ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

New Screening Methods for Barrett Esophagus

Michael S. Smith, MD, MBA
Chief of Gastroenterology and Hepatology
Director, Esophageal Program
Mount Sinai West & Mount Sinai Morningside Hospitals
Associate Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, New York

G&H How are patients typically screened for Barrett esophagus?

MS The most common way gastroenterologists screen for Barrett esophagus (BE) is with upper endoscopy (ie, esophagogastroduodenoscopy [EGD]). During visualization of the mucosa in the distal esophagus, the location of the squamocolumnar junction (or Z line) is identified. This border between cell types should be located along the top of the gastric folds in patients with normal findings. When the location of this boundary moves up into the tubular esophagus, there is salmon-colored mucosa found in the region between the top of the gastric folds and the Z line. The configuration can include circumferential salmon-colored mucosa, tongues, and/or islands. When such a finding is appreciated by the endoscopist, tissue sampling is performed to look at the cells under a microscope and confirm the presence of specialized intestinal metaplasia, which contains goblet cells. Most often, the cells are obtained through forceps biopsy, although other options, including wide-area transepithelial sampling brush biopsy (CDx Diagnostics), also can be used. The histologic finding of goblet cell metaplasia is required to make the diagnosis of BE in the United States.

While most patients undergo traditional EGD under sedation, some sites have utilized unsedated transnasal endoscopy (uTNE) as a more efficient means of screening the distal esophagus for the presence of BE. Avoidance of sedation speeds up the process of completing the procedure, and patients have reported reasonable tolerance of the endoscope despite being awake the entire time. This approach lowers costs and expands outreach, as uTNE is a relatively portable technique that does not require an endoscopy center to be performed.

Who gets selected for endoscopy to screen for BE also is an important issue. With limited endoscopic resources, only patients who have significant symptoms consistent with gastroesophageal reflux disease (GERD) over an extended period of time (as BE is thought to take years to develop) generally are scheduled for endoscopy. However, epidemiologic studies have shown that a significant percentage of patients who develop BE have absolutely no reflux-associated symptoms noted on a pre-endoscopy questionnaire. Still others do not have the typical GERD symptoms of heartburn or regurgitation, but instead have symptoms such as a chronic cough, lump in the throat, voice change, or chest pain that are easily attributed to a nongastrointestinal cause. It may take years before these patients find themselves in a gastroenterologist's office to discuss a possible diagnosis of GERD and the risk they have of developing BE. Several groups have been working on risk-stratification devices such as prediction models, in which a score is generated by assigning points to specific demographic, physiologic, and lifestyle factors. If a patient

reaches a certain score, the risk of having developed BE rises and endoscopy is recommended. While none of these scores have reached widespread, everyday practice, they are a good first step in bridging the gap between the patients who should be screened and the patients who actually are screened. It is estimated that up to or even more than 90% of patients who actually have BE do not know it—nor do their doctors.

G&H What new tools are available to screen for BE that do not involve endoscopy? How are they performed?

MS A number of devices have been developed to try to obtain samples without putting patients through endoscopy. Many of these devices involve the patient swallowing a small object approximately the size of a pill, or perhaps a little larger. Each device is attached to a string or small flexible tube that allows the cell collection mechanism to be advanced through the esophagus. The Cytosponge (Medtronic) consists of a sponge made of a slightly abrasive mesh that is connected to a string. The sponge is surrounded by a gelatin coating that dissolves when it reaches the stomach, within approximately 5 minutes. At that time, the sponge is pulled up through the esophagus using the string. Once the sponge leaves the mouth, the device is collected and sent to a laboratory, where immunohistochemical staining is performed to look for a Barrett biomarker called trefoil factor 3. This biomarker, when present, indicates the presence of BE, although it cannot tell whether dysplasia is present.

A similar device, known as Sponge on a String or EsophaCap (CapNostics), also contains a sponge compressed within a capsule covered by a disposable shell. This capsule dissolves within 8 minutes, after which the sponge is pulled through the esophagus to collect cells for analysis. If certain methylated DNA markers are present on polymerase chain reaction performed on the cellular material retrieved, then the patient is likely to have BE.

