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Budesonide Improves Outcomes in Eosinophilic Esophagitis

In a multicenter, randomized, double-blind, placebo-controlled, parallel group trial, budesonide oral suspension improved symptomatic, endoscopic, and histologic outcomes in patients with symptomatic eosinophilic esophagitis.

Eosinophilic esophagitis is characterized by eosinophilic infiltration of the esophageal mucosa, resulting in symptoms of dysphagia and food impaction. Topical corticosteroids delivered as swallowed asthma preparations have been shown to reduce esophageal eosinophilia and are the mainstay of treatment of this condition. However, this approach, which is not approved by the US Food and Drug Administration, is limited by variation in the adequacy of topical esophageal delivery and lack of rigorous evaluation in relation to patient-reported symptom measures. In this issue of *Gastroenterology*, Dellon et al report the result of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel group trial of a viscous oral suspension of budesonide (2 g) twice daily for 12 weeks among 93 patients 11–40 years of age. Patients were eligible if an initial screening upper endoscopy showed >15 eosinophils per high-power field in biopsies taken from ≥2 levels of the esophagus and ≥4 days with symptoms of dysphagia over the last 2 weeks of a 4-week placebo run-in period. The primary outcome was change in a validated dysphagia symptom questionnaire and the proportion of patients with a histologic response defined as ≤6 eosinophils per high-power field. Compared with placebo, budesonide treatment decreased mean dysphagia symptom score significantly ($P = .00096$), equivalent to approximately 3 fewer

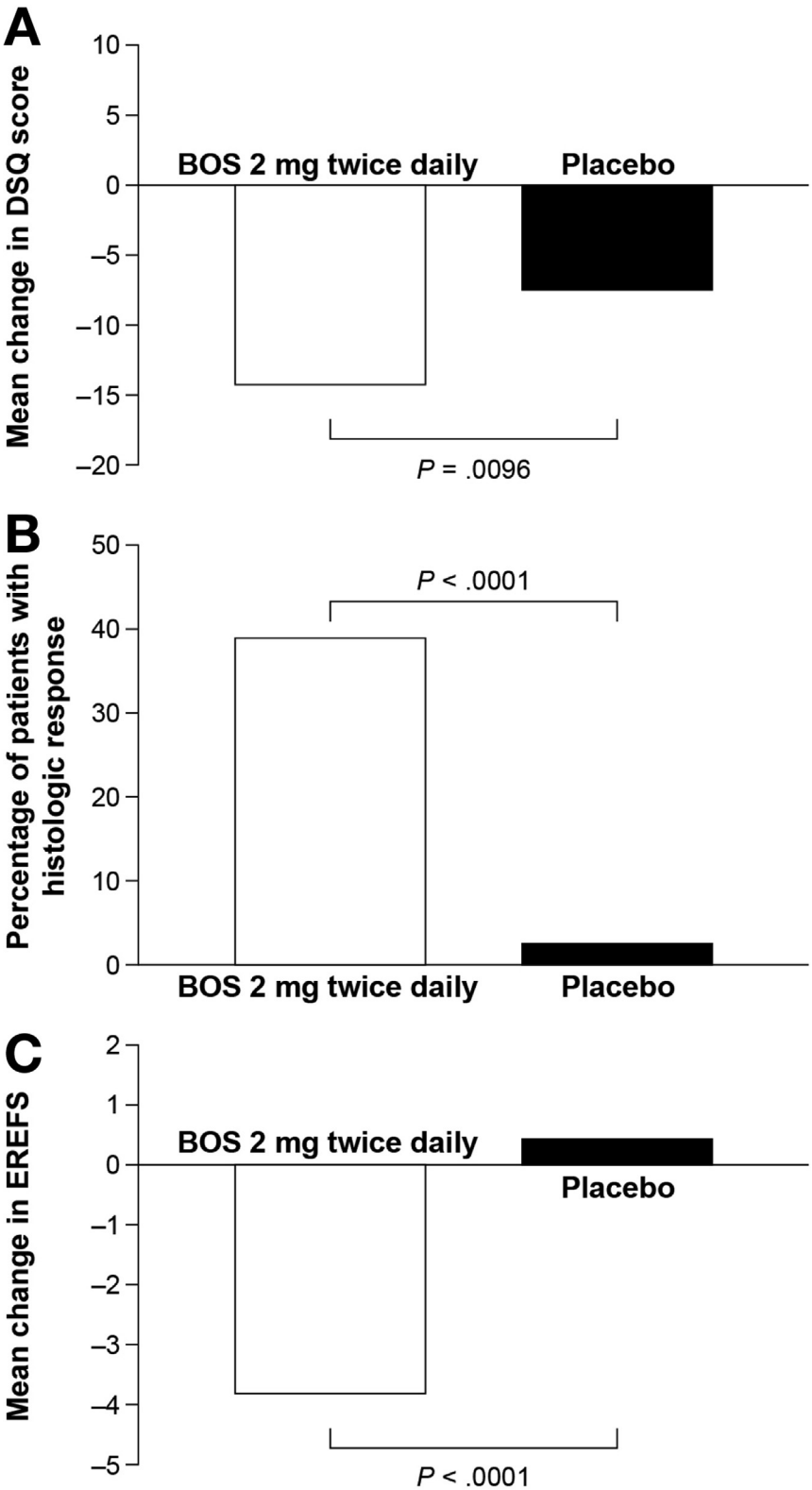

Figure 1. (*A*) Mean change in dysphagia symptom score. (*B*) Percentage of patients with histologic response. (*C*) Mean change in eosinophilic esophagitis endoscopic reference score. BOS, Budesonide.

