Respected physicians debate the current status of this condition, as well as the true efficacy of medical treatment.

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END OF AN ERA?

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AGA Perspectives
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The Role of an Allergist in the Management of Eosinophilic Esophagitis
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This issue of AGA Perspectives addresses several important issues: some have already had an impact on the clinical practice of gastroenterology, while others are in the process of validation. Our lead point-counterpoint article examines much awaited data that was hitherto unavailable, providing great clarity on sphincter of Oddi (SOD) dysfunction. We have two divergent perspectives of experts who review the results of the NIDDK-funded EPISOD trial that was funded by NIDDK, which addressed the effects of sphincterotomy in patients with symptoms attributable to SOD.

Discussed in this issue are several important advances in the diagnosis and management of esophageal diseases. It is easy to see the impact of the pretty pictures in high-resolution manometry that has brought the diagnosis of esophageal motility disorders to a new level of understanding and enabled application outside specialty centers. Other articles discuss the “revolution” in eosinophilic esophagitis, which continues to evolve with greater clarity of the interactive roles of allergists and gastroenterologists, as well as the validation of endpoints for therapeutic trials in this disorder.

The article on esophageal cancer takes us beyond the confines of adenocarcinoma, which is increasingly identified in the Western world especially in association with Barrett esophagus, to the realization that, from a global perspective, squamous cell cancer of the esophagus accounts for 80 percent of all esophageal cancers. Environmental and genetic predisposition is being investigated and has the potential to lead to preventive strategies at the population level. Another topic discussed is visceral hypersensitivity of the esophagus, which impacts several symptoms: reflux, dysphagia, and chest pain. The methods of testing have improved; what is needed is a breakthrough in therapy.

Finally, readers may be particularly interested in the article on Choosing Wisely, the imperative to provide quality, safe and cost-effective care; the future of all our practices depends on the disciplined approach to prove quality at affordable cost.

Michael Camilleri, MD, AGAF
INTERIM EDITOR

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SPHINCTER OF ODDI DYSFUNCTION

END OF AN ERA?

OR

STILL ALIVE?

Respected physicians debate the current status of this condition, as well as the true efficacy of medical treatment.
Like many long-time ERCPists and sphincterotomizers, I was attracted to the concept of sphincter of Oddi dysfunction (SOD) as a cause of biliary pain, and, for many years, was convinced that my treatments were helpful in many if not most cases. This despite an early comment from a respected mentor, Professor Solly Marks (grandfather of South African gastroenterology), who kindly remarked after my eloquent lecture on the subject: “Peter, that sounds like sewing flatus to moonbeams.”

Probably like many other “experts” seeing patients referred from considerable distances, I did not keep careful track of their outcomes, and counted failure subconsciously only by those few patients brave enough to complain or return. One well-known center suggested a success rate of 75 percent simply because only 25 percent underwent re-intervention at the same center; what about all those who went elsewhere or battled on in pain?

Sphincter dysfunction is traditionally divided into three types. Type I includes patients with biliary pain, a dilated bile duct

END OF AN ERA - CONTINUED ON PAGE 6

STILL ALIVE?

The status of the sphincter of Oddi in health and disease has a rich history dating back to 1861. A PubMed search identified 2,769 publications on this topic. Despite the above body of data involving thousands of patients, recent ongoing research notes that one subcategory of suspected sphincter of Oddi dysfunction patients do not benefit from endoscopic intervention. We must examine new data within a setting of all data.

The recently published one-year follow-up of type III suspected sphincter of Oddi (EPISOD Study) showed that medical therapy plus short-term pancreas stenting via ERCP (called sham) had poor efficacy similar to biliary and/or pancreato-biliary sphincterotomy with continued medical therapy. The overall success rate for endoscopic therapy was only 23 percent. This figure suggests that sphincter-level obstruction is not a very important contributor to pain in type III patients or that a complete sphincterotomy

STILL ALIVE - CONTINUED ON PAGE 7
and abnormal liver function tests. Type II patients have a dilated bile duct or abnormal labs, but not both. Type III patients have none of those criteria. Type I patients mostly have an organic cause (sphincter stenosis or small stones) and seem to be well-treated by endoscopic sphincterotomy. Nowadays those patients can be best diagnosed by endoscopic ultrasound.

SOD, at least type III, dissolves like moonbeams under the searchlight of science.

Over the last two decades, type II and III patients have been referred increasingly to approximately 25 centers in the U.S. performing sphincter manometry, because the “experts” continued to espouse its value and community physicians believed it to be dangerous. Manometry itself is actually not dangerous, but ERCP is indeed so in these patients. As a result of this trend, my own clinic and ERCP practice became dominated by complex and often desperate patients with “suspected SOD,” expecting to be cured quickly with a simple cut. My colleagues and I began to wonder if we were indeed tilting at moonbeams, and decided to explore the problem objectively. It has taken almost 10 years. A lot of preparatory work and a planning grant led to the EPISOD research study funded by NIDDK, the results of which were published recently in *JAMA*.

We took patients aged 18 to 65 with burdensome post-cholecystectomy biliary-type pain, no evidence for pancreatitis and no prior sphincter intervention. We excluded patients with bile ducts larger than 9mm in diameter, those taking narcotics daily and those with marked psychological problems. They were essentially “SOD type III” except that we did allow some minor elevations of liver and pancreas lab tests.

After consent, application of multiple questionnaires and some other resulting exclusions, 214 underwent ERCP with manometry (of both sphincters) and were randomized (2:1), irrespective of the manometry results, to sphincterotomy or to sham. Those randomized to sphincterotomy who had elevated pancreatic sphincter pressures (PSH) were randomized again (1:1) to biliary sphincterotomy or to both biliary and pancreatic sphincterotomy. All patients, including those treated with sham, received a temporary small pancreatic stent. Patients, caregivers and research staff were blinded to the treatment allocation during the follow-up of one year. Success was defined as a marked reduction of the pain score as measured at nine and 12 months, without any sphincter re-intervention and no narcotics in the last three months.

