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Modified oral enteric-coated budesonide regimens to treat pediatric eosinophilic gastroenteritis, a single center experience

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To the Editor:

Eosinophilic gastrointestinal diseases (EGID) can present with a variety of symptoms including abdominal pain, vomiting, and diarrhea, as well as eosinophil-predominant mucosal inflammation leading to malabsorption and poor weight gain.¹ Reports from a large national database suggest that eosinophilic gastroenteritis (EG) is represented in 8.4/100,000 of the population; children represent the majority of cases.²

Significant attention has been directed towards optimal treatment strategies given the negative side effects of systemic steroid use in children³, including investigation into elimination diets which are not as successful in treating disease distal to the esophagus.⁴ At our institution we found that only approximately 25% of patients with EGID respond to dietary intervention.⁵ Several case reports describe successful use of “triphasic” or modified enteral budesonide therapy in EGID.^{7–9} However, there is limited information available about this approach in children. Here we describe a series of EGID patients treated with a modified enteral budesonide strategy at the Children's Hospital of Philadelphia.

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Budesonide is a steroid with high first pass metabolism. Enteral-coated capsules have been designed to release medication in the distal small intestine for treatment of Crohn's disease. Previously, "triple phase" enteral, targeted budesonide has been described for use in diffuse enteropathy.⁶ This involves a combination of crushing, opening or swallowing intact, enteral-coated budesonide capsules.⁶ Manipulation of the capsules targets the gastric and proximal small intestinal mucosa with a topical steroid thus avoiding systemic immunosuppression. Crushing the capsule bypasses the time- and pH-dependent release of the medication, permitting release into the stomach. The opened capsule releases into the upper small intestine. The whole, unopened capsule targets the distal small intestine. Oral viscous budesonide can be added for the treatment of esophageal involvement, however, it is possible to forgo treating the esophagus by ingesting budesonide capsules without swallowed slurry.

We reviewed the electronic medical records of 8 pediatric patients ages 0-18 years with biopsy confirmed EG managed with triphasic enteral budesonide therapy from April 2017 through February 2018. Approval was granted for this retrospective review from the Institutional Review Board of the Children's Hospital of Philadelphia. Patients were included if biopsy results were available before and after therapy and regardless of a history of eosinophilic esophagitis (EoE). In total, 8 charts were reviewed to determine treatment regimen, accompanying laboratory studies including absolute eosinophil count, total protein and albumin as well as any history of atopic disease. One patient was excluded due to loss of follow up. Peak gastric eosinophils were measured by a blinded pathologist if not reported. As shown in Table 1, patients were treated with a total of 9 mg Entocort® daily. Patients were instructed to follow varying administration regimens recommended by the treating physician based on endoscopy-determined target areas of EGID as well as previous published case reports from patients with EGID, enteropathy, or GVHD.⁷⁻⁹

As demonstrated in Figure 1, all 7 patients had improvement in gastric eosinophil count. The gastric eosinophil count in the treated group (median 16 IQR 0-25 eos/hpf) was significantly lower compared to biopsy results before treatment (median 140 IQR 50-260 eos/hpf) after 3-7 months of designated treatment course ($p < 0.01$, Wilcoxon matched-pairs signed-rank test). Due to the retrospective nature of this case series, complete follow up data was not available for every patient. Peripheral blood absolute eosinophil counts before and after treatment were available in 3 patients, and did not show striking changes (Table 1). Total protein and albumin were not consistently measured. One patient was noted to have duodenal eosinophilia, which persisted following treatment. Two patients had resolution of abdominal pain and vomiting with treatment. One patient exhibited improved weight gain and cessation of vomiting, however, with tapering Entocort® therapy symptoms returned. Subjective symptoms were not recorded for the remaining patients in the immediate post-treatment period.

Six patients remained on a form of elimination diet prior and during treatment, either by personal choice or due to IgE-mediated food allergies. Of note, only 1 of these patients remained on a classic 6-food elimination diet with the intention of treating EGID; this was deemed unsuccessful prior to triphasic therapy initiation. One patient chose a vegan diet lifestyle. Another withheld egg due to IgE mediated food allergy, but parents also chose to

remove milk and peanut from the diet. The remainder eliminated foods specific to their known IgE-mediated food allergies which included milk, egg, peanut/tree nut and fish/shellfish.

Prior to treatment, 4 patients were trialed on systemic corticosteroids with relief and rebound of symptoms with tapering. Two patients had been trialed on enteral cromolyn without success. All patients remained on proton pump inhibitor during treatment. Interestingly, 1 patient was a liver transplant recipient. Five patients had a history of atopic disease, most commonly allergic rhinitis. Four patients had a history of endoscopy consistent with diagnosis of EoE, although due initiation of prior therapy only 3 had active esophageal inflammation when beginning triphasic therapy as shown in Table 1.

There are several limitations to our review. We capture the first biopsy results following initiation of therapy, which may indicate short-term success at reducing inflammation present in EG. Further investigation is needed to determine the long-term efficacy and safety of this off-label delivery of budesonide and to consider if standardization is possible. Long-term side effects, including risk of candidiasis and adrenal suppression, have not been examined in this population. Future work may also benefit from measurement of peripheral blood disease correlates as a means of defining success of a regimen such as absolute eosinophil count, total protein and albumin. Lastly, we acknowledge the possibility of intra-observer variability in peak eosinophil measurements amongst different pathologists.

In summary, we report preliminary success in implementing a triphasic enteral steroid approach for pediatric EGID. The therapeutic options for EGID distal to the esophagus are limited and typically require long-term therapy. This review demonstrates significant improvement in gastric eosinophil counts using targeted combinations of opened, crushed and intact Entocort® capsules. This modality has the potential to spare patients the adverse side effects of systemic immunosuppression and in some cases may lessen the need for avoidance of numerous foods.

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Clinical Implications:

Treatment of pediatric eosinophilic gastrointestinal disease remains challenging due to the negative side effect profile of systemic steroids. A multiphasic approach to therapy with enteral steroids may be optimal due to targeted mucosal effects.

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Figure 1: Treatment with triphasic budesonide decreases gastric biopsy eosinophil count. Seven patients were treated with triphasic budesonide over 4.5 ± 1.5 months prior to next esophagogastroduodenoscopy (mean $\pm$ SD). Peak gastric eosinophil count/hpf was quantitated before (median 140 IQR 50-260 eos/hpf) and after therapy (median 16 IQR 0-25 eos/hpf), overall $p < 0.01$ by Wilcoxon matched pairs signed rank test. Each individual's response to treatment is represented here.

Table 1.

Summary of patient profiles before and after multiphasic treatment

Modality *	Age	Atopy	Results before treatment				Results after treatment		
			Peak eosinophil count/hpf				Peak eosinophil count/hpf		
			AEC / μ l	Esophagus	Stomach	Duration between EGD (mo.)	AEC/ μ l	Esophagus	Stomach
2 crushed, 1 open	1	no	252	0	168	5	33	0	0-8
2 crushed, 1 open + slurry	14	yes	576	60	140	5	n/a	>80	35-50
3 crushed	17	no	40	2	50	3	200	0	0-16
2 crushed, 1 open + slurry	17	yes	1360	60	350	7	n/a	0	0-25
Diet restriction, 1 whole, 1 crushed, 1 open	5	yes	3350	3	260	4	1030	0	0-6
Diet restriction, 1 whole, 1 crushed, 1 open	13	yes	310	80	60	5	n/a	0	0
Diet restriction, 1 whole, 1 crushed, 1 open	17	yes	200	5	40	7	n/a	0	0-25

* Modality of daily Entocort® 3mg capsules used