



Clinical Pearls

Is the consistency more important than the ingredients for steroid treatment in eosinophilic esophagitis?

Introduction

Eosinophilic esophagitis (EoE) is an increasingly prevalent condition characterized by chronic inflammation of the esophagus with a proposed cause focused on dietary antigens.¹ This theory is further supported by the fact that most patients with EoE have a family history of allergic disorders.² In the pediatric population, symptoms include food aversion, dysphagia, food impaction, failure to thrive, generalized abdominal pain, heartburn, nausea, and vomiting. Because many other pediatric illnesses can present with these symptoms, multiple criteria are used in the diagnosis of EoE, including symptoms suggestive of esophageal dysmotility, histologic evidence of eosinophilic infiltration, resolution of esophageal eosinophilia with elimination diet or topical corticosteroid therapy, and esophageal eosinophilia not responsive to proton pump inhibitor (PPI) therapy alone. Diagnosis is confirmed via mucosal biopsy when greater than 15 eosinophils per high-power field are present in the proximal and distal esophagus in a symptomatic patient. In addition to this histologic evidence, many visual findings can be suggestive of EoE, including endoscopic findings of white exudative plaques, mucosal rings or trachealization of the esophagus, esophageal strictures, linear furrows, and edema.^{1,4}

Current treatment for EoE involves diet modification, oral steroids, or both.^{1,3} Many studies have been performed comparing different steroid regimens, including systemic, topical, and nebulized, with the safest and most typical steroid regimen consisting of viscous budesonide respules (Pulmicort; AstraZeneca, London, United Kingdom) mixed into a slurry-type solution with sucralose artificial sweetener (Splenda; Tate & Lyle, London, United Kingdom, and Johnson & Johnson, New Brunswick, New Jersey).^{1–3,5–7}

Diagnosis

The patient is a 2-year-old, full-term male with a history of breastfeeding who had no oral intake issues until he began eating solid foods at 10 months. When he was weaned from breast milk and started on solid food, he began having multiple episodes of emesis every day. Although never appearing to be nauseated, he continued vomiting after every meal and multiple times overnight until he was admitted to the local children's hospital in March 2012 for failure to thrive. His chief symptom at that time was a loss of weight at multiple previous office visits and a diagnosis of failure to thrive (less than first percentile starting at 9 months old). While the patient was in the hospital, a nasogastric tube was placed, and he was started on continuous tube feeds with a hypoallergenic baby formula (Elecare Jr vanilla flavored; Abbott Laboratories, Abbott,

Illinois). An upper gastrointestinal and small bowel series was performed, which revealed reflux with no anatomical abnormalities. Because of failure to thrive, no PPI trial was attempted. After an upper endoscopy, he was diagnosed as having EoE based on esophageal biopsy results (upper biopsy, 5 eosinophils per high-power field; middle, 50 eosinophils; and lower, 15 eosinophils) and visual evidence (furrows and erythema; Figs 1 and 2) and was prescribed 1 mg of viscous budesonide mixed with the sucralose artificial sweetener (1 mg of budesonide mixed with five 1-g packets of Splenda to create approximately 4 mL of a slurry-type mixture) and lansoprazole (Prevacid; Novartis, Basel, Switzerland). Throughout his life, the patient was very active, reached appropriate milestones, and exhibited no symptomatic issues (eg, nausea and lethargy) when he was not vomiting.

After Treatment

His follow-up upper endoscopy 3 months later revealed near-complete resolution of eosinophils (upper, 3 eosinophils; lower, 2 eosinophils), but his symptoms, although lessened, were still present, in addition to a new symptom of daily episodes of lethargy. He had been strictly tube fed via nasogastric or nasoduodenal tube from the time of his admission to the hospital in March to his June endoscopy. He continued having multiple episodes of emesis, including every night, but he had good weight gain (8.3 kg in March and 9.5 kg in June).

Because of his reflux, continued emesis, and the presumed need for long-term tube feeding, he underwent laparoscopic Nissen fundoplication and gastrostomy tube placement. While in the hospital, his steroid and reflux medications were withheld because of difficulty increasing his tube feed rate, but on postoperative day 3, the patient demonstrated that he was hungry and tolerated a half jar of baby food with no vomiting. He continued eating a daily small meal in addition to his tube feeds and was discharged on postoperative day 5 tolerating his tube feeds at goal with no retching or vomiting.

Postoperative Course

He was again given the budesonide-sucralose slurry on his return home, but during the next several weeks and months, he continued experiencing daily episodes of retching, emesis, and lethargy. Changes were made to his feeding regimen but rarely to his medication regimen. Beginning in January 2013, he stopped taking his medications because no other interventions were helping and an attempt at increasing his oral intake was made. Surprisingly, his oral intake increased to the point that tube feeds were only used at night, and his episodes of emesis decreased to one every few days. Unsurprisingly, his February 2013 endoscopy revealed a return of his eosinophils on his esophageal biopsies

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Figure 1. Endoscopy of the lower third of the esophagus showing linear furrows and erythema (March 6, 2012).