A third device also captures cells from the esophagus in a nonendoscopic manner, but its approach is somewhat different. The EsoCheck (Lucid Diagnostics) device consists of a small balloon that has textured ridges. When the device is inserted into the mouth and swallowed by the patient, the balloon is deflated and inverts on itself so as to keep the collection area away from the mucosa. Once the device has reached the desired depth of insertion, the balloon is inflated and pulled up through the lower esophagus. The ridges grab the cells along the esophageal wall and obtain sample tissue for analysis. Once the device has traversed the desired area, the balloon is deflated and inverts again to protect the specimen from contamination by other parts of the aerodigestive tract as it is removed from the body. The tissue then is sent for analysis to detect the presence of vimentin and cyclin-A1 methylation signatures at 31 sites within these 2 genes, which, if present, indicate the presence of BE.

Another swallowed device utilizes volumetric laser endomicroscopy (VLE), a form of optical coherence tomography in which images acquired by laser can assess the esophageal wall for changes consistent with BE. A commercially available form of VLE (NvisionVLE Imaging System, NinePoint Medical) utilizes a catheter containing both the laser and a balloon to center it within the esophageal lumen. In this version, the laser is contained within a tethered capsule and is turned on to provide real-time imaging once it has reached the esophagus.

Still other capsule-based devices take photographic images of the esophagus as part of BE screening. These capsules are very similar to what is used to evaluate the small bowel and, in some cases, the colon. Technical adjustments, such as an increased rate of image capture, allow for improved assessment. Of note, both free-moving and tethered versions of such capsules have been described.

Using a completely different approach, a device called the Aeonose (The eNose Company) involves a completely noninvasive manner of evaluating for BE, looking for exhaled volatile organic compounds as a marker of BE. This technology also is being studied to potentially identify other gastrointestinal malignancies such as colon and pancreatic cancer.

G&H What are the benefits and limitations of these nonendoscopic approaches?

MS The greatest benefit of these devices is that they allow providers to reach many more patients who are appropriate candidates to screen for BE than are currently reached. If endoscopists are able to accurately assess patients for having this precancerous condition without having to incur the significant resources and costs while performing an EGD, it would be a major win from a public health perspective. These tests are relatively simple and could be performed in a primary care office, a gastroenterologist's office, or even a commercial laboratory setting. Instead of having to take up valuable endoscopy slots for these BE screening cases, endoscopists could focus on following patients with disease already identified through these methods of testing. Only approximately 10% of patients with GERD have BE, so it makes sense to save endoscopy time for the group that actually has the precancerous condition. There are clearly cost and resource allocation implications to finding many more patients who need to enter a surveillance protocol, but that is an issue worth facing once providers improve their ability to find BE

in less symptomatic patients and/or in patients who do not seek care from a gastroenterologist and may not have ready access to endoscopy.

From the perspective of the devices themselves, the greatest limitation is patient tolerability. For the swallowed devices, patients have to be willing to have a small object pulled up through their throat and out of their mouth. While many patients may see this as preferable to swallowing an endoscope (even if they are asleep for it), others may balk at the idea given the potential for discomfort. Clinical studies will need to show that patients are willing to undergo the procedure and can tolerate it well before providers are ready to prescribe it. Additionally, biomarkers for BE have been looked at for a long time, so whichever assay is used in the analysis must be shown to have sufficient sensitivity and specificity that gastroenterologists would feel comfortable replacing their standard screening method with a new one, while not placing patients at risk.

G&H Compared to endoscopy, how accurate are these methods at detecting BE?

MS Thus far, the data are encouraging but results are somewhat mixed. Five years ago, data from a UK-based Cytosponge study involving over 1000 patients demonstrated reasonable tolerability of approximately 94%, with an overall sensitivity of nearly 80% and a specificity of 92%. The sensitivity improved with long-segment BE, and if 2 sponge tests were performed, it reached nearly 90%. Unfortunately, a US-based trial did not show results that were as robust. EsophaCap was found to have a sensitivity of 94% and a specificity of 62% in an 80-patient prospective validation study using patients with long-segment BE. A trial of over 400 patients utilizing the EsoCheck cell capture device and the EsoGuard (Lucid Diagnostics) molecular assay for methylation markers demonstrated a sensitivity of 90.3% and a specificity of 91.7% for finding any form of BE or esophageal adenocarcinoma. Video capsule endoscopy for screening detected only 75% of BE segments found on endoscopy. Data for the VLE-tethered capsule and Aeonose are very limited given the relatively early stage of development of these devices.