The results were striking and definitive. The success rate for sham treated patients was 37 percent, but only 23 percent in the sphincterotomy arm. In those with PSH, 30 percent responded to dual sphincterotomy, and 19 percent to biliary alone. Re-interventions occurred in 26 percent of treated patients and 34 percent of the controls. Post-procedure pancreatitis occurred after 11 percent of primary sphincterotomies and 15 percent of controls. There were two perforations, one requiring surgery, no bleeds and no deaths.

It is noteworthy that three-quarters of the patients had abnormal manometry (64 percent pancreatic, with or without biliary, and 12 percent biliary alone). The results of sphincter manometry did not correlate with the outcomes. Furthermore, we could not identify any clinical features that made success more or less likely (e.g., presence or absence of daily pain, lab abnormalities, reasons for the cholecystectomy and response to it, presence of other functional digestive disorders, or psychological factors).

Seventy-two patients eligible for the study but who declined randomization entered into an observational study (EPISOD 2) where sphincterotomy was directed by the manometry results, as in current standard practice. The success rates were equally unimpressive, 31 percent for dual sphincterotomy, 24 percent biliary and 17 percent for none.
was not achieved. Unfortunately, one sphincterotomy attempt (especially pancreatic) is often not effective in normalizing basal sphincter pressure. Sherman and others\(^2\) noted residual high-basal pancreatic sphincter pressure in the majority of re-evaluated symptomatic patients. The optimal technique for pancreatic sphincterotomy is unknown. Some authorities prefer cutting current alone (without coagulation current). The current type and amplitude were not standardized in EPISOD. A high rate of residual elevated pancreatic basal sphincter pressure suggests an inadequate sphincterotomy or excess coagulation current.

EPISOD considered any need for endoscopic retreatment as a failure point. Similarly, any narcotic use at the end of the first year was a failure. These classifications are too strict. Should a type III (or II) patient with initial pain relief after sphincterotomy, but then with relapse requiring narcotics, be considered a success or failure?

Retrospective and some prospectively collected case series\(^3\) from the last several decades show that endoscopic or surgical sphincter therapies with several years follow-up have a 60 to 70 percent pain improvement rates (usually on linear 1 to 10 pain scale) for type III patients. Such simple scoring methodology was not reported in EPISOD initial publication. Historically, these results have been good enough for referral centers to continue to offer ERCP therapy for medical failure type III patients (after full informed consent). The EPISOD study success rate of 23 percent is contrary to nearly all prior publications. The scoring outcome must be questioned. The RAPID pain assessment test is proposed as a new scoring method based on objective criteria. This tallies days (objective) of dysfunction (subjective) due mainly to symptoms of pain or nausea (subjective). More studies are needed to evaluate the clinical utility of the RAPID scoring method.

There are also other confounding variables in this problematic type III group. Irritable bowel syndrome (IBS) was identified in 34 percent of EPISOD patients. Differentiating pancreatobiliary and IBS symptoms may be difficult. I have had the opportunity to follow many type III patients for up to 40 years. An increasing number of these patients have recurrent pancreatitis (unrelated to ERCP) or chronic abdominal pain associated with EUS criteria for chronic pancreatitis. More detailed evaluation for chronic pancreatitis at study entry and/or exit is needed to further define this study group. Almost certainly chronic pancreatitis is a contributor to type III disability.

As is well-known, coined the Hawthorne effect, workers whose functional performance is scrutinized closely change their outcome behavior. In a similar fashion, the EPISOD study scrutinized patients very closely. Over one year, subjects were personally asked more than 2,500 performance questions and subquestions. Does detailed monthly questioning of patients about their disabilities alter disability reporting?

Historically, these results have been good enough for referral centers to continue to offer ERCP therapy for medical failure.

EPISOD noted a lack of correlation of normal versus abnormal basal sphincter manometry and symptom outcomes. What are normal pancreatic sphincter pressures? While normal volunteer data are limited, the larger series by Gregg\(^4\) (n=43) and Guerard\(^5\) (n=20) combine to show a mean pancreatic basal pressure of 16.3 + one standard deviation of 6 mmHG. If 40 mmHG is taken as the lower limit of abnormal this would equal 16 mmHG + 4 standard deviations. Would two standard deviations be more appropriate? Pancreatic sphincter pressures are not reported in the JAMA...
We conclude that most if not all of the "successes" in the study were due to a powerful placebo effect in very distressed patients coming to known "experts" and supported for a year by contact with research staff.

It appears that Solly Marks was right. SOD, at least type III, dissolves like moonbeams under the searchlight of science.

Where does that leave the overall concept of SOD? The justification for doing manometry-directed sphincterotomy in type II patients is based on many unblinded cohort studies with results that are not totally convincing; and from three small and old randomized trials. Pooling the data from the randomized studies (no doubt not an appropriate thing to do) showed that 78 percent (29/37) of the patients with post-cholecystectomy pain and abnormal biliary manometry were relieved by biliary sphincterotomy. While that figure is impressive, it is noteworthy that success was reported also after biliary sphincterotomy in a third (11/35) of patients with normal manometry, and in no fewer than half (13/25) of those with elevated pressures and no sphincterotomy. What is also a little odd is the high rate of success when the studies focused exclusively on the biliary sphincter. Yet we know now that pancreatic sphincter hypertension is just as common in these patients. Despite those reservations, these studies gained a lot of traction and have bolstered the field effectively for years.

