TABLE I. Major elements of suggestion therapy

- Approach the patient with confidence that the coughing will be stopped.
- Explain the cough as a vicious cycle that started with an initial irritant that is now gone and that now the cough itself is causing irritation and more cough.
- Instruct the patient to concentrate solely on holding back the urge to cough for an initially brief timed period, such as 1 minute. Progressively increase this time period and use an alternative behavior, such as sipping lukewarm water or inhaling a soothing cool mist from a vaporizer, to "ease the irritation."
- Tell the patient that each second the cough is delayed makes it easier to suppress further coughing.
- Repeat expressions of confidence that the patient is developing the ability to resist the urge to cough: "It's becoming easier to hold back the cough, isn't it?" (Nodding affirmatively generally results in a similar affirmation movement by the patient.)
- When ability to suppress cough is observed (usually by about 10 minutes), ask in a rhetorical manner, "You're beginning to feel that you can resist the urge to cough, aren't you?" (said with an affirmative head nod)
- Discontinue the session when the patient can repeatedly respond positively to the question, "Do you feel that you can now resist the urge to cough on your own?" This question is only asked after the patient has gone 5 minutes without coughing.
- Express confidence that if the urge to cough recurs that the patient can do the same thing at home (autosuggestion).*

*Autosuggestion involved expressing confidence in 15-minute sessions at home concentrating on holding back the cough with sips of lukewarm water to "ease the irritation causing cough."

asleep is sufficient to make the diagnosis of this disorder. Once identified, a simple behavioral methodology can provide sustained cessation of cough for most children with this disorder.

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Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis

To the Editor:

Eosinophilic esophagitis (EoE) is a common cause of chronic esophageal symptoms characterized by an eosinophil-rich inflammatory infiltrate limited to the esophagus.[1] Despite being first categorized as a distinct clinicopathological disorder 2 decades ago,[2,3] EoE has rapidly become recognized in recent years as the most prevalent cause of chronic dysphagia among children and young adults in Western countries.[4-6]

Increasing knowledge of the disease has led to gradual changes in interpreting the eosinophilic infiltration within the esophageal mucosa, and these changes are reflected in the differing guidelines categorizing EoE since 2007.[1,7-9] Until the early 1990s, a dense esophageal eosinophilia was mostly associated with gastroesophageal reflux disease (GERD).[E1,E2] The ineffectiveness of antireflux therapies in patients with characteristic EoE profile, however, led to the recognition of EoE as a new entity.[2,3,E3] Consensus guidelines published in 2007 rigidly separated EoE from GERD[7]: EoE was defined by either clinical and/or histologic unresponsiveness to proton pump inhibitor (PPI) therapy or a normal esophageal pH, whereas GERD was defined by either complete remission on PPI therapy or a pathological esophageal pH.

Soon after this distinction was made, a few retrospective studies suggested the existence of pediatric patients with clinicopathological features of EoE who fully responded to PPI therapy.[E4-E6] A large prospective adult series published in 2011 corroborated this finding, showing that PPIs effectively induced remission of both esophageal inflammation and accompanying symptoms in 50% of the patients with a presumptive diagnosis of EoE.[E7] Notably, most of these patients presented with an associated atopic background as well as symptoms of dysphagia and food impaction instead of heartburn. Furthermore, PPI responsiveness was independent of pH-monitoring results. These observations gave rise to the new "PPI-responsive esophageal eosinophilia (PPI-REE)" concept, which referred to patients who not only appeared to have EoE clinically but also achieved complete remission after PPI therapy. This novel phenotype was recognized in the 2011 updated consensus recommendations on EoE[1] and endorsed in all subsequent guidelines.[8,9]

Currently, several retrospective and prospective studies in both children and adults consistently show that at least one-third of the patients with suspected EoE eventually receive a PPI-REE diagnosis.[E8] Interestingly, PPI-REE and EoE remain indistinguishable based on clinical, endoscopic,[E9,E10] and histologic findings[E11]; pH monitoring[E17]; and the measurement of tissue markers,[E12,E13] cytokines related to eosinophilic inflammation,[E14,E15] and esophageal gene transcripts from esophageal tissue.[E16] In addition, PPI monotherapy completely reverses cytokine[E14,E15] and esophageal gene transcript[E16] levels in patients with PPI-REE, similar to the way that topical steroids do in EoE. Collectively, these data support the idea that PPI-REE may constitute a subphenotype of EoE rather than a distinct disease entity and that PPIs may be considered a therapeutic option to effectively manage a high proportion of patients with EoE.