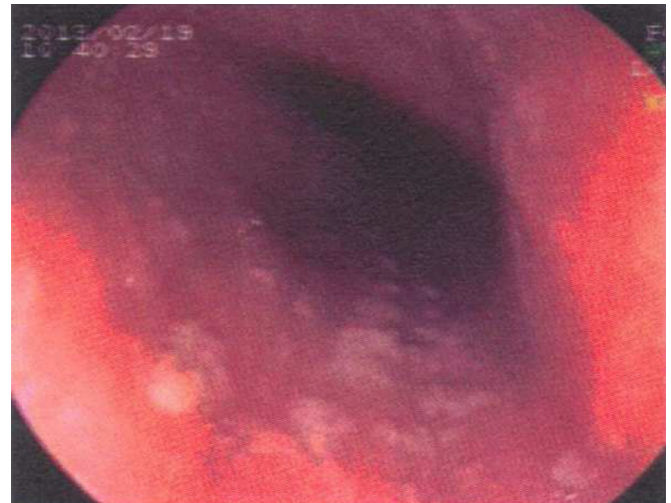


Figure 3. Endoscopy of the middle third of the esophagus with white exudative plaques and erythema (February 19, 2013).

(upper, 25 eosinophils; lower, 40 eosinophils) with continued visual evidence (Figs 3 and 4) of inflammation and white exudative plaques.

Alternative Treatment Plan

Attempts made to restart the viscous budesonide-sucralose slurry were refused by the patient and parents because they had learned that another family member had reportedly had a cutaneous reaction to sucralose artificial sweetener that resulted in patches of an erythematous and pruritic rash with eosinophilia. The suggestion was made to try mixing the budesonide with honey instead of the sucralose artificial sweetener. However, the amount of honey needed to create a thick, slurry-like consistency was too much for the patient to ingest at one time. An assumption was made that the steroid could be mixed with any substance as long as the consistency of the slurry was such that the steroid coated the esophagus, so the family searched for substances at home to mix that the patient could tolerate and settled on mixing viscous budesonide with 2 tsp of powdered sugar. The mixture was tolerated by the patient as far as taste, consistency, and amount (approximately 5 mL). He was not limited to an exclusive elemental

diet as long as he was taking his steroid mixture daily, so the family enrolled the patient in an 8-week feeding program to assist in increasing his oral intake and the variety of foods in his diet, while still receiving nightly tube feeds.

His symptoms were unchanged, and he continued having an episode of emesis every few days. To evaluate whether there were any new anatomical or mechanical issues, a repeat upper gastrointestinal series and a gastric-emptying study were performed, the results of which were negative. Because of the lack of symptom relief, everyone was unsure whether the powdered sugar–budesonide mixture was working. However, his endoscopy in June 2013 (4 months after the new steroid mixture was taken) revealed no evidence of EoE visually (Figs 5 and 6) or on biopsy specimens. Because his symptoms had remained unchanged but not resolved, his formula was changed from Elecare Jr vanilla to unflavored Neocate, which contains no sucralose artificial sweetener, with near-complete resolution of his symptoms 1 month later.

Discussion

EoE seems to be an ever-changing disease, from patient to patient and from year to year in the same patient. Improvements in



Figure 2. Endoscopy of the middle third of the esophagus showing linear furrows and erythema (March 6, 2012).



Figure 4. Endoscopy of the lower third of the esophagus with white exudative plaques and erythema (February 19, 2013).



Figure 5. Endoscopy of the lower third of the esophagus with minimal erythema and no plaques or furrows (July 2, 2013).

these patients' lives have been made with the realization that elimination of dietary antigens helped with symptom relief, and treatment with topical steroids assisted in eradication of esophageal eosinophils.

Our case has 2 important aspects that should be emphasized. The first aspect is the realization that it may be consistency of the steroid mixture rather than the ingredients that infer the effectiveness of the EoE treatment. The second aspect is the willingness of the medical team to listen to the research and suggestions of the patient's parents and applying them to the treatment plan.

This case is potentially an example of a reaction or intolerance to the artificial sweetener. Most studies have evaluated using sucralose artificial sweetener in the mixture.^{5–7} It is known, easy to measure, and dissolves well, but when the patient refuses the treatment whether it is due to taste or intolerance, the known and studied alternatives are lacking. Perhaps the consistency is the most important aspect of the steroid mixture, and ensuring that the mixture is of a consistency that it is thick enough to coat the esophagus is more important than the mixing ingredient. Finding a mixing food that the child tolerates is potentially the most

important part, whether it is powdered sugar or honey or pancake syrup or simply the last bite of a pureed meal.