If sphincterotomy does indeed help some type II patients, we certainly need more research into optimal methods for identifying them. Which clinical factors are really predictive? Is dynamic biliary scanning really worthwhile? Is a Botox trial helpful?

Since SOD type III does not exist, and many type I patients have an organic explanation that can be revealed by EUS, it is time to ditch the old I, II, III classification. We are left with one problem syndrome called "suspected SOD," whose complexities and components will be revealed gradually by further research.

SOD is also postulated as a cause of recurrent acute pancreatitis. The recent report that dual sphincterotomy is no more effective than biliary sphincterotomy alone also raises doubts about the relevance of SOD in that context.

This is indeed the end of an era, but also, hopefully, the beginning of a new one. It is time for a comprehensive reappraisal of "functional" biliary (and pancreatic) disorders. The clinical problems are important and need our best attention. There are plenty of very genuine patients with burdensome biliary pain (before and after cholecystectomy). It is time to delve further into the mechanisms of pain and to improve our diagnostic and therapeutic approaches. We need to reduce the number of unnecessary (and potentially dangerous) interventions.

REFERENCES


publication except to note 40 mmHg cut off. Geenen\(^6\) considered upper limit of normal as 30 mmHg and excluded borderline patients with 30 to 40 mmHg. What portion of the EPISOD “normal pancreatic pressure” patients were truly normal? Our local data showed that only half the “normal” patients had basal pressure less than 30 mmHg. Other controlled trials have addressed type III patients.\(^7\) Our group carried out a single-blind randomized controlled trial of type II (n=23) and III (n=29) sphincter of Oddi patients treated by surgical sphincteroplasty, endoscopic biliary sphincterotomy or sham. Eleven of 19 (58 percent) endoscopically or surgically treated type III patients had symptom improvement or resolution versus three out of 10 improved with sham (p <.05) over two to three years of follow up. This study encouraged us to selectively offer invasive therapy to type III patients. Unfortunately, this abstracted data was not fully published (but renewed efforts are in progress).

Wehrmann\(^8\) treated sphincter of Oddi type III patients with intrasphincteric Botulinum toxin (a known temporary treatment). Fifty-five percent of patients reported complete pain resolution, but treatment benefit disappeared over six months, i.e., no persisting benefit. How long will the EPISOD sham benefit last?

Unfortunately, the new EPISOD data does little to tell us how to improve patient care/pain relief in this difficult patient group. It suggests we should avoid ERCP and therapy (while chronic pain persists and becomes centralized?). Pending further data, I’m inclined to continue pre-EPISOD practices, inform patients of new and old data, use NSAIDS to decrease ERCP risk and probably help the 50 to 70 percent of patients reported in prior literature.

Overall, the EPISOD study when completed should shed light on an important clinical problem. As with many good studies, more questions are raised and there is much more work to do. Type III patients will not likely disappear soon. Optimal management strategies are needed.

The new EPISOD data does little to tell us how to improve patient care/pain relief in this difficult patient group.

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COMPETENCY IN ENDOSCOPY

How to measure and maintain competency in clinical practice

Competency is defined as the ability to do something well enough to meet a defined standard. For example, a sixteen-and-a-half year old is deemed competent to drive a car in my state if they complete a state-approved driver’s education course, have 40 hours of supervised driving and pass a road test. Yet anyone who has ever driven with teens knows that competency does not guarantee rational use of a motor vehicle, let alone a high-quality experience. Much has been written and debated about defining competency in endoscopy as it relates to trainees early in their careers. As technology advances however, those of us in clinical practice encounter an ever-changing array of new endoscopic devices and therapies. Frequently we must decide which new tools and techniques to implement ourselves and which to refer to colleagues.

Yet, historically, little has been done to ensure we attain competency when we choose to incorporate these novel technologies into our practice. Some devices simply reflect a change in design, such as a new polypectomy snare, or represent a simple-concept, easily operated machine, such as a water pump for more effective flushing through an endoscope. In these cases, a seasoned endoscopist likely does not need to demonstrate competency. However, some devices, such as the over-the-scope clip, are a significant enough departure from what we typically use every day that we probably should have some way to ensure we know 1) when to employ the device, 2) exactly how to set up and

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REFERENCE
But beyond devices, we are also faced with new techniques that appear daunting at first, such as endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA). In time, these new methods often undergo refinements that make them quite accessible to most endoscopists. EMR with band ligation is now a reasonable and quite simple technique for resection of the small rectal carcinoids we all encounter. RFA can now be performed with a simple through-the-scope device and used to treat small foci of flat Barrett's dysplasia. Clearly, most of us will never seek to adopt more complex new procedures such as full-thickness gastric wall resections or endoscopic pancreatic necrosectomy, partly because of the demanding learning curve, but also because the cases will be too infrequent to maintain competency even if we did learn the techniques. But for those seeking to learn EMR, RFA, how to use over-the-scope clips for hemostasis and other new endoscopic skills, we must ensure a practical way to measure and maintain competency.

The traditional model of “see one, do one, teach one” (or in the case of devices, “read about it, have a device company representative show you how to use it ex vivo, give it a try in a patient”) is being replaced by a more rigorous process.

use the device, and 3) what complications may arise from its use and how to manage those complications.