Here, we provide additional evidence to support that PPI-REE and EoE should be considered within the spectrum of the same disease by showing that patients with PPI-REE also respond to dietary/topical steroid treatment and that some patients with EoE respond to PPI therapy. Databases containing information on patients with an EoE diagnosis who had prospectively attended 2

TABLE I. Clinical, demographic, and therapeutic characteristics of our series of patients with EoE who presented dual response to dietary/topical steroid and PPI therapy

Patient	Age (y)	Sex	Atopy background	Familial history of atopy (relative)	Ph monitoring	Baseline peak eosinophil density (eosinophils/hpf) (proximal; distal)
1	36	Male	Seasonal allergic rhinitis	No	Normal	50; 50
2	45	Male	Seasonal rhinoconjunctivitis	Rhinoconjunctivitis (brother)	Normal	56; 60
3	41	Male	Seasonal bronchial asthma and rhinoconjunctivitis	No	Normal	10; 20
4	10	Male	Oral allergy syndrome with fruits	No	Normal	30; 60
5	36	Male	Seasonal rhinoconjunctivitis	Fish- and seafood-induced anaphylaxis (mother)	Not done	100; 45
6	28	Female	Seasonal bronchial asthma and rhinoconjunctuvitis	Bronchial asthma (brother)	Not done	15; 30
7	32	Female	Seasonal rhinoconjunctivitis	Seasonal rhinoconjunctivitis (mother and sister)	Not done	76; 92
8	29	Male	Seasonal bronchial asthma and rhinoconjunctivitis	No	Not done	25; 34
9	18	Male	Seasonal bronchial asthma and rhinoconjunctivitis Fish-induced anaphylaxis Oral allergy syndrome with nuts and fruits	Seasonal bronchial asthma and rhinoconjunctivitis (brother)	Not done	114; 87

Spanish reference centers for EoE (Tomelloso General Hospital and San Pedro de Alcántara Hospital) between January 2014 and April 2015 were retrospectively analyzed to identify those who responded to both dietary/topical steroid treatment and PPI therapy. Nine patients (7 males, 2 females) were identified (Table I), and all presented with an atopic background. (Of note, despite this atopic background, the esophageal eosinophilia diagnosis or the documentation of its remission in esophageal biopsy samples was not made more frequently in the spring or summer months when environmental allergens peak [see Table E1 in this article's Online Repository available at www.jacionline.org].)

Patients 1 to 4 had esophageal eosinophilia and were diagnosed with EoE after ruling out pathologic reflux by pH monitoring; no PPI trial was performed because exclusion of PPI-REE was not required before 2011. These patients showed disease remission after undergoing a 6-food elimination diet. Although patient 1 prematurely abandoned food reintroduction, specific food triggers were identified in the other 3 patients by a previously described sequential food reintroduction protocol,[E17] and food avoidance maintained disease remission for more than 3 years. Remarkably, 2 or more foods were involved in the origin of disease in these patients, hampering complete adherence to the diet. A 2-month-long PPI trial was thus offered to all the 4 patients, and a free diet was allowed up until the moment that new esophageal endoscopic biopsies were obtained. These patients were considered PPI responders because esophageal eosinophilia did not recur, and all preferred receiving PPI while on a liberalized diet.

