Editorial

Testing to no avail? the diagnostic and treatment conundrum in patients with extraesophageal manifestations of gastroesophageal reflux disease

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Extraesophageal reflux (EER), which includes cough, asthma, and laryngopharyngeal reflux (LPR), is an important and prevalent disease state with a large economic burden of up to fifty billion dollars, largely due to the pharmaceutical costs of empiric treatment (1). Patients with presumed EER are often treated with empiric acid suppressive therapy (AST), but if symptoms remain refractory, they are then referred for further testing. Despite advent of ambulatory reflux monitoring and impedance testing, diagnostic testing in this population have poor test characteristics with suboptimal sensitivity and specificity (2,3). Esophagogastroduodenoscopy (EGD) is specific for GERD, but lacks sensitivity (less than 30%) due to lack of overt esophagitis in some patients with GERD. Ambulatory pH testing and intraluminal impedance are gold standard for diagnostics, but are also limited due to a limited period of testing, which is often challenged by patient comfort and compliance with intranasal catheter (4). The presence of dilated intracellular spaces (DIS) has been suggested as a marker of chronicity in patients with GERD both with esophagitis and non-erosive GERD, but there remains uncertainty on optimal biopsy, need for costly EGD, and the use of transmission electron microscopy limiting the applicability of this test (5). Mucosal impedance (MI) uses indirect measurements of mucosal conductivity and studies have shown lower intraluminal impedance in patients with GERD compared to controls (6). Finally, in highly selected patients, surgery can be performed for treatment of EER, where symptom relief after surgery can confirm a diagnosis of EER though conclusions are limited by lack of high quality randomized control studies as recently published by this group (7).

In this article in the *Annals of Surgery*, Sidhwa *et al.* performed a review of 271 articles with 128 meeting their study criteria to ask three important questions: (I) how are extraesophageal manifestations of reflux diagnosed? (II) What is the effect of medical therapy? and (II) what is the effect of surgical therapy? (8). In evaluating the triumvirate of cough, asthma, and LPR, the authors found that there is lack of diagnostic criterion for all three diseases. Patients with suspected EER associated symptoms initially undergo a PPI-trial ranging from 8 to 16 weeks with improvement in symptoms indicating GERD as the underlying etiology. In patients that are unresponsive to PPI trial, further testing including multichannel intraluminal impedance with pH (MII-pH) might be helpful in determining if reflux might be a contributing factor in this difficult group of patients. Authors also suggest that symptom association probability (SAP) determined by the association of reflux events defined by MII-pH and self-reported cough might be helpful with a specificity of 82% in one study (9). However, clinical utility of SAP is very limited. We would suggest the readers to review important data in this regard about lack of reliability on SAP in patients with cough (10-12). Symptom associations are problematic and should not be used to make important clinical decisions in patients with EER symptoms

because patients often do not push the symptom button when they have symptoms and most patients with chronic cough have symptoms related to hypersensitivity rather than GERD related etiology (10,13). Thus, given the low predictive value of pH testing and the lack of reliability of SI and SAP, the use of pH testing in patients with chronic cough is discouraged (14). Diagnosis of EER is fought with great uncertainty due to lack of gold standard test, which has resulted in difficulties in proper study enrollment limiting the robustness of data from the current trials. Sidhwa *et al.* delineate this problem when discussing the current randomized controls studies, where they point out that there may be a large amount of patients without EER enrolled in the disease arm of these studies biasing the trials towards a type II error.

An important theme resonates on treatment response for EER, which is that patients with concomitant typical GERD symptoms or positive pH monitoring may response to therapy better than those without concomitant GERD symptoms (15,16). Prior evaluation of patients with EER have shown that both heartburn with or without regurgitation and esophageal pH <4 more than 12% of a 24-hour period predicted post-fundoplication resolution of the presenting EER related symptom (12). These findings were expanded on by a recent retrospective cohort study of 115 patients (79 with GERD, 36 with EER) who were evaluated for an average of 66 months after antireflux surgery (ARS), where efficacy of ARS was related to response to AST and less predictable with those having primarily EER symptoms (17).

Sidhwa *et al.* should be applauded for their work evaluating the current body of literature on EER. A common theme resounded through this analysis involving the lack of high quality randomized control studies despite the prevalence of this disease and number of anti-reflux surgeries performed. Overall, the authors appropriately point out the difficulty in establishing a true causal link between patients' presenting extraesophageal symptoms and GERD based on current sub-optimal diagnostic testing. One novel technology which may be helpful in this area, though not well studied, is MI. In patients with symptoms of EER and evidence of acid reflux, MI values are lower than those without EER showing that MI may be used a tool to detect the presence of GERD in patients presenting with EER associated symptoms (18). In addition to further high quality studies, the role of this modality should continue to be investigated.

Current guidelines on management of EER are highly dependent on the society evaluating the literature with variation in management of cough, asthma, and LPR. The authors state referral for ARS for LPR and asthma, though caution should be advised to the patients on the potential lack of benefit. We would support a more vigorous screening based on the aforementioned studies on response to AST and concomitant typical GERD symptoms to help define referral patterns for ARS to improve success rate of symptom control as defined by symptom recurrence post-surgery.

Thus, EER is a commonly encountered clinical problem for many gastroenterologist and surgeons and has a large economic burden partly due to indiscriminate use of long term PPI therapy. We would urge the readers to question the utility of high dose PPI therapy after 2-month of empiric therapy. If patients report improvement of extraesophageal symptoms with AST, tapering to once daily and eventually leaving patient on the lowest effective dose of AST is recommended. Diagnostic testing in this group can only be employed as surrogate markers for GERD and doesn't necessarily imply response to anti-reflux therapy, medications or surgery. We urge the readership to avoid the use of symptom association alone in assessing possible link between GERD and EER. ARS is an important management technique for those with EER; however, strict selection should be performed to avoid unnecessary surgery in those who may not truly have reflux related symptoms.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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