As we enter a new health-care delivery era where transparency and quality measurement become expectations, we are likely to see more requirements to demonstrate competency in our endoscopic methods. We need our professional societies and the endoscopic community to continue to define and measure benchmarks indicating competency in newly acquired skills. And while our hospitals, payors and ABIM may ask for proof or maintenance of competency, it is really our patients to whom we owe the effort to ensure we are keeping up in a meaningful way with new endoscopic technology. ■
High-resolution manometry (HRM) was the brainchild of Ray Clouse, a distinguished clinician, esophagologist and researcher at Washington University in St. Louis, MO. Clouse realized early in his career that pressure profiles of peristalsis obtained from widely spaced sensors used in conventional esophageal manometry provided only limited thumbnails of esophageal motor function. He hypothesized that additional pressure data collected during swallow-induced esophageal peristalsis could help generate topographical pressure maps of esophageal peristalsis. Clouse started by pulling the conventional manometry catheter out 1 cm at a time, obtaining swallows at every location. After digitization, the individual pressure profiles were overlayed, and best fit pressures were interpolated between recorded pressures to generate smooth pressure contours. Colors were assigned to pressures amplitudes, and the topographic map thus created (now termed the Clouse plot in his honor) was viewed as if flying over the esophageal pressure profile.

In the 25 years since the first HRM concepts were tested out, esophageal manometry has become much less cumbersome. Modern catheters have up to 36 circumferential solid-state sensors, sometimes with impedance sensors interposed to collect bolus transit data. The stationary pull-through maneuver is obsolete, as the entire esophagus can be visualized by the operator in real-time, while obtaining pressure data. Standard esophageal HRM with basal pressure recordings and a 10 swallow complement can now be completed within a 10-minute span in most instances. The concepts underlying esophageal HRM have been applied to interrogation of the anal sphincter, as well as other regions of the gut including antroduodenal, small bowel and colonic motility. Finally, a denser sensor complement has been used to address sphincter function, the so-called three-dimensional or 3D manometry, utilized clinically in anorectal manometry.

The vivid colors assigned to Clouse plots make for pretty pictures, but HRM is much more than just that. One of the first revelations of HRM was that esophageal peristalsis consisted of a chain of relaxing sphincters and contracting segments, with seamless transmission from skeletal to smooth muscle function when normal. Esophageal smooth muscle contraction was found to consist of two sequential contracting segments, corresponding to proximal cholinergic dominance and distal inhibitory dominance recognized decades before HRM. Behavior of these contraction segments has allowed for better understanding of esophageal neural control, which consists of a balance between excitatory and inhibitory influences. Vigor of contraction can now be mapped for the entire smooth muscle esophagus, using a metric (distal contractile integral, DCI) that is more intuitive and reliable than averaged pressure amplitudes used previously. DCI takes into account the length, amplitude and duration of the entire smooth muscle contraction profile. Distal latency of peristaltic contraction, measured from upper sphincter relaxation to the point where contraction slows in the distal esophagus prior to esophageal emptying (contractile deceleration point), is a better marker of esophageal inhibitory dysfunction than peristaltic velocity used previously. Isobaric contours can be digitally drawn around assigned pressures, and a baseline intact contour of 20 mmHg in the smooth muscle esophagus correlates with adequate bolus transit, hence representing intact peristalsis.
However, it is HRM interrogation of the lower esophageal sphincter (LES) that has made the most clinical impact over conventional manometry. Since HRM pressure data is collected electronically, software tools can be applied to assess LES relaxation. The integrated relaxation pressure is extracted electronically during expected LES relaxation and represents four contiguous or non-contiguous seconds of nadir pressure where flow occurs across the LES. This metric has a sensitivity of 98 percent in the diagnosis of abnormal LES relaxation or esophageal outflow obstruction, significantly higher than the 50 percent sensitivity of unidirectional point-pressure sensors.

Using HRM, achalasia has now been subtyped into three categories based on HRM features, and esophageal outflow obstruction with retained peristalsis (from variant achalasia mechanisms or structural obstruction) is now recognized, an entity incompletely recognized and rarely diagnosed with conventional manometry. HRM has allowed easy identification of esophageal shortening from longitudinal smooth muscle contraction, which can pull the LES high-pressure zone several centimeters proximal to its basal location — this ‘pseudorelaxation’ resulted in failure to diagnose achalasia with conventional manometry. With HRM, most of what we knew as diffuse esophageal spasm turns out to be achalasia with retained but spastic or premature esophageal body contraction (achalasia type III), uncovering decades of missed achalasia diagnoses.

But there are benefits of HRM that cannot be directly quantified in the individual patient. The Chicago Classification of esophageal motor disorders is based on HRM, and has made nomenclature and definitions more uniform across the globe. Combination of HRM with impedance can demonstrate esophageal bolus transit, allowing improved understanding of esophageal transit. Provocative maneuvers during HRM continue to be studied in assessing peristaltic reserve, and in bringing subtle obstructive mechanisms to light. But most importantly, HRM Clouse plots have vivid and colorful contraction patterns that can be recognized even without precise pressure interpretations. This has moved the art and science of esophagology to a whole new level, demystifying esophageal pathophysiology, improving diagnostic impressions and allowing for intuitive image-based paradigms for teaching esophageal physiology and pathophysiology. With esophageal HRM, the pretty pictures are truly worth a thousand words.

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Almost 70 percent of patients with reflux symptoms have no macroscopic evidence of esophageal mucosal damage, and are termed as having either non-erosive reflux disease or functional heartburn. Compared to patients with demonstrable erosive esophagitis, these patients respond less well to proton pump inhibition (PPI). In addition to the classical symptoms of heartburn, a portion experience chronic, angina-like chest pain, which is often referred to as non-cardiac chest pain (NCCP). Chest pain occurring in the absence of evidence of reflux disease and histological abnormalities is classified by the Rome III criteria as functional chest pain of presumed oesophageal origin (FCP). While a plethora of pathophysiological mechanisms for symptom generation have been proposed, heightened sensitivity of the esophagus to stimuli may be conceptualized as being a critical facet. Esophageal hypersensitivity can be characterized by allodynia, where a non-painful stimulus is perceived as being painful, and hyperalgesia, whereby a normally painful stimulus is felt as more painful than usual. In this brief article, we shall discuss the overarching mechanisms that culminate in visceral hypersensitivity of the esophagus and provide our perspective with respect to the management of such patients.

