

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Advances in Screening for Barrett Esophagus



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G&H Which individuals are most at risk for Barrett esophagus and progression to adenocarcinoma?

DP Barrett esophagus (BE), also known as intestinal metaplasia, is a fairly prevalent condition. Studies commonly quote a prevalence of approximately 5% to 6% of the general population, although some studies report rates as high as 20%.

BE may present with or without premalignant changes (dysplastic or nondysplastic, respectively). Detection of this condition is critical because of the higher risk of progression from dysplastic BE to esophageal adenocarcinoma (EAC), particularly in high-grade dysplasia (HGD).

In the assessment of risk, demographics, symptoms, and environmental factors, including lifestyle habits, need to be taken into account. The individuals at greatest risk are male, white, and 55 years of age and older. Obesity (body mass index >30) also is a risk factor, specifically in patients with a high waist-to-hip ratio and central adiposity. Patients who have acid reflux or heartburn symptoms, especially those who have gastroesophageal reflux disease (GERD) and those whose GERD has advanced to erosive esophagitis, are at particularly high risk for the development of BE, with a roughly 5-fold increase in risk. Peptic strictures confer risk as well. Tobacco use or exposure, which is an independent risk factor due to a synergistic effect in patients with GERD, adds an

approximately 1.6-fold increase in BE risk. Family history plays a role as well, although it is unclear whether genetics or environmental and lifestyle factors have the greater impact in this regard.

The risk of EAC is at least 30-fold higher in patients with BE than in the general population. The greatest risk factor for progression is the length or degree of the affected mucosa. The longer the segment of Barrett mucosa, the greater the risk. A segment greater than 3 cm in length is a threshold for increased risk, as is the degree of maximal extent and circumferential involvement per the Prague classification. Whereas patients with nondysplastic disease are at relatively low risk for progression to malignancy (0.54% per year), dysplasia—particularly HGD—poses a far greater threat for progression to EAC, with rates of up to 4% to 8% annually.

G&H What are the potentially avoidable consequences or complications of missed early detection?

DP Carcinogenesis, of course, is the main feared consequence of missed early detection. The longer BE remains undetected, the higher the likelihood of progression to dysplasia and, ultimately, EAC. Diagnosis at a later stage along the spectrum from nondysplastic to dysplastic BE and HGD (particularly EAC) increases the potential need for invasive therapies, including endoscopic ablation,

resection, or surgery in more advanced disease. Intervention in advanced disease is associated with higher rates of morbidity and complications than intervention in earlier disease.

Complications related to endoscopic ablation and resection may include bleeding, perforation, and the development of often refractory strictures. In cases where

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EAC is diagnosed, surgical resection is typically used along with radiation therapy and/or chemotherapy, exposing patients to associated complications, including strictures and accelerated atherosclerosis.

G&H How can clinicians best identify patients who would benefit from screening?

DP Patients with an established diagnosis of reflux disease or history of known esophagitis need to be screened and carefully followed because active inflammation as well as the healing of that inflammation may predispose them to intestinal metaplasia and subsequent complications.

In patients without an established esophagitis diagnosis, demographics and symptoms need to be carefully assessed. In terms of demographics, the clinician looks at the characteristics previously mentioned. Screening selection based on symptoms, however, can be challenging. Manifestations of reflux are sometimes classic and sometimes atypical. Classic symptoms are those of GERD, such as heartburn. Atypical reflux symptoms may take the form of a chronic or postprandial cough or a cough that occurs when lying down after eating. It is also not uncommon for a patient with chronic cough to be referred to a gastroenterologist by a primary care physician or otolaryngologist who detected, on laryngoscopy, changes suggestive of reflux in the folds surrounding the vocal cords. There are also large numbers of patients who have been to

one physician after another because of chronic cough and finally present to a gastroenterologist when acid reflux is suspected as a potential symptomatic trigger.

G&H What have recent studies found regarding screening and outcomes for BE and EAC?

