# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

## Topical Steroid Therapy for Eosinophilic Esophagitis

Jeffrey A. Alexander, MD
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic College of Medicine
Rochester, Minnesota

### G&H What is the first therapeutic step for patients with suspected eosinophilic esophagitis?

**JA** The first step is to exclude gastroesophageal reflux disease (GERD) as the cause of the symptoms. However, this may be somewhat difficult to do because of the overlap between GERD and eosinophilic esophagitis (EoE). In general, in adults, EoE presents primarily with dysphagia and, less commonly, with chest pain. GERD usually presents with heartburn or regurgitation, but the symptoms of dysphagia and chest pain are not uncommon with GERD. pH testing can be used to differentiate between the 2 conditions, but it has a false-negative rate of approximately 20%. Besides having similar overlapping symptoms, GERD and EoE are not uncommonly both present in many adult patients. In clinical practice, it is recommended to administer a high-dose 8-week proton pump inhibitor (PPI) trial (twice-daily therapy with standard PPIs) and then perform a follow-up endoscopy with biopsy at multiple levels throughout the esophagus to determine whether a patient has a histologic response to PPI medication. However, even this method is not perfect for distinguishing GERD from EoE because some patients with GERD may not respond to high-dose PPIs, and PPIs have been shown to have anti-inflammatory effects unrelated to acid suppression. Patients with EoE with a histologic response to PPI treatment are deemed to have PPI-responsive esophageal eosinophilia (PPI-REE). By consensus, once PPI-REE has been excluded, the patient is considered to have EoE, and treatment usually begins with either dietary or steroid therapy.

### G&H When should topical steroids be used, and when should dietary therapy be used?

**JA** There is no right or wrong answer to this question, as it is difficult to choose between these 2 therapies. My personal preference is to start with a topical steroid therapy unless the patient is very motivated for dietary therapy, as the latter option (usually 6-food elimination diet) is quite involved, requiring multiple endoscopies over several months. Most patients are not motivated enough for dietary therapy right out of the gate, and it can be good for a physician to see patients for a few months and see how they do. This is an area of significant controversy, but if a patient has a widely patent esophagus and responds quite quickly to topical steroids with no flare-up or symptoms after stopping for a few years, then intermittent short courses of topical steroid might be the best option for him or her. If a patient has more significant fibrotic disease, requires dilation, or has a flare or symptoms after stopping steroids, the patient might be best treated with dietary therapy long term.

### G&H How effective is topical steroid therapy at inducing both symptomatic and histologic response in EoE?

**JA** Unfortunately, this is difficult to determine because trials have used different agents, delivery systems, and dosages. I would estimate that at least a partial symptomatic response is seen in 60% to 75% of adults with EoE who take topical steroids. In contrast, histologic response has fared better; complete histologic response is seen in approximately 60% to 70% of adults with EoE who are treated with high-dose

topical steroids, and partial response is seen in approximately 90%. In all trials but one (a trial conducted by my colleagues and I), patients have shown symptomatic response. The differing results may have been related to the instrument used to measure response in our trial, as the placebo response was quite high. We know that EoE can cause fibrosis of the esophagus and loss of compliance in the esophagus; therefore, when histologic disease is treated, dysphagia may persist in some patients related to fibrosis with esophageal narrowing and loss of compliance. We suspect that eosinophil products may also cause dysphagia by inducing mucosal stickiness or roughness. Many patients are treated with a topical steroid, and their dysphagia resolves in a few days as a result of decreasing this stickiness. It is highly unlikely that a few days of steroid therapy will have significant effects on reversing esophageal fibrosis. It is very possible, and likely probable, that treating patients with topical steroids eliminates the inflammatory component, perhaps thereby decreasing the stickiness of the esophagus. Therefore, some patients with a scarred-down, narrowed esophagus have dysphagia as a result. This will not get better by treating the eosinophils alone; the patients may need mechanical disruption or dilation of the underlying fibrosis. This would be my leading guess for why histologic response is a little better than symptomatic response in EoE.