MECHANISMS OF VISCERAL HYPERSENSITIVITY OF THE ESOPHAGUS

The concept of visceral hypersensitivity of the esophagus was first demonstrated in the mid-1990s by Richter, et al., who demonstrated that, in comparison to healthy controls, a higher percentage of patients with NCCP reported pain to intraluminal esophageal balloon distension, results that we have replicated in FCP (see figure 1).

However, this enhanced sensitivity is not confined to mechanical distension in that heightened chemosensitivity in functional heartburn patients has also been reported. Nevertheless, despite this evidence, it remains important to...
Gabapentin
EMPATHY
responses to therapeutic interventions, especially
Multiple different physicians
Multiple investigations
Poor outcomes to treatment
Chronic unexplained symptoms
TIME
EMPATHY
Disenfranchised
VALIDATION OF PATIENT’S SYMPTOMS

Figure 2
Breaking the cycle of the patient visceral hypersensitivity of the esophagus who “over-utilizes” health-care resources.

PPI. Furthermore, this is often associated with a “sixth sense” of trepidation that the consultation is going to be a “difficult” one. Frequently patients undergo further investigations, often of an increasingly invasive nature, which rarely provide a diagnosis. Understandably both parties, i.e., the clinician and the patient, can become disenfranchised with each other, and there is a risk that the therapeutic relationship irrevocably breaks down. This invariably initiates a referral to another clinician, and so the cycle begins again (see figure 2).

BREAKING THE CYCLE
From the gastroenterologist’s point of view, the key intervention is to break this cycle ab initio, although sadly, there is no “magic formula.” The first and central facet of successful management is the doctor–patient relationship. This enables trust building with the patient, acknowledging their symptoms are real and to impart empathy. Often the key is not to repeat investigations, but to acknowledge that our current armamentarium has limited resolution, particularly when it comes to various underlying mechanisms that underlie chronic pain syndromes. Repeated negative investigations often instill into a patient’s mind a sense of diagnostic uncertainty, even if there is little doubt in the mind of the clinician. Unfortunately for the clinician in a hard-pressed service, such an approach takes time and cannot be realistically achieved in a 15-minute consultation.

SPECIFIC MANAGEMENT
Despite a widely held perception that there is little that can be done from a therapeutic standpoint for the patient with chronic esophageal pain beyond PPI therapy, the evidence base suggests otherwise. The agreement of realistic goals in terms of the reduction of symptom burden helps manage expectations. A step-up management regimen, interspersed with regular reviews, consisting of both pharmacological and psychological therapies (see figure 3) is beneficial in the majority of recalcitrant patients. Both approaches should be directed at improving pain management, with the former focussing upon the modulation of the hyperalgesic/allodynic state.

Even with such therapeutic interventions, we cannot afford to sit on our laurels. The absolute place of endophenotyping individuals (leading to personalized medicine) remains to be fully defined and offers an exciting, and potentially fruitful, avenue of future research.

Figure 3
Suggested algorithm for the management of chronic esophageal pain, in addition to standard measures such as PPI, adapted from Farmer and Aziz.1

- **General measures**
  - Supportive environment
  - Validation of symptoms
  - Patient education
  - Agree and set realistic treatment goals

- **Pharmacological**
  - Tricyclic antidepressants
  - Serotonin noradrenergic reuptake inhibitors

- **Psychological interventions**
  - Cognitive behavioural therapy
  - Hypnotherapy

- **Step-up therapy**
  - Gabapentin
  - Pregabalin

**REFERENCES**
First-line management strategies for eosinophilic esophagitis (EoE) include swallowed, or “topical,” corticosteroids and dietary elimination. Typically, the initial course is followed by an upper endoscopy, at which time treatment response can be assessed clinically, endoscopically and histologically. On the surface, this would appear to be a simple issue — is the patient better or not? But from a practical standpoint, how to select the appropriate endpoints of treatment is one of the most vexing questions in EoE management. This issue is confronted during patient encounters as well as in research. For this discussion, I will focus primarily on endpoints in clinical practice, as others have discussed the challenges in outcome selection for EoE research and clinical trials.

What are the possible endpoints of EoE treatment? The two most obvious are symptoms — does the patient feel better? — and histology — are the biopsies better? However, there are other issues that should be considered. Has the endoscopic appearance or esophageal compliance improved or normalized? Have the treatments impacted quality of life, and if so, is it for better or worse? In children, there are also important issues related to tolerating oral intake, ensuring adequate feeding, nutrition and growth, and reaching developmental milestones. It is also not clear whether one endpoint should hold primacy over the others, or if all should be considered together. Currently, there are no biomarkers that have been validated to use as endpoints.

Beyond selecting specific outcomes is the issue of how to measure these outcomes.

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Dr. Dellon is a consultant for Aptalis, AstraZeneca, Receptos and Regeneron, and has received research funding from AstraZeneca and Meritage. There are no conflicts of interest pertaining to this paper.
For example, a patient can provide a subjective sense of global clinical improvement, but if this degree of improvement needs to be quantified, it is more difficult. In fact, there are as of yet no fully validated symptom instruments for EoE that have been shown to be responsive, though these are under development. Most prospective studies of EoE have chosen to use a primary histologic outcome, the level of esophageal eosinophilia (measured in eosinophils per high-power field [eos/hpf]). The exact histologic outcome varies by study design, with some trials requiring complete histologic normalization (0 eos/hpf) and others using different cut-points (≤ 5 eos/hpf; ≤ 6 eos/hpf; 90 percent decrease in peak count; etc). This heterogeneity of outcomes in the literature makes it difficult to know what level of inflammation constitutes a response in practice.