G&H How do these new screening methods fit into clinical practice?

MS At this time, the only combination of cell collection device and molecular assay that is commercially available in the United States is EsoCheck and EsoGuard. Due to the limited familiarity of primary care providers (PCPs) with BE, I expect that gastroenterologists will be the early adapters of any nonendoscopic screening technology. The most likely scenario I envision is that community-based gastroenterologists will start to utilize these screening techniques in order to free up more endoscopy time for other procedures, choosing to endoscope only those patients with an abnormal result. If gastroenterologists can better educate PCPs and perhaps provide them with better risk-stratification tools, those algorithms could be integrated into an electronic medical record that can recommend screening through best-practice advisories. Under that scenario, it is reasonable to expect more screenings to be generated from PCP offices in the future. While PCPs have limited time to discuss preventive care with patients, ordering a screening test along with checking cholesterol could become the norm for patient care.

G&H What are the economic implications of these approaches?

MS There is always a cost involved when introducing new tests into everyday care, especially a test that may be relevant and appropriate for up to one-third of the US population. Cost-effectiveness studies definitely will be necessary once we understand how and where the testing will be integrated into patient management. The additional costs of testing will have to be added to the costs of ongoing surveillance for patients found to have BE, as well as the cost of endoscopy for patients with any false-positive results. However, the benefit of avoiding costs of managing esophageal adenocarcinoma is significant, including the potential use of chemotherapy, radiation, and surgery, as well as hospitalizations. I am optimistic that we will find a way to make such testing sufficiently valuable that it can expand our ability to diagnose BE and prevent cancer.

G&H Do you see DNA biomarkers playing a role in the future of early detection?

MS Biomarkers are central to the detection of BE in several of the screening tools that have been previously discussed. Biomarkers that can distinguish between nondysplastic BE, dysplastic BE, and adenocarcinoma also will be very helpful as part of risk stratification. However, the value of biomarker use for early detection extends beyond the screening population. In particular, several studies have been published looking at the value of using biomarkers to evaluate BE deemed nondysplastic on histologic assessment. Depending on expression patterns of these markers, an algorithm can generate a risk of disease progression. Early eradication of BE in these patients may save both dollars and lives by decreasing the costs associated with surveillance of nontreated disease as well as with the risk of progression to cancer during

that period. A nondysplastic BE segment with a low risk of progression also may be able to enter a surveillance protocol with extended intervals, allowing for fewer endoscopies to be performed without generating excess risk to the patient.

G&H What are the priorities of research in this area?

MS As screening options improve, we must focus on optimizing our ability to identify who is at risk of developing BE. These nonendoscopic tests will work best within the health care system if we can better target patients who truly need them, rather than the entire GERD cohort. Optimizing risk-stratification techniques will be critical as a parallel to the enhanced screening tools, which of course must be validated as tolerable, safe, and efficacious. Anything we can do to improve the screening rate for at-risk patients while not overwhelming the system will be a win for our patients and for us.

Disclosures

Dr Smith is a consultant for Lucid Diagnostics, Medtronic GI Health, and Merit Medical/NinePoint Medical, and serves as a member of the medical advisory board for Lucid Diagnostics.

Suggested Reading

Critchley-Thorne RJ, Duits LC, Prichard JW, et al. A tissue systems pathology assay for high-risk Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 2016;25(6):958-968.

Honing J, Kievit W, Bookelaar J, Peters Y, Iyer PG, Siersema PD. Endosheath ultrathin transnasal endoscopy is a cost-effective method for screening for Barrett's esophagus in patients with GERD symptoms. *Gastrointest Endosc*. 2019;89(4):712-722.e3.

Moinova HR, LaFramboise T, Lutterbaugh JD, et al. Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. *Sci Transl Med*. 2018;10(424):eaao5848.

Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al; BEST2 Study Group. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. *PLoS Med*. 2015;12(1):e1001780.

Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. *Am J Gastroenterol*. 2013;108(3):353-362.