**G&H** Which topical steroid is the most effective for EoE therapy, and what dose is ideal?

**JA** The 2 most commonly used steroids for EoE are budesonide and fluticasone. Budesonide can be administered as a liquid (in respules) or as a powder that can be compounded. Due to the bitter taste of budesonide, patients often mix it with a sweetener, such as sucralose, pancake syrup, chocolate syrup, or honey, to make a slurry, which is called oral viscous budesonide. Other mixing agents used to help the patient swallow the solution include applesauce and Rincinol, a topical adherent. Budesonide can also be given in a nebulized form, which is often done in Europe. However, Dellon and colleagues have shown that patients experience greater esophageal contact time and response with the slurry formulation than the nebulized formulation.

A variety of budesonide doses have been examined in clinical trials. Studies have found reasonably good results with 1 mg twice-daily budesonide in adults. However, in clinical practice, my colleagues and I have used higher doses, occasionally as high as 3 mg twice daily in some patients (although doses above 2 mg twice daily have not been formally studied). An abstract presentation (which should be published in full soon) by Gupta and colleagues on a multicenter trial of oral viscous budesonide in adolescents found a complete histologic response rate (defined as ≤6 eosinophils per high-power field) of 17% for .5 mg once daily, 44% for 2 mg once daily, and 100% for 2 mg twice daily. This last dose is actually much higher than the dose typically used in adult studies, which is significant because patients in this study were only adolescents. Therefore, it is unclear whether the standard 1 mg twice-daily dose of budesonide is enough.

The other EoE treatment option, fluticasone, can be given in a swallowed aerosolized formulation of 110 or 220 µg per puff. Adult studies that used 880 µg of fluticasone twice daily have had good histologic response rates, and 1760 µg daily is the standard dose of this medication. Adult patients using 440 µg twice daily of fluticasone have experienced less robust histologic response in studies, suggesting that the dose of fluticasone should be 880 µg twice daily. Further studies are needed with higher doses.

Appropriate dosing is an area of controversy in pediatric patients as well. Currently, the standard dose for budesonide is usually .5 mg twice daily until the patient is over 5 feet tall or 11 years of age, and then adult dosing of 1 mg twice daily should be used. In contrast, the current dose for fluticasone might be 440 µg twice daily for younger children and 880 µg twice daily for adolescents. However, appropriate dosing and vehicles of drug delivery to the esophagus clearly need further study. There are currently ongoing studies on this issue, and I suspect, in the next several years, that we will have a better indication of proper dosage as well as commercially available products designed to deliver these compounds directly to the esophagus.

**G&H** How long should topical steroid therapy be given to patients with EoE?

**JA** We do not know the answer to this question. Standard steroid therapy for EoE is anywhere from 2 to 8 weeks, and most trials use 6 to 8 weeks of therapy. Interestingly, Straumann and colleagues conducted a trial with budesonide (1 mg twice daily) and found a very strong (>70%) histologic response rate with only 15 days of therapy. Thus, it is unclear what the length of therapy should be.

**G&H** Is lifelong topical steroid therapy ever needed?

**JA** Some physicians argue strongly for lifelong therapy for all patients with EoE. Examining their EoE database, Schoepfer and colleagues found that the longer people with EoE are without treatment, the greater the chance they have esophageal stricturing disease. The researchers found that patients who saw a gastroenterologist after 20 years of untreated disease have a 70% risk of having an esophageal stricture. This would support the use of maintenance therapy in all patients with EoE. However, there are likely patients who have eosinophilia present in their esophagus who have mild or minimal symptoms and never present to a gastroenterologist. A population-based

study found significant esophageal eosinophilia present in 1.1% of the population, which is approximately 20 times more frequent than the prevalence of clinically diagnosed EoE. There have not been any good long-term natural history studies prospectively following diagnosed EoE patients. Therefore, it is currently the practice of my colleagues and I to offer maintenance therapy to those who have a small-caliber esophagus or esophageal stricturing as well as those who experience frequent symptom recurrence after stopping steroid therapy. This encompasses the majority of patients with EoE but not the entire pool. It is unclear whether patients with EoE who have a normal-caliber esophagus and infrequent symptoms should receive maintenance therapy. However, I do not think that we have enough evidence to insist on this; moreover, it is very difficult to get asymptomatic patients to take steroid therapy long term unless the physician can make a strong case to them that they will clearly benefit from that treatment.