The situation is easy when, after treatment, a patient feels better, the endoscopic findings have resolved and the biopsies have normalized. How frequently does this happen? Data from our center suggest all three features improve in approximately two-thirds of patients after an initial course of topical steroids. The situation is much harder when there is discordance between the symptom and histologic response, which happens because the inflammatory and fibrotic aspects of EoE can have differential responses to treatment. If symptoms of dysphagia continue in the setting of histologic normalization, it is possible that there is a residual stricture or esophageal narrowing that persisted after the eosinophilic inflammation resolved. Conversely, symptoms can improve after esophageal dilation or if a patient modifies their eating habits (chewing carefully, eating slowly, avoiding meats) while inflammation remains. Intermediate scenarios with varying degrees of response are also possible. These situations are challenging because the degree of eosinophilic inflammation does not always correlate with symptom severity. Two recent cases illustrate this point. Consider a patient with 200 eos/hpf on initial biopsy, who after treatment has 25 eos/hpf with symptom resolution. Contrast this with a patient who has 25 eos/hpf on initial biopsy, but has 20 eos/hpf after treatment with persistent symptoms. The latter patient’s post-treatment absolute eosinophil count is lower, but it is difficult to argue that this patient had more clinical improvement compared with the former.

**How to select the appropriate endpoints of treatment is one of the most vexing questions in EoE management.**

Discussing the treatment endpoints for EoE often raises more questions than are answered, which is fitting for what is still a new disease. Even in IBD, for which there are decades more clinical experience and research, there is an ongoing debate as to whether symptom resolution, or improvement in a disease activity index, is an appropriate outcome, or whether it is better to target treatment to endoscopic or even histologic normalization. In time, researchers will link symptomatic, endoscopic and histologic improvement in EoE to meaningful clinical outcomes such as decreased food bolus impactions, decreased dilation requirements for esophageal strictures, decreased health-care utilization and improved quality of life.

Until then, what is a practical approach? Because EoE is defined as a clinico-pathologic disease, it makes sense to me that the treatment endpoints should be clinico-pathologic as well, with both symptom and histologic improvement required. Recently published guidelines echo this sentiment, by stating:

“The endpoints of therapy of EoE include improvements in clinical symptoms and esophageal eosinophilic inflammation. While complete resolution of symptoms and pathology is an ideal endpoint, acceptance of a range of reductions in symptoms and histology is a more realistic and practical goal.”

How low should you go with the eosinophil count? This is something that needs to be individualized based on a patient’s history, tolerance of treatment and impact of treatment on quality of life. I typically will aim to get the eosinophil count below the diagnostic threshold (<15 eos/hpf), and as low as possible in patients with persistent symptoms or prior EoE complications such as food bolus impaction, critical strictures or prior esophageal perforations. Recognizing that it is not always possible to normalize the esophageal biopsies, my clinical endpoint goals are: symptom improvement, endoscopic improvement and a low eosinophil count.

In patients who have had a good clinical response, what is a reasonable approach for long-term management? Should treatment be stopped or maintained indefinitely? This also needs to be individualized, but with the knowledge that EoE is chronic, and in almost all cases, when treatment is stopped esophageal eosinophilia and symptoms will return. In general, I discuss maintenance therapy with all of my EoE patients. For patients with prior food impactions, severe or frequent symptoms, esophageal remodeling or fibrotic complications (esophageal strictures or narrowing), or rapidly recurring symptoms, I strongly recommend maintenance therapy. For patients with mild and intermittent symptoms and no complications, “on-demand” therapy for recurrent symptoms is a reasonable approach, but I now have relatively few patients for whom I do not recommend maintenance therapy. If symptoms recur in a patient who has known EoE but who has been weaned off treatment, I will consider a repeat endoscopy to re-stage the disease if there has been a major clinical change, but do not feel that an endoscopy is mandatory prior to resuming treatment in every patient.

Because the natural history of EoE is still being determined and treatment approaches are evolving rapidly, it is important to partner with patients, use shared decision-making models to individualize management strategies and provide follow-up over time. This is only way to be sure that the EoE treatment endpoints and long-term strategies currently selected for a patient optimize their health status, and to allow changes to endpoints as new data inform clinical practice.

**REFERENCES**


PATIENT CARE

THE ROLE OF AN ALL

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Dr. Atkins is on the medical advisory committee for the American Partnership for Eosinophilic Disorders.

Dr. Furuta is co-founder of Enterotrack, LLC. He also receives research support from Nutricia and Morphotek. Dr. Furuta serves on the executive council of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.
Over the last 20 years, eosinophilic esophagitis (EoE) has emerged as a leading cause of dysphagia in adults and reflux-like symptoms and feeding problems in children. Diagnostic criteria have become clearer for the majority of patients, but the division of care for patients longitudinally remains an ongoing topic of debate. For instance, at the recent Digestive Disease Week® in Chicago, a session addressing the role of the allergist in the care of EoE patients generated robust discussion. Similarly, during a day-long symposium organized by The International Gastrointestinal Eosinophil Researchers (TIGERS) at the American Academy of Allergy, Asthma and Immunology (AAAAI) in 2013, comparable discussions were held amongst the more than 400 attendees.

