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Eosinophilic Esophagitis: Leaky Gullet or Leaky Gut?

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Abstract: Eosinophilic esophagitis (EoE) is a food allergen disorder driven by antigen recognition in the gastrointestinal tract. The study by Warners *et al.*, strongly supports the esophageal epithelium as the area of disturbed permeability and primary target for initiation of the TH2-induced allergic pathway. In contrast, small bowel assessment reveals a lack of clear change in aspects of permeability compared to controls. It is not clear, however, if the available testing used for this purpose accurately assesses the mechanisms by which antigen recognition may occur in this organ. As a result, the role of the small bowel in EoE remains unclear.

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That immune recognition of food antigens in the gastrointestinal tract is a key and primary event in eosinophilic esophagitis (EoE) is indisputable. The firmest support for this principle is evidenced by the response of EoE to an elemental diet, that is, a diet of nutrients devoid of food allergens. In children, this response is nearly 100% (1) whereas in adults, it is about 80% (2,3). The presence of confounding gastroesophageal reflux disease could account for the lower response in adults. Nevertheless, some controversy exists as to where this antigen recognition occurs. To date, studies have primarily emphasized the role of the esophagus. Many types of data support this emphasis. For example, the esophageal epithelium in active EoE is characterized histologically by dilation of intercellular spaces, which theoretically would facilitate transport of fluids, ions, and proteins. The epithelium has also been demonstrated to lose its integrity as evidenced by increased flux in Ussing Chamber studies (4) and increased flow of current on impedance measurement (5). Indeed, investigators have demonstrated a decrease in both tight junction proteins (6) and desmosomes (7), two of the key regulators of intercellular space function, in

active disease with restoration of normal levels in treated disease. Finally, the complex immune pathway involving a TH2 reaction in the esophagus with activation of multiple cytokines, and recruitment and degranulation of copious eosinophils has been carefully characterized in both animals (8) and humans with EoE. As a result, the evidence that the esophageal epithelium is the sole culprit in EoE would seem insurmountable.

On the other hand, intuition suggests that this seems unlikely. After all, a bolus of food has only 10 s to be exposed to esophageal mucosa. How could such transient mucosal contact lead to an unrelenting chronic inflammatory disease that commonly leads to diffuse stricture formation. Ingested food also is non-digested. In other words, there is minimal exposure of the antigen as it is enveloped in the complex food bolus. Furthermore, the esophagus is hardly known as an immunogenic organ. It is normally devoid of eosinophils, has few lymphocytes and has not been described as an organ capable of allergic disease until now. As a result, this begs the question where else could food recognition occur? The logical answer is the small intestine. It is the most immunogenic organ in the gut. The small bowel transit time is 4–6 h enabling a long period of contact between antigen and mucosa. The food is partially digested once it reaches the duodenum and almost fully digested in the jejunum, thus allowing extensive free antigen exposure to the epithelium. And finally, the surface area of the small bowel is expansive, which is more than enough surface to allow adequate antigen penetration and/or recognition.

In this issue, Dr Warners *et al.* (3,9) elegantly explore further the status of mucosal integrity in the esophagus and small intestine in patients with active- and elemental-diet-treated EoE. In this study, 95% of the 17 patients studied had either complete (12) or partial (4) response to the diet. Interestingly, although dilation of intercellular spaces improved, it only became normal in 1 patient. Whether this reflects a low threshold of eosinophilia required (even when <15 eosinophils/high power field) for ongoing spongiosis or that intercellular space dilation is a primary defect of EoE is of interest. This also corresponds to the authors finding persistently low mucosal impedance and expression of filaggrin (6) and desmoglein 1 (7) in EoE patients after success-

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ful diet therapy when compared to controls. These reductions further corroborate previous findings in EoE (6,7). In contrast, transepithelial flux across esophageal mucosa of small and larger molecules returned to normal control values. This is important as one of the molecules used, rhodamine (40 kDa), is a similar size to gliadin (30–38 kDa) (10). There was also good correlation between mucosal integrity, peak eosinophil count, and *FLG* and *DSG1* expression. This further suggests that although there may be an underlying primary defect in esophageal mucosal function in EoE patients, the majority of dysfunction associated with active disease may be treated. This is reassuring.

