent with EoE.

Module 7: Summary

Discussion Points:

- Rising global incidence and prevalence of EoE due to improved disease recognition.
- Comorbid TH2-mediated inflammatory diseases are common, including atopic and autoimmune conditions.
- Diagnosis of EoE requires exclusion of other causes of esophageal dysfunction/irritation.
- EoE cannot be diagnosed by symptoms alone.
- Prolonged trials of treatments for other potential diagnoses such as acid reflux can delay diagnosis and increase the risk of long-term sequelae.
- EoE diagnostic criteria are based on symptoms, endoscopic appearance, and histologic findings.
- Barriers such as cost have been associated with lack of follow-up, particularly once acute symptoms have resolved.
- An option for first-line pharmacologic treatment is daily PPI therapy due to its low cost, wide availability, and ease of use.
- Dupilumab was recently approved in the US for treatment of EoE in adult and pediatric patients aged 12 years and older, weighing at least 40 kg.
- Society guidelines are being updated.
- Promising new therapies are at various stages of development.
- Shared decision making and comanagement can assist in important ways (adherence, care planning, treating comorbidity): primary care provider, dietitian, behavioral health, etc.

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Faculty Discussion

Ikuo Hirano, MD: The rising global incidence and prevalence of EoE is being driven by increased disease recognition, but also by a true increase in disease incidence. Comorbid type 2 inflammatory-mediated diseases are common, with the majority of patients having atopic disease, but also there is an increase in the rate of autoimmune disease. Diagnosis of EoE requires exclusion of other secondary causes of esophageal dysfunction symptoms as well as confirmation of eosinophilic inflammation. EoE cannot be diagnosed by symptoms alone. You need histopathologic confirmation with detection of 15 or more eosinophils per HPF

from esophageal biopsies. Prolonged trials of treatment for other potential diagnoses, such as GERD, can delay the recognition and diagnosis of EoE, and delayed diagnosis can lead to significant consequences, including stricture formation.

EoE diagnostic criteria are based on the combination of symptoms and histopathology, but keep in mind there are highly relevant endoscopic changes that can be detected in the majority of adults and children.

Mirna Chehade, MD: Barriers, such as cost, have been associated with lack of follow-up with many patients, particularly once acute symptoms have resolved. So, it's important that we keep an eye on patients and try to see what we can do to educate them about EoE and encourage them to follow up. An option for first-line pharmacological treatment is daily PPI therapy due to its low cost, wide availability, and ease of use. Dupilumab was recently approved in the United States for treatment of EoE in adult and pediatric patients aged 12 years and older, weighing at least 40 kg.

Currently, society guidelines being updated, so we will soon know where all the different treatment options fall in the algorithm for patients with EoE. Promising new therapies are at various stages of development in the form of multicenter clinical trials, so we'll keep an eye on that. Finally, shared decision-making and comanagement among specialists and primary care providers are important to provide proper care for patients with EoE, enabling us to address issues that may arise, including adherence to medication, care planning, and treating comorbidities so that the best outcome can be achieved for patients with EoE.

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