**G&H** What is the ultimate goal of therapy in these patients?

**JA** We do not really know the appropriate goal of therapy—should it be histologic remission or symptomatic remission? What are the costs of the drug along with the adverse effects of therapy to induce histologic remission? My colleagues and I usually aim to achieve histologic remission with the goal of having an esophageal peak eosinophil count of less than 10. However, it is unclear at this point in time what level of eosinophilia leads to significant long-term complications such as fibrosis. It may be that knocking eosinophil counts down to a certain number, for example less than 20, may be enough to prevent fibrosis, but we do not know.

**G&H** Are there any significant concerns with long-term steroid use, particularly in children?

**JA** We know that children receiving inhaled steroid therapy for asthma have a 1 to 2 cm lower height than their counterparts, and growth can be affected into adulthood. Another concern is infection, as 15% to 25% of people taking topical steroids develop *Candida* infections of the esophagus. These infections are generally asymptomatic and are usually discovered on endoscopy. In the only maintenance steroid trial of EoE, which was conducted by Straumann and colleagues, who used the fairly low dose of .5 mg twice-daily budesonide, there were no *Candida* or herpetic infections. Lastly, there is a concern about bone density with long-term steroid use; however, data on people using inhalers for asthma for 1 to 3 years have not shown a change in bone density. We know that, in normal controls taking these steroids by mouth, serum levels are significantly lower than those seen with inhaled steroids. This might suggest that the swallowed steroids used to treat EoE may be safe to take long term.

There are also a few other caveats. One study showed that budesonide has poorer metabolism in EoE patients than in normal controls. I cannot explain this finding; it needs confirmation in another study. We also know that people with EoE have increased esophageal permeability, and it is not clear that serum pharmacokinetic studies on normal controls would be similar to those of patients with EoE. Oral, inhaled, high-dose steroids for asthma have shown some effects on the hypothalamic pituitary axis, but these were not of great clinical concern. All of the above concerns make it imperative that steroid toxicity be further evaluated in long-term studies.

**G&H** Do topical steroids differ greatly in terms of cost and insurance reimbursement?

**JA** There is a dramatic difference in price and reimbursement among steroids. Importantly, steroid therapy in EoE can be quite expensive. Some insurance companies will pay for commercially available products and refuse to pay for compounded products, even though they are much less expensive. For example, my colleagues and I did an analysis of several pharmacies in Rochester, Minnesota and found that a formulation of budesonide respules (Pulmicort, AstraZeneca) at 1 mg twice daily cost $1,613 for 6 weeks of therapy and a fluticasone inhaler at 880 µg twice daily cost $967 for 6 weeks of therapy, whereas compounded budesonide at a dose of 3 mg twice daily (which is 3 times the dose of the noncompounded formulation) mixed with a sweetener cost only $141 for 6 weeks of therapy. Thus, a compounding pharmacy can deliver these medications at a price that is manageable, particularly for maintenance therapy. We await commercially prepared products for the treatment of EoE.

*Dr Alexander has been a consultant for Aptalis and Meritage and has had a financial interest in Meritage.*

## Suggested Reading


Alexander JA. Steroid treatment of eosinophilic esophagitis in adults [published online March 27, 2014]. *Gastroenterol Clin North Am*. doi:10.1016/j.gtc.2014.02.001.

Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2012;10(7):742-749.e1.

Contreras EM, Gupta SK. Steroids in pediatric eosinophilic esophagitis [published online March 31, 2014]. *Gastroenterol Clin North Am*. doi:10.1016/j.gtc.2014.02.008.

Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012;143(2):321-324.e1.

Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology*. 2013;145(6):1230-1236.e1-2.

Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2011;9(5):400-409.e1.