However, patients 5 to 7 were first diagnosed with esophageal eosinophilia in 2013 and then subsequently diagnosed with PPI-REE after their esophageal inflammation remitted after a 2-month-long PPI course. Because all patients expressed concerns regarding long-term PPI consumption, we offered them further dietary therapy. After discontinuing PPIs, disease remission was achieved with a 4-food elimination diet, and specific food triggers were identified by subsequent food challenge.[E18]

Patient 8 was diagnosed with PPI-REE and maintained full remission with long-term omeprazole treatment (40 mg/d). After 15 months of follow-up, the patient suddenly developed tinnitus, and PPIs were withdrawn at the request of the otorhinolaryngologist. Esophageal symptoms relapsed 6 weeks after discontinuation of PPI therapy. Topical steroid therapy was then prescribed, leading again to clinical and histologic remission of the disease. Patient 9, an 18-year-old man with a severe atopic background, was diagnosed with esophageal eosinophilia attributed to EoE in 2011 (without a PPI trial) and achieved clinicohistologic remission after immediately starting topical steroid therapy. In 2014, the patient voiced concerns about long-term intake of corticosteroids, and topical steroid therapy was discontinued. Clinical and histologic remission was redocumented after a 2-month-long PPI trial (omeprazole 40 mg twice a day), which was maintained as long-term treatment.

We report here the first series of patients with EoE exhibiting a complete response to either PPI therapy or dietary/topical steroid therapy. Our clinical observation emphasizes the similar nature of EoE and PPI-REE because they are indistinguishable entities not only in the genetic and phenotypic sense but also in the

TABLE I. *(Continued)*

Initial therapy (year instituted)	Posttreatment peak eosinophil density (eosinophils/hpf) (proximal; distal)	Secondary therapy	Posttreatment peak eosinophil density (eosinophils/hpf) (proximal; distal)	Identified EoE food triggers (by individual food reintroduction)	Maintenance therapy
Six-food elimination diet (2008)	0; 5	Omeprazole 20 mg twice a day	3; 0	Wheat. Food reintroduction protocol abandoned	Omeprazole 20 mg twice a day
Six-food elimination diet (2009)	0; 4	Omeprazole 20 mg twice a day	0; 0	Egg, fish, and legumes	Omeprazole 40 mg every day
Six-food elimination diet (2009)	1; 2	Esomeprazole 20 mg twice a day	0; 0	Milk, egg	Esomeprazole 20 mg twice a day
Six-food elimination diet (2010)	5; 10	Omeprazole 20 mg twice a day	1; 5	Milk, wheat, and legumes	Omeprazole 20 mg twice a day
Esomeprazole 40 mg twice a day (2013)	0; 0	Four-food elimination diet	0; 3	Milk and wheat	Milk and wheat exclusion from the diet
Omeprazole 40 mg twice a day (2013)	2; 8	Four-food elimination diet	10; 10	Wheat	Ongoing food reintroduction protocol
Omeprazole 40 mg twice a day (2013)	0; 4	Four-food elimination diet	2; 6	Milk, legumes	Milk and legumes exclusion from the diet
Omeprazole 40 mg twice a day (2013)	0; 0	Fluticasone propionate 800 μg twice a day	0; 0	—	Swallowed fluticasone propionate 400 μg twice a day
Fluticasone propionate, 800 μg twice a day (2011)	0; 0	Omeprazole 40 mg twice a day	2; 3	—	Omeprazole 40 mg every day

therapeutic sense, which we show here for the first time. As has recently been pointed out,[E18] defining a disease (eg, PPI-REE) by its responsiveness to a specific therapy (eg, PPI therapy) instead of its clinical and mechanistic characteristics (eg, indistinguishable from EoE) is counterintuitive. Our data are especially important for patients with EoE who did not undergo a PPI trial before receiving an EoE diagnosis because the opportunity to treat with a safe, effective, and convenient therapeutic asset may have been missed.