In 2007, we as a team of gastroenterologists and allergists started a multi-disciplinary program that cares for children with EoE. We had the conviction that, because of our different backgrounds, our shared individual and collective insights would enable us to continue to develop a high-quality standard of care and generate new research interests. This opinion evolved from observation of earlier models at Cincinnati Children’s Hospital and Children’s Hospital of Philadelphia where similar unions shaped critical initial insights into this disease. The type of collaborative care we, and many others in this field, practice has promoted outstanding clinical care, research and advocacy resulting in important advances that could not have been accomplished in the same time frame if we were to work as specialists in isolation. So the question is, why is the allergist so key in the management of EoE? Here we provide our opinion as it pertains to the daily management and the global advancement of knowledge regarding this disease.

First, allergists are trained in caring for all mucosal allergic diseases, not just those related to gastrointestinal illness. Since up to 67 percent of patients with EoE may also have other atopic diseases, such as IgE-mediated food allergy, asthma, atopic dermatitis, allergic rhinitis and/or allergic conjunctivitis, the care of these co-morbid diseases is critical to the overall mucosal healing. Given the intimate relationship shared by mucosal associated lymphoid tissues, one cannot help but consider the fact that limiting mucosal inflammation in associated organs, such as the skin, with its squamous epithelial surface, or the nose with its secretions that are often swallowed, also benefits the esophagus. In addition, by virtue of seeing a large number of patients with other allergic conditions, allergists are in a unique position to screen patients at higher risk for that food is the trigger for many EoE patients. Alternatively, other patients do not have an identifiable food trigger and require topical steroid treatment. The allergist’s expertise in aiding in the identification of food triggers, identifying potential seasonal and environmental allergen triggers, the methods to best use topical steroids, and optimally managing co-morbid allergic disease provides an invaluable contribution to the care of EoE patients.

Finally, the relationships shared between gastroenterologists, allergists and many other subspecialties has advanced discovery at an unprecedented pace. For instance, the seminal article published in Gastroenterology in 1996 identified the role of food allergens in EoE. This work was performed by pediatric gastroenterologists and allergists and set the stage for many of the forthcoming discoveries in clinical care and research. Importantly, approximately 20 percent of research publications to date have been co-authored by gastroenterologists and allergists. These novel publications have focused on the identification of allergen triggers, new forms of allergen testing, the discovery of EoE genes (eotaxin-3, filagrin, thymic stromal lymphopoeitin, desmoglein-1 and others), the development of a new treatment methodology (oral viscous budesonide), and many other aspects of EoE. The success of consensus recommendations has been fostered by contributions from allergists in addition to other specialists. In fact, the first two consensus recommendations were the most highly cited publications in their respective journals. Without this multi-disciplinary dialogue and cross-fertilization, the pace of advancement in this field would be much slower, and the quality of patient care would be compromised. For these reasons, we believe that the involvement of the allergist in the longitudinal care of most patients with EoE is clearly justified and valued.

... the relationships shared between gastroenterologists, allergists and many other subspecialties has advanced discovery at an unprecedented pace.
Esophageal cancer is a growing problem. Adenocarcinoma, the most common type seen in the U.S., is linked to chronic gastroesophageal reflux and Barrett’s esophagus. But worldwide, 80 percent of cases are squamous cell cancers. Many of these cases cluster in specific regions found in southern South America, East and South Africa, and a geographic belt extending from the Caucasus Mountains eastward to China. In these regions the incidence of esophageal cancer is up to 20-fold the Western incidence, and esophageal cancer is a leading cause of cancer death.

What causes “endemic” squamous cell cancer, and are there reasons for optimism about this typically fatal disease?

In America and Europe, the risk factors for esophageal squamous cell cancer (ESCC) include alcohol and cigarette use, achalasia, tylosis, and previous caustic injury. These factors are probably not the principal causes of ESCC in endemic areas. Global research conducted over the past 25 years has identified leads such as the following:

1. In some regions, ESCC has been linked to high urinary levels of polycyclic aromatic hydrocarbons (PAH), carcinogens typically found in smoke. The source of ingested PAH exposure probably varies: in Brazil, it is linked to drinking mate (a traditional tea), while elsewhere it may be related to eating heavily smoked foods or condiments, occupational exposures or a smoky fire in a poorly ventilated home.

2. Thermal injury can also play a role. In some regions with endemic ESCC, people pride themselves on drinking scalding hot beverages. A large-scale prospective study performed in Iran showed that people who drank the hottest tea had an eight-fold higher risk of ESCC.

3. Selenium deficiency has been linked to ESCC.

4. Demographics suggest that genetic factors...
must exist; however, specific genetic markers predictive of ESCC have not been definitely identified.

5. The precursor lesion of ESCC is esophageal squamous dysplasia (ESD). Unlike Barrett’s esophagus, this flat mucosal change is often undetectable during routine endoscopy, but is easy to see using Lugol’s iodine chromoendoscopy. Asymptomatic persons harboring ESD have an up to 30-fold increased risk of ESCC compared to their unaffected neighbors.

Taken together, these hard-won insights suggest a multifactorial pathogenesis of ESCC, with variations in different regions of the globe. Our knowledge is incomplete but is already changing the esophageal cancer equation in some endemic areas. In Brazil, commercial manufacturers now market PAH-free mate. Elsewhere, there is active investigation into the environmental and dietary sources of ingested carcinogen exposure. The Chinese have led the way in establishing ESCC screening programs, which aim to detect and treat asymptomatic ESD endoscopically, and similar programs are now being piloted in Iran and Kenya. Esophageal cancer prevention has become a reality for some at-risk groups. Lessons learned overseas may lead to effective endoscopic screening programs in American high-risk patients, such as those with prior head and neck squamous cell cancers.