In the duodenum, however, no differences in impedance values were seen before or after treatment. As a result, one must question why a change in duodenal impedance did not occur in EoE patients when compared to controls. It may well be that the impedance of small bowel columnar epithelium is so low to begin with that no further change could be recorded in the absence of complete destruction of the mucosa and free flow of fluid and electrolytes. Notably, even in a study of Barrett's epithelium, an imperfect recapitulation of intestinalized mucosa, impedance levels are similar to what was found in controls in this study (11). It was also noted that no flux of molecules in the Ussing chamber were detected across duodenal epithelium from any group. This latter observation is curious given that the small bowel is functionally, and understandably, considered a far more permeable epithelium than esophageal squamous mucosa. Furthermore, normal absorption of food nutrients is through the epithelium and not the intercellular spaces as is measured with impedance and molecular flux. In the case of protein, it also occurs through a H⁺ gradient and not through an electrochemical exchange that could be detected with impedance measurement. Thus, although there may be correlations of current measurement and molecular flux to epithelial permeability, it does not necessarily equate to the process of food antigen penetration and recognition in the small intestine.

Finally, it is not clear that altered small bowel permeability is the *sine qua non* of allergic disorders but perhaps, more likely, a surrogate. The gut is quite capable of mounting an allergic response without underlying alterations of abnormal di-sugar absorption or altered electrical permeability. Perhaps we are chasing the wrong metrics to assess mechanisms that enhance food antigen recognition by the gut. Further, why should some atopic diseases such as asthma (12), atopic dermatitis (13), and celiac disease (6), be associated with altered small bowel permeability but not EoE? They are all at least partly antigen driven, and may share similar microbiome risk factors such as lack of breast feeding, early exposure to antibiotics and higher likelihood of Cesarean section (14–17). I would speculate these groups of diseases are more likely to have a similar core pathophysiology.

In summary, however, and at the very least, this excellent study provides compelling evidence that these perturbations of esophageal epithelial integrity lend further support to the esophagus as the major point of food allergen recognition in EoE. As a result,

continued EoE research will focus on this area particularly with regard to therapies that might enhance barrier function. Is it game over for the small bowel? I admit, the score is gullet 1, gut 0. Then again, I think that the gut has a man on base and a couple of outs to go.

CONFLICT OF INTEREST

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REFERENCES

1. Spergel JM, Andrews T, Brown-Whitehorn TF *et al.* Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–43.
2. Peterson KA, Byrne KR, Vinson LA *et al.* Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:759–66.
3. Warners MJ, Vlieg-Boerstra BJ, Verheij J *et al.* Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. *Aliment Pharmacol Ther* 2017;45:777–87.
4. van Rhijn BD, Weijenberg PW, Verheij J *et al.* Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1815–23 e2.
5. Katzka DA, Ravi K, Geno DM *et al.* Endoscopic mucosal impedance measurements correlate with eosinophilia and dilation of intercellular spaces in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:1242–1248 e1.
6. Katzka DA, Tadi R, Smyrk TC *et al.* Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1824–9 e1.
7. Sherrill JD, Kc K, Wu D *et al.* Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;7:718–29.
8. Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. *Gastroenterology* 2015;148:1143–57.
9. Warners MJ, Vlieg-Boerstra BJ, Verheij J *et al.* Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet. *Am J Gastroenterol* 2017;112:1061–71 (this issue).
10. Qian Y, Preston K, Krokhin O *et al.* Characterization of wheat gluten proteins by HPLC and MALDI TOF mass spectrometry. *J Am Soc Mass Spectrom* 2008;19:1542–50.
11. Hemmink GJ, Alvarez Herrero L, Bogte A *et al.* Esophageal motility and impedance characteristics in patients with Barrett's esophagus before and after radiofrequency ablation. *Eur J Gastroenterol Hepatol* 2013;25:1024–32.
12. Knutson TW, Bengtsson U, Dannaeus A *et al.* Effects of luminal antigen on intestinal albumin and hyaluronan permeability and ion transport in atopic patients. *J Allergy Clin Immunol* 1996;97:1225–32.
13. Bjarnason I, Goolamali SK, Levi AJ *et al.* Intestinal permeability in patients with atopic eczema. *Br J Dermatol* 1985;112:291–7.
14. Vajpayee S, Sharma SD, Gupta R *et al.* Early infant feeding practices may influence the onset of symptomatic celiac disease. *Pediatr Gastroenterol Hepatol Nutr* 2016;19:229–35.
15. Pozo-Rubio T, de Palma G, Mujico JR *et al.* Influence of early environmental factors on lymphocyte subsets and gut microbiota in infants at risk of celiac disease; the PROFICEL study. *Nutr Hosp* 2013;28:464–73.
16. Jensen ET, Kappelman MD, Kim HP *et al.* Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2013;57:67–71.
17. Stelmach I, Bobrowska-Korzeniowska M, Smejda K *et al.* Risk factors for the development of atopic dermatitis and early wheeze. *Allergy Asthma Proc* 2014;35:382–9.