Evolving evidence points toward reclassifying patients with PPI-REE as PPI-responsive patients with EoE.[E19] Moreover, PPIs should now be considered as the first step in the treatment algorithm for patients with EoE so as to rule out patient responsiveness to PPI therapy rather than to just rule out GERD. This novel concept was foretold in a visionary review article in 2007[E20] in which the authors suggested that "a PPI trial should be recommended even when the diagnosis of EoE seems clear-cut" and "a favorable response to PPI therapy does not preclude a diagnosis of EoE." Some aspects related to PPI responsiveness in patients with EoE require further understanding and clarification, including the following: 1) the ultimate underlying mechanisms explaining a distinct response among patients who share apparently identical characteristics; 2) whether both variants of the disease share an identical natural history with fibrostenotic progression; and 3) the potential ability of PPIs to reverse esophageal fibrous remodeling. Nevertheless, we believe that there is enough evidence at present to consider abandoning the PPI-REE concept in favor of reclassifying patients with PPI-REE as having EoE that responds to PPI therapy.

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Association of eosinophilic esophagitis and hypertrophic cardiomyopathy

To the Editor:

Eosinophilic esophagitis (EoE) usually presents with upper gastrointestinal symptoms, although chest pain can be the primary symptom. We report the association of EoE and hypertrophic cardiomyopathy (HCM) in 3 patients and genetic data indicating a linkage between EoE and HCM.

The index patient was a 26-year-old white man who presented with dysphagia and chest pain and was given a diagnosis of EoE according to consensus criteria.[1] After both swallowed and oral glucocorticoid therapy, his dysphagia improved, but he continued to experience chest pain that was increasingly accompanied by palpitations and syncopal episodes postprandially or with exertion. After an extensive cardiac work-up, he was given a diagnosis of HCM according to consensus criteria (see Table E1 in this article's Online Repository at www.jacionline.org)[2] and heterozygosity for a known disease-causing missense mutation (E542Q) in the cardiac myosin-binding protein C3 *(MYBPC3)* gene.[3]

An electronic chart review of 1,281,475 patient records at Cincinnati Children's Hospital Medical Center identified 2,100 and 241 possible cases of EoE and HCM, respectively, by using International Classification of Diseases, Ninth Revision codes. Of these, 2 cases other than the index case met the diagnostic criteria for both EoE and HCM. Case 2 was a male subject with osteogenesis imperfecta (OI) type I, and case 3 was a male subject with 1p36 deletion syndrome whose deletion was 10.88 Mb and included 5 actomyosin cytoskeleton–associated genes (*ARHGEF16*, *ACTRT2*, *PLEKHG5*, *AJAP1*, and *CTNNBIP1*; see Table E1). It is important to note that OI1 is a mild form of OI and is not associated with heart or gastrointestinal symptoms, and therefore the presence of OI1 is likely a secondary finding. However, it is interesting to note that OI1 is a connective tissue disease associated with collagen 1 deficiency and that EoE has recently been associated with other connective tissue diseases.[4] Additionally, although patients with 1p36 deletion syndrome are known to have cardiomyopathy, there are no reports of EoE associated with this disease. Thus even with regard to these patients, unexpectedly, HCM and EoE are co-occurring. Also, because EoE is not a Mendelian disorder and likely requires multiple genetic hits for disease presentation, it is not surprising to find patients with multiple genetic hits. By using these data, the odds ratio is 7.69 (95% CI, 2.46-24.03; $P < .001$), suggesting that the co-occurrence of EoE and HCM is not likely due to chance. It is important to note that our hospital-based data exhibit enrichment for EoE (population prevalence, 1:2,000; our data, 1:600), as well as for HCM (population prevalence, 1:200,000; our data, 1:5,000), likely because our center is a tertiary referral center for both EoE and HCM. Although there is enrichment in both conditions, we do not expect that the co-occurrence of both conditions will be affected by this bias because patients seeking care for EoE are not routinely evaluated by cardiologists and patients seeking care for HCM are not being screened for EoE.