There is much more to be done: identification of additional risk factors, public education about dietary exposures and thermal injury, and development of cost-effective alternatives to endoscopic screening in high-risk, resource-constrained areas. But the tide is beginning to turn. Now is the time to redouble our efforts; we can tame this dreaded killer.

Figure 1. Squamous dysplasia of the esophagus, visible as an unstained lesion with Lugol’s chromoendoscopy.

Figure 2. A Kenyan man enrolls in an esophageal cancer screening study.
CHOOSING WISELY

Rajeev Jain, MD, FACP, AGAF, FASGE
Partner, Texas Digestive Disease Consultants

Dr. Jain is chair of the AGA Institute Practice Management and Economics Committee.
AGA contributed to the Choosing Wisely campaign with the following five recommendations:

1. For pharmacological treatment of patients with gastroesophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine-2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals.

2. Do not repeat colorectal cancer screening (by any method) for 10 years after a high-quality colonoscopy is negative in average-risk individuals.

3. Do not repeat colonoscopy for at least five years for patients who have one or two small (< 1 cm) adenomatous polyps, without high-grade dysplasia, completely removed via a high-quality colonoscopy.

4. For a patient who is diagnosed with Barrett’s esophagus, and who has undergone a second endoscopy that confirms the absence of dysplasia on biopsy, a follow-up surveillance examination should not be performed in less than three years, as per published guidelines.

5. For a patient with functional abdominal pain syndrome (as per ROME III criteria), CT scans should not be repeated unless there is a major change in clinical findings or symptoms.

AGA’s five recommendations for the Choosing Wisely campaign are aimed at common disorders with the goal of minimizing unnecessary testing and/or treatment (low-value care). With health care in the U.S. consuming nearly one-fifth of our gross domestic product, patients, insurers and the government are demanding better outcomes at same or lower costs (high-value care).

We all try to practice high-value gastroenterology. During a busy clinic or endoscopy schedule, it can be difficult to follow every guideline or recommendation, especially for less common disorders. In order to implement these and other guideline recommendations, clinical decision support tools need to be available that seamlessly integrate into our electronic health record (EHR) and workflow. AGA is creating evidence-based guidelines with companion clinical decision support tools as part of the AGA Roadmap to the Future of GI Practice strategic plan.

I try to incorporate all five of these recommendations into my daily practice. For me, the most commonly used recommendations are those for colonoscopy intervals. Our practice is incorporating these colonoscopy interval recommendations into our EHR by creating guideline-based, templated messages to push to our patients via the patient portal and to create a colonoscopy recall within our EHR. The pre-populated messages in the EHR will be organized by the pathology results so that the appropriate guideline-based interval for the next colonoscopy is generated. Unfortunately, our EHR will require the physician to perform a three-step process of selecting the portal message, letter to the referring physician and recall reminder. Ideally, a more robust EHR system would allow one “click” to generate all three messages.

With regards to GERD and acid suppression therapy, I try to have a common-sense discussion with my patients on why they take these medications, and specifically the duration, severity and prior complications of GERD. Often patients will have been empirically placed on acid suppression for mild GERD or dyspepsia. I take the opportunity to discuss the benefits and risks of therapy while raising the possibility of titrating off acid suppression. I find most patients are appreciative of the attempt to minimize or even stop a medication. For the patient initially diagnosed with Barrett’s esophagus, I will have the patient follow up with our physician assistant within one to two weeks after the new diagnosis to discuss the diagnosis, prognosis and treatment plan. Using the AGA guideline on Barrett’s esophagus, the EHR will be populated with an assessment and plan that is evidence-based and follows the Choosing Wisely campaign’s recommendation.

IBS can be a challenging disorder to manage. At the time of this AGA Perspectives article submission, AGA has submitted IBS guidelines for public comment. The fifth recommendation from the Choosing Wisely campaign reminds us to minimize harm of radiation in young patients with functional bowel syndromes by avoiding unnecessary CT scans. It is always easier to order a test than explain the rationale for not performing some diagnostic intervention including laboratory studies, radiology and endoscopy. However, in my opinion, both physicians and patients need to find a more reasonable level of uncertainty to accept in the diagnostic evaluation of symptoms of presumed IBS that lack alarm features.

AGA’s contribution to the Choosing Wisely campaign has highlighted recommendations for gastroenterologists to deliver high-value care to our patients. By following these recommendations, gastroenterologists can reduce potential harms (i.e., radiation exposure), reduce costs (i.e., minimizing overutilization of medication and procedures) and standardize the management of common disorders.
CALIFORNIA

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Please send CV to maryl@mtviewsurgery.com or any questions to Mary Lamoureaux (909) 796-7803, ext. 4.

CALIFORNIA

UCSF Fresno and the Central California Faculty Medical Group (CCFMG) are seeking a full time faculty member for the Gastroenterology Division. Applicants should be board certified or board eligible in gastroenterology. Responsibilities will include patient care, teaching residents and fellows, endoscopic procedures, and clinical research. Interest and expertise in esophageal disease is desirable. Faculty appointment with UCSF will be commensurate with the applicant’s background and accomplishments.

The UCSF Fresno Gastroenterology Division is a growing division currently utilizing a newly expanded endoscopy suite. In addition they have an ACGME accredited GI Fellowship. The program is based in Fresno, California, where residents enjoy a high standard of living combined with a low cost of living. The result is a quality of life uniquely Californian, yet surprisingly affordable. Limitless recreational opportunities and spectacular scenery is all accessible in a community with abundant affordable housing.

While there is much to see and do in Fresno, the city is ideally located for fast, convenient getaways to the majestic Sierra (just 90 minutes away) as well as the scenic Central Coast, just two and one-half hours away. Fresno is the only major city in the country with close proximity to three national parks, including renowned Yosemite National Park.

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NEW YORK

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