days of dysphagia over a 2-week period. Budesonide also resulted in histologic response in 39% of patients compared to only 3% in placebo ($P < .0001$; Figure 1). In secondary analyses, budesonide improved endoscopic findings as quantified by validated endoscopic scoring. Budesonide was well-tolerated with reports of treatment-emergent adverse events largely similar to placebo. As the largest clinical trial of topical steroids in eosinophilic esophagitis to date, these findings support the use of oral budesonide for the treatment of symptomatic eosinophilic esophagitis.

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Sterile Fecal Filtrate for Treating *Clostridium Difficile* Infection

Administration of sterile fecal filtrates restored normal stool habits and eliminated symptoms in 5 patients with Clostridium difficile *infection for ≥6 months.*

Fecal microbiota transplantation using either fresh or cryopreserved stool from healthy donors has revolutionized the treatment of *Clostridium difficile* infection. Although highly effective in resolving symptoms, the use of fecal microbiota transplantation has been limited owing to concerns about the lack of standardization of fecal specimens and uncertainty regarding the long-term consequences of transferring live microorganisms between individuals. In this issue of *Gastroenterology*, Ott et al report an open label case series of 5 patients with chronic-relapsing *C difficile* infection who underwent transfer of fecal filtrates depleted of microorganisms through nasojejunal tubes. In all 5 patients, fecal filtrate transfer restored normal bowel habits and eliminated symptoms of *C difficile* infection for ≥6 months. Proteome analyses of fecal filtrates did not reveal obvious protein candidates that could explain the efficacy of fecal filtrate transfer. Although filtrate transfer showed significant bacterial community shifts and changes in the virome, it was not clear if such differences were a cause or effect of *C difficile* clearance. Although these results require validation in larger, rigorously conducted clinical trials, they suggest the possibility that sterile fecal filtrate transfer may be a viable treatment option for *C difficile* infection that does not incur the potential risks of transfer of living microbes. Moreover, these findings provide important biological insights into the mechanism by which fecal microbiota transplantation may effectively treat *C difficile*. It is widely assumed that the efficacy of fecal microbiota transplantation is due to the transfer of a more diverse, healthy microbial community. However, these data suggest that the nonmicrobial contents of stool water, including dead bacteria, their debris, metabolites, or bacteriophages, may be the component of fecal microbiota transplant that mediates elimination of *C difficile* infection.

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Fusobacterium and Neoplastic Proliferation in Colorectal Cancer Cells

Fusobacterium nucleatum *promotes proliferation in colorectal cancer cells via TL4-mediated NF-κB–driven expression of miR-21, resulting in reduced RASA1 expression and activation of MAPK signaling.*

Colorectal cancer (CRC) is the third most common cancer worldwide and is one of the leading causes of morbidity and mortality. In addition to genetic factors, environmental factors such as diet, obesity, alcohol consumption, and, like many other cancers, infectious agents, are implicated in CRC development. In support of this concept, tumor prone mouse models such as the Apc^{Min}, TCR/p53-KO, IL-10 knockout, and *Gpx1/Gpx2* double knockout mice all have reduced polyp/cancer burdens when raised in germ-free conditions. *Fusobacterium nucleatum* is indigenous to the human oral cavity; however, it has also been identified in advanced adenomas and CRC. Earlier groups have demonstrated that *F nucleatum* adheres to the colonic epithelium and promotes tumorigenesis in the Apc^{Min} model. However, the precise mechanism whereby *F nucleatum* contributes to the pathogenesis of CRC has yet to be established. In this issue of *Gastroenterology* (with an editorial by Holt and Cochrane), Yang et al, link microRNA-21 (miRNA-21), previously shown to increase colitis-associated carcinoma in animal models, and *F nucleatum* infection and in so doing demonstrate that miR-21 is a functionally relevant down-stream target of the organism. *F nucleatum* treatment of CRC cell lines enhanced proliferation, invasion, and their subcutaneous growth as xenografts in the nude mouse model. miR-21 was the most markedly increased microRNA in CRC lines treated with *F nucleatum*, and miR-21–deficient mice were protected from inflammatory carcinogenesis in the AOM/DSS model. Mechanistically, *F nucleatum* treatment activated TLR4/MYD88/nuclear factor-κB signaling to induce miR-21 expression and the authors identified RASA1, a member of the RAS GAP family, as a novel miR-21 target (Figure 2). Because RASA1 functions as a negative regulatory of the MAP kinase pathway, *F nucleatum* treatment also suppressed RASA1 and resulted in MAPK pathway activation in a miR-21–dependent manner. Last, the authors turned to clinical CRC samples and observed that *F nucleatum* infection was associated with elevated miR-21 and poor clinical outcomes. This interesting study implicates *F nucleatum* in the pathogenesis of CRC via its induction of miR-21, although the bacterial factors responsible for this signaling have yet to be determined. It is worth noting that *F nucleatum* deregulated expression of a number of other microRNAs and although this study dissected the role of miR-21, these other miRNAs alone