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ESOPHAGUS

Diagnostic Testing in Extraesophageal GERD: Another Case of *"Furor Medicus"*?

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Abstract: Proton pump inhibitors (PPIs) work for most patients with gastroesophageal reflux disease (GERD). But when PPIs fail to work, or when there are atypical extra-esophageal symptoms, diagnostic and management decisions become much more difficult. Although atypical GERD is common, there are limited data about how best to approach these patients. The temptation is often to perform extensive diagnostic testing, sometimes to little avail. In this issue of The Journal, Francis *et al*. present a new study to help close the research gap in understanding the costs and benefits of testing in atypical GERD. The authors conclude that diagnostic testing is very expensive and real-life benefits are modest. This editorial reviews the findings, places them into clinical perspective, and concludes that diagnostic testing in atypical GERD may be another example of "furor medicus" — an old but descriptive term referring to the instinct of doctors to implore "don't just stand there, do something!" The data from Francis *et al*. suggest we might do the opposite in atypical GERD: "Don't just do something, stand there."

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There was a time when gastroenterologists were "knights without swords," capable of diagnosing illnesses but often poorly equipped to provide highly effective therapy. Just three decades ago, we relied mainly on steroids, thiopurines, and 5-aminosalicylic acid for managing inflammatory bowel disease, sent most patients with large subepithelial lesions to the surgeon, and used histamine-2 receptor antagonists for gastroesophageal reflux disease (GERD). Even now, our therapeutic arsenal remains limited for many common digestive disorders (think of irritable bowel syndrome (IBS), gastroparesis, and functional abdominal pain), but at least we have treatments that provide substantial value for many patients.

GERD is the shining example of progress. For those of us who entered Gastroenterology after proton pump inhibitors (PPIs) were approved and widely disseminated into practice, we sometimes take the PPI revolution for granted. I can only speak for myself, but as a medical resident in the late 1990s, I was inculcated that PPIs were a panacea for most foregut complaints; everything from heartburn to chest pain, to dyspepsia, could dissolve away with the right PPI prescription. And if PPIs didn't work, then it must be the patient's fault—make sure they took the PPI before the first meal of the day, check for compliance, or suggest the patient needed another PPI formulation altogether. Just keep trying PPIs until the symptoms improved or, perhaps, the patient decided to move on.

Of course, this is far-fetched. It takes 1 day of outpatient gastrointestinal (GI) practice to realize that PPIs have considerable limitations. Patients might take them at the wrong time, be resistant to particular formulations, or not take them altogether, but sometimes PPIs just don't work—at least, not like we hope they will. Although about 80% of community-based GERD patients fully respond to PPI therapy, another 20% have persistent symptoms. Moreover, many GERD patients describe "extraesophageal" manifestations that seemingly span most of *Harrison's Internal Medicine*: cough, sinusitis, pneumonitis, laryngitis, pharyngitis, globus, otitis, asthma, bronchitis, sleep apnea, and dental erosions, among others. What is a gastroenterologist to do when PPIs fail? Sometimes we use more PPIs. And then we use more again.

When patients do not follow the script, we often turn to diagnostic testing to bolster our failing approach. There is no shortage of potential tests: barium swallow, upper endoscopy, esophageal biopsy, pH-metry, Bravo probe, impedence testing, esophageal manometry, pulmonary function tests, head and neck computerized tomography, chest radiography, allergy testing, video fluoroscopic swallowing study, laryngoscopy, and bronchoscopy, among others. These tests cost money and their benefits are often unclear. It is worth our time (and more importantly, our patients' time) to pursue all these diagnostic avenues?

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In many respects, the problem of recalcitrant or atypical GERD is similar to the diagnostic challenge presented by IBS (1)—in both cases, we may seek an organic explanation for ongoing symptoms or try to understand why first-line therapies failed. But the role of diagnostic testing in IBS is controversial (2). In fact, data show that some clinicians conduct an excessive diagnostic work-up despite most tests having a low yield (2).

There are many reasons why we keep testing. In light of the medical–legal interface in the United States, one possibility is that some clinicians believe that diagnostic testing is a form of inoculation against litigation. Clearly, this is a suboptimal reason to pursue diagnostic testing; the quality of the physician–patient relationship is a more important predictor of litigation than testing proclivity. A second possibility is the belief that even negative diagnostic tests are useful, because they can allay patient concerns about serious illness and provide reassurance. But we have shown that a negative colonoscopy, in particular, is not associated with reassurance or improved quality of life in young IBS patients (3). In fact, we found a trend towards less reassurance in patients receiving a negative colonoscopy vs. no colonoscopy at all. A third possibility is that patients with high levels of somatization—a process marked by multiple unexplained symptoms potentially related to psychosocial distress—are sometimes misclassified as having underlying organic conditions, and subsequently undergo diagnostic tests to chase the symptoms. We found a strong relationship between levels of somatization and the amount of diagnostic testing in IBS, suggesting that clinicians should remain on the lookout for somatization and aggressively treat or refer such patients in lieu of performing potentially unnecessary diagnostic tests (4).