DP Unlike some cancers, the incidence of EAC has been increasing over the past 4 decades. EAC will be diagnosed in roughly 0.5% of individuals in the United States during their lifetime, and the condition currently has a prevalence of approximately 47,000 individuals. The 5-year survival rate remains low, at approximately 20%. The annual cancer incidence associated with BE ranges from 0.1% to nearly 3.0%. As mentioned, this is 30 times higher than in the general population. One contributing factor is inadequate screening and early detection.

Therefore, early detection of BE—while dysplasia is still absent or incipient—is critical. As mentioned, approximately 0.25% and 0.5% of patients with BE and low-grade dysplasia, respectively, progress to cancer each year, whereas 4% to 8% of patients with HGD progress to malignancy annually.

G&H What nonendoscopic screening options are available, and how do they compare with the standard screening approach?

DP The standard evaluation has been, and currently remains, esophagogastroduodenoscopy. It is now performed with high-resolution white-light endoscopy using high-resolution endoscopes. With improvements in endoscopes and high-resolution white-light endoscopy, the ability to detect endoscopic features suggestive of BE has improved dramatically. Chromoendoscopy, which has been useful for examining changes in the squamocolumnar junction, is also helpful for evaluation. Traditional and currently used techniques include the use of various dyes that are sprayed via the endoscope to highlight differences in the mucosa suggestive of BE. Most available endoscopes now include electronic chromoendoscopy, including narrow-band imaging.

Nonendoscopic screening methods are also emerging. These are minimally invasive and, thus, potentially more cost-effective than endoscopy. Patients undergoing nonendoscopic screening typically do not require sedation, thereby avoiding potential associated adverse issues, improving efficiency, and decreasing cost.

One available nonendoscopic screening modality is the Cytosponge cell collection device (Medtronic). This device is a cell collection sponge housed within a gelatin capsule that is attached to a string. When the patient swallows the capsule, the capsule dissolves in the stomach. The

sponge is released, expands, and captures cells within the esophagus for assessment of the biomarker trefoil factor 3 (TFF3) as the sponge is manually withdrawn from the esophagus via the mouth.

Clinical research on Cytosponge has shown that the device improves detection of BE. A recently published trial by Fitzgerald and colleagues randomly allocated 13,514 patients with GERD to usual care that included endoscopy if indicated by the treating physician or to the Cytosponge-TFF3 procedure with subsequent endoscopy if Cytosponge testing was positive for TFF3. At 12-month follow-up, the rate of BE diagnosis was significantly ($P < .0001$) higher in the intervention group than in the usual care group. Sensitivity and specificity were 73% and 94%, respectively, in patients whose Barrett lesion was at least 1 cm in length, with these performance characteristics improving to 90% and 94%, respectively, for BE segments greater than 2 cm.

The advantages of this device are that it is easy to administer, rapid, safe, and well-tolerated. No sedation is needed, and the device can be used in the office setting. A disadvantage, as with many tests, is the potential for false-positive results. This potential is largely due to the device involving nondirected sampling, and not being guided by endoscopic visualization. Another disadvantage is that this screening tool cannot provide information about the stomach or upper small intestine, unlike endoscopy. It is also important to note that Cytosponge requires a pathologist who is specifically trained to analyze the specimens.

Another novel screening modality that is less invasive than endoscopy is EsoCheck (Lucid Diagnostics). It is a soft, pliable, inflatable balloon catheter system. Like Cytosponge, it is passed through the mouth into the esophagus in an office setting, with a similar goal of sampling distal esophageal mucosa. The pliable balloon has ridges and grooves that capture cells for sampling when inflated at the gastroesophageal junction. The inflated balloon is then slightly deflated to allow passage across the gastroesophageal junction, withdrawn 5 cm proximally, fully deflated, and pulled into a protective soft cap to retain the tissue sample. Finally, it is withdrawn from the patient.