Another important aspect of this case was the medical team and parents working together to determine the cause of continued symptoms. The parents noticed that when they would stop use of many of the patient's medications, including the steroid mixture, when he was experiencing an illness (eg, cold or ear infection) and after his operation, he was not as lethargic, and the only symptoms that were present were from his acute illness. Parents' suggestions and ideas must be taken into account by medical teams because the parents see the patient every day and are able to see which treatments are most and least effective and also because the parents are dedicated to a single patient and are able to perform much more focused research and studying than physicians and nurses. The fact that this patient's parents made the extra effort to not only research their child's illness but also research their family's medical history contributed heavily to this case and may have prevented future unnecessary and/or invasive testing.

Every patient is different. Sometimes physicians' own biases regarding disease management may cause them to overlook or ignore valuable input from the patient or the patient's caregivers. The need to step outside the typical treatment regimen should always be considered, and in this case, changing the regimen may have prevented further unnecessary and possibly invasive testing. By taking that extra step, the medical team was able to determine what was causing many of the patient's symptoms. Randomized trials are needed to assess whether this could be an alternative treatment, to determine whether it is the mixture or the consistency that matters most, and to evaluate premixed EoE treatments.

A Father's/Physician's Perspective

As the lead author, I was asked to add a section explaining the personal tone of the paper. The patient in this example is my son. As a new father and a "seasoned" physician, in my third month of a general surgery residency, I loved every second of being a father and thought about him nonstop. When I finally came to the realization that he was sick and the things going on with him were not normal, I felt like a failure as both a father and a physician. How could I not have seen what was going on? Had our delay in treatment caused significant problems?

When he finally began receiving the needed treatment, feeling better, and gaining weight, I felt like a hero again, as both a father and a physician. As an inpatient on the pediatric surgery service, any question we had regarding his care was answered quickly because I could pick up my telephone and call the chief, mid-level or first-year resident, or even the attending physician, and we knew what the day's plan would be. These were my friends and co-workers who were taking the time to answer my questions. Without my considerable advantages in obtaining the knowledge, the experience would have been potentially more frustrating. As physicians, sometimes we forget that the asymmetry of information is powerful leverage, and we need to be sure that patients' parents stay as informed as possible. However, once we were finished as surgical patients, I quickly came to realize that I was the father to "just another patient."

We received care from the allergy and immunology department, gastroenterology and nutrition department, general pediatrics department, otolaryngology department, and the pediatric feeding clinic. Because EoE is not an illness commonly encountered on any surgical service, this was new territory for me, and my wife and I had lots of questions and concerns, especially regarding invasive testing. Yet, far too often, the questions we deemed appropriate for one care team were quickly dismissed as another team's issue, which were then passed off to another team and then another. As a physician I was more than familiar with this exercise. It was always



Figure 6. Endoscopy of the middle third of the esophagus with minimal to no erythema and no plaques or furrows (July 2, 2013).

part “I don’t know the answer” and part “I don’t want to be responsible for the outcome if I am wrong.” I was also familiar with the use of excessive medical terms and talking in circles to get out of a discussion for which you do not have the answers. The answer we really wanted was simple, but nobody would say it. Just tell me you don’t know what’s going on. Tell me you don’t know why he’s still throwing up and why he still can’t eat anything after what has been appropriate treatment. Tell me you haven’t seen this before, but you are going to help us figure out what is going on. As a parent or a patient, I want my physicians to be honest when they do not have all the answers. Patients can accept that as long as we trust that you are going to research the question further or involve someone with more expertise who does know the answer.

In addition to the issues with communicating with our medical teams, I struggled with the thought that I was hindering my son’s care. I would not call myself difficult to deal with because I was never confrontational, argumentative, or rude, but I did demand a reason for testing and an explanation for things that my wife may have agreed to without me. Why do an expensive and time-consuming gastric-emptying study when you can just give erythromycin and see if it helps? It’s cheap, and if he doesn’t improve, we have our answer. Explain how continuing to give him a PPI helps with EoE when he has had a Nissen fundoplication and no further evidence of reflux on his tests. After a while, I got the feeling that suggestions regarding new medications or testing that a physician would normally make were no longer being made to prevent a flurry of questions. I don’t know that this was actually happening, but it made me regret being so involved in my son’s care. My residency had taught me to have a reason for everything I do, and if you cannot explain why you are doing it, you probably should not be doing it. Maybe it was unfair of me to question what other physicians and nurses believed was right, but I did not want my son to follow an algorithm. I wanted thought and care involved in every decision. With every decision, I wanted them to answer the question, “What would you do if this were your son?”

As physicians, we all encounter parents or patients who want justification for every care measure taken, and this can seem obstructive to care. What we have to realize is that this may be motivated by fear, concern, a loss of control, or other personal factors. Having been on both ends of this situation, this was a particularly enlightening experience that will help me communicate with families in the future. We have to remain sensitive to the patient experience.

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