Does the IBS experience pertain to atypical GERD? Despite the prevalence of GERD, the frequency of diagnostic dilemmas in GERD, and the enormous costs of managing this condition (between $9 billion and $12 billion annually (5)), there is surprisingly little research evaluating the benefits and cost of diagnostic testing in atypical GERD. We have extensive research in IBS evaluating the cost benefit of testing, but less so in atypical GERD.

In this issue of the Journal, Francis *et al.* (6) present a new study to help close the research gap in understanding the costs and benefits of testing in atypical GERD. The investigators studied patients referred to a large, university-based, multispecialty consortium dedicated to the care of patients with symptoms attributed to extraesophageal reflux. Most of these patients received upper endoscopy with or without wireless 48-h pH testing of acid suppression, and/or 24-h impedence and pH-metry on PPI therapy. When the GI specialists failed to identify a "GI-related cause" of the extraesophageal symptoms, they referred the patient to ancillary specialists, including providers at the "Voice Center" and the "Allergy, Sinus and Asthma Program" at Vanderbilt University—the site of the research.

The authors tracked both resource utilization and symptom improvement over a 5-year period. On the resource side, they measured the number of office visits and consultations of each of the participating specialty centers in the GERD consortium. They assigned third-party payer costs using the Medicare reimbursement scheme for both office visits and related diagnostic procedures. In addition, the authors tracked medication use, including both prescription and over-the-counter therapies related to the GERD diagnosis. Furthermore, the investigators measured non-medical costs related to lost or impaired ability to work. They accounted for time lost from outpatient and inpatient visits, and valued the time using the national average hourly wage ($21.29 in this study).

In addition to resource utilization, the authors tracked patient symptoms over the course of the study period. They rated symptoms as "resolved" (complete elimination of chief complaint), "improved" (greater than 50% better), "stable" (no change), or "worse" (increase in severity or frequency). These assessments were not based on a standardized questionnaire. Instead, the authors seemed to employ a pragmatic assessment of the medical records.

Francis *et al.* (6) report data from 281 patients with extraesophageal symptom—a large cohort compared with the existing limited research. Nearly three-quarters of the group was female (72%), resembling a functional GI or IBS cohort more than a typical GERD cohort. The most common presenting extraesophageal symptoms were cough (50%) or hoarseness (23%), followed by globus/post-nasal drainage (15%), asthma (9%), and sore throat (3%). The median follow-up was 32 months.

The authors report that patients had a mean of 10.1 consultations with specialists and underwent 6.4 diagnostic procedures on average during the study—a substantial diagnostic burden. The mean direct cost was $5,438 per patient during the first year of management. Medical and nonmedical components contributed $5,154 and $283. More than half of the overall cost (61%) of managing extraesophageal symptoms came from PPIs alone, suggesting that PPIs remained the cornerstone of treatment regardless of all the diagnostic testing. Compared with historical data of patients with typical GERD, patients with atypical GERD in this series expended 5.6 times more direct costs. Yet, despite all this, only 54% of patients in this highly specialized consortium reported symptom improvement by the end of the study period. When all the numbers were crunched, the authors found an overall cost of $13,700 per "improved patient."

What should we make of these results? Although this is not a controlled trial and the symptom outcomes were unstandardized, this is a large and well-described case series of patients with atypical GERD seeking subspecialty care. The results indicate that despite our best efforts to test and treat, nearly half of these patients with extraesophageal GERD have persistent symptoms anyway. It seems like the testing makes little difference—but again, it is hard to make this conclusion firmly without a control population not undergoing diagnostic tests. Still, the picture again resembles IBS, where extensive testing often fails to advance the diagnosis and may not track with symptom improvements.

The findings in the current study are reminiscent of "*furor medicus*," an old but descriptive term referring to the unbridled frenzy of doctors to just do something, especially when the clinical situation is confusing or desperate (7); the term is often used to describe diagnostic testing in IBS (8,9). Atypical GERD might be another example of *furor medicus*. Drossman (9) points out that *furor medicus* depends on two factors: the uncertainty of the

doctor and the insistence of the patient to get something done. When the clinical situation is confusing and the patient wants answers, doctors often start to test—a lot.

Atypical GERD is a "perfect storm" for unbridled testing, as the diagnosis is often unclear, the evidence linking acid to extraesophageal symptoms is imperfect, and patients remain bothered by their symptoms despite ongoing PPI therapy; they often want answers. And we want to provide answers. But this study provides more evidence that PPIs often fail, that our therapeutic armamentarium is often limited, and our capabilities remain imperfect. Rather than continuously treating with PPIs, recommending more diagnostic testing, or even pushing for surgical interventions, we might instead do the opposite: "*Don't just do something, stand there!*"(9). It is okay to be limited; we need to be honest with our patients that we cannot solve everything, and sometimes doing less—and carefully explaining why—is better than doing more.

CONFLICT OF INTEREST

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