The balloon is then reinflated to remove it from its protective cap, and the sample is placed into a cell-preserving solution. A DNA test called EsoGuard (Lucid Diagnostics) is performed in the laboratory. Positivity for methylation is assessed at 31 sites on 2 genes—*vimentin* and *CCNA*—that have been associated with BE (both nondysplastic and dysplastic) and EAC. A laboratory capable of assessing methylation changes in *vimentin* and *CCNA* DNA is required. A study by Moinova and colleagues showed excellent accuracy for EsoGuard, with 95% sensitivity and 91% specificity.

The EsoCheck and EsoGuard system is currently undergoing large multicenter trials, including at NYU Langone Health in New York City. Early studies at NYU Langone Health demonstrated that the vast majority of patients tolerate EsoCheck in the outpatient setting. The learning curve for physicians to perform EsoCheck is shallow, and the procedure takes roughly 3 minutes to complete. Early study results have been promising.

G&H How can a clinician choose the most appropriate screening method for a particular patient?

DP Many factors go into the decision-making process. The most basic strategy is to look at the degree of invasiveness and have a frank discussion with the patient about the relative risks and benefits of screening methods. The approach to the patient should be tailored to his or her knowledge base, the degree to which he or she wishes to help guide and share in the decision-making process, and other factors. Some patients may not be interested in having such a discussion, whereas others may want to know results of clinical trials, real-world clinical experience, and more detailed information about performance characteristics (eg, sensitivity, specificity, positive predictive value, negative predictive value). Other important factors that influence decision-making are the available resources, whether special expertise is needed, and cost-effectiveness concerns.

G&H What impact will less-invasive options have on screening for BE?

DP Less-invasive options will broaden screening opportunities. These options will increase access to screening because they are simple and frequently office-based. They can be performed by a gastroenterologist, an internist, or an advanced practice provider such as a nurse practitioner or a physician assistant. These options can also be performed in a separate clinic or at the point of care by a general physician or a specialist.

As previously mentioned, these options are well-tolerated, with a very good safety profile. No sedation is needed, and cost is reduced because a procedural suite or operating room and endoscopy are not needed. These options are cutting edge in terms of interpretation of the data that they can generate but are excitingly low-tech in their design. This is beneficial, as simpler tools present fewer opportunities for device failure, as seen with more complicated technologies. The devices are stable at room temperature and easy to transport, which helps to get them to where people need them and where resources otherwise may be more limited. These options also allow

for risk stratification and identification of the patients who are in the greatest need of endoscopy and those who need expedited evaluation. The options also help avoid performing invasive and expensive procedures in patients who are statistically likely to test negative for BE.

G&H Where should future research be directed?

DP More real-world research is needed on utilization, workflow, and patient acceptance. Not surprisingly, early studies suggest that patients prefer a less-invasive option.

Adoption by physicians and other clinicians is also an important topic of investigation. There is the question of whether clinicians are comfortable with nonvisual, nonendoscopic techniques. Many physicians can be hesitant to change their approaches and have concerns about implementing new technologies. There may be concerns about whether the new options will reduce procedural volume, for example. To counter concerns, the goals of early detection, risk stratification, and prioritization must be stressed. Finally, head-to-head studies of screening options are needed to determine who really needs or does not need endoscopy.

The future is bright, with well-tolerated, safe, efficient, effective, and inexpensive noninvasive modalities.

These options can provide reassurance to low-risk patients and direct those who may be more likely to have BE, dysplasia, or EAC to the endoscopy unit in an expeditious manner for diagnosis, earlier therapy, and potentially superior outcomes. The goals remain the same: to reassure patients without disease and to begin treatment on the patients who need it the most.

Disclosures

Dr Poppers is a consultant for Salix/Bausch Health, Olympus Medical, Lucid Diagnostics, Exact Sciences, Steris, Ambu, and RedHill Biopharma, and he is a member of the advisory board of Tenasors Medical.

Suggested Reading

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