Another way to consider what the odds ratio signifies is to examine the expected co-occurrence on the basis of our center's population. From our center's prevalence of EoE (1:600) and HCM (1:5,000), random co-occurrence would be expected to be 1:3,000,000. Yet the observed co-occurrence rate for our center's population was 1:400,000 (or 3 in 1,281,475).

Next, we performed a candidate gene association study assessing the frequency of *MYBPC3* genetic variants in the EoE versus non-EoE control cohorts (see Table E2 in this article's Online Repository at www.jacionline.org).[5] EoE was significantly associated with 24 single-nucleotide polymorphisms (SNPs) in the linkage disequilibrium block containing *MYBPC3*, including 6 SNPs in close proximity to the *MYBPC3* gene on chromosome 11; this association was significant after permutation analysis (Fig 1 and see Table E3 in this article's Online Repository at www.jacionline.org). One SNP, rs3729986, is a missense mutation (V158M) but is a variant that occurs in 11% of the general population.[3] Evaluating the 24 known HCM-causing genes,[6] we found 62 EoE-associated genetic variants within 5 kb of 17 of the 24 cardiomyopathy genes ($P < .05$, see Table E4 in this article's Online Repository at www.jacionline.org). EoE-associated variants ($P < .05$) were significantly enriched for variants near cardiomyopathy genes (permuted $P < .015$). Interestingly, of these genes, calreticulin 3 *(CALR3)* is decreased by 17% ($P = .001$) in the epithelial biopsy specimens of patients with EoE compared with those of control subjects, as assessed by means of microarray (see Fig E1 in this article's Online Repository at www.jacionline.org).[7] This evidence suggests that HCM-associated genes also contribute to EoE susceptibility. Actomyosin proteins are important in mechanotransduction, a process recognized to be involved in chemotaxis of leukocytes, muscle contraction required for esophageal motility, and migration and proliferation of epithelial cells, which are processes germane in patients with EoE. Collectively, we have identified a putative interaction between EoE and HCM with clinical and pathogenic implications.

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TABLE E1. Histologic and therapeutic characteristics and month each endoscopic examination was carried out in our series of patients with EoE who presented dual response to dietary/topical steroid and PPI therapy

Patient	Baseline peak eosinophil density (eosinophils/hpf) (proximal; distal) (month)	Patient on PPIs at the moment of baseline endoscopy	Initial therapy (year instituted)	Posttreatment peak eosinophil density (eosinophils/hpf) (proximal; distal) (month)	Secondary therapy	Posttreatment peak eosinophil density (eosinophils/hpf) (proximal; distal) (month)
1	50; 50 (July)	No	Six-food elimination diet (2008)	0; 5 (September)	Omeprazole 20 mg twice a day	3; 0 (February)
2	56; 60 (January)	No	Six-food elimination diet (2009)	0; 4 (March)	Omeprazole 20 mg twice a day	0; 0 (November)
3	10; 20 (March)	No	Six-food elimination diet (2009)	1; 2 (April)	Esomeprazole 20 mg twice a day	0; 0 (May)
4	30; 60 (October)	No	Six-food elimination diet (2010)	5; 10 (December)	Omeprazole 20 mg twice a day	1; 5 (July)
5	100; 45 (March)	No	Esomeprazole 40 mg twice a day (2013)	0; 0 (May)	Four-food elimination diet	0; 3 (January)
6	15; 30 (June)	No	Omeprazole 40 mg twice a day (2013)	2; 8 (August)	Four-food elimination diet	10; 10 (November)
7	76; 92 (February)	No	Omeprazole 40 mg twice a day (2013)	0; 4 (April)	Four-food elimination diet	2; 6 (March)
8	25; 34 (November)	No	Omeprazole 40 mg twice a day (2013)	0; 0 (January)	Fluticasone propionate 800 μg twice a day	0; 0 (April)
9	114; 87 (November)	No	Fluticasone propionate, 800 μg twice a day (2011)	0; 0 (February)	Omeprazole 40 mg twice a day	2; 3 (February)