ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Nonendoscopic Testing for Esophageal Precancer in an At-Risk Population

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G&H What are the challenges of the current national society screening strategy for Barrett esophagus?

DL One major problem is that there are 3 sets of US guidelines, from the American Gastroenterological Association (AGA), the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy, with different recommendations on who should be screened for Barrett esophagus (BE). Gastroenterologists have had guidelines on BE screening for years, yet this guidance has not led to a decrease in the incidence rates of esophageal adenocarcinoma (EAC), according to the Surveillance, Epidemiology, and End Results database. From my perspective, the management of BE needs to fundamentally change, or our efforts will not alter the trajectory of EAC.

Another challenge has been that screening for BE is primarily based on the presence of gastroesophageal reflux disease (GERD) symptoms. One of the problems with longstanding GERD is that patients may stop having symptoms. Once BE develops, many patients will no longer have heartburn, and patients who do not feel the reflux may think they are better. My major fear, with proton pump inhibitors (PPIs) being available over the counter, is that patients who are self-medicating may not realize that they can have disease in the absence of reflux symptoms. Over time, these patients may be worse off than they were when they first started PPI therapy because now they may have developed BE. If patients do not relay their reflux history to their family physician, then the physician will not know to send them for screening. These current trends in GERD management could lead to a surge in the incidence of EAC 10 to 15 years from now.

G&H Why should nonendoscopic cell collection devices be considered as an option to screen for BE?

DL One reason for considering a nonendoscopic screening method is the high cost of upper endoscopy. Compared with screening colonoscopy, which insurance companies (including Medicare) often cover 100% of the cost of, with no out-of-pocket expense for the patient, screening esophagogastroduodenoscopy (EGD) is frequently not covered by insurance, and patients referred for BE screening often have to pay out of their deductible for this test. There has to be a better way to screen these patients. If there could be a test that is inexpensive, that patients undergoing the test and the persons driving them to the test do not have to take a day off of work for, physicians would be more likely to be able to screen a larger number of patients and detect BE early on. Early detection is necessary for this disease because we know that the precursor to EAC is BE, and the vast majority of patients who are diagnosed with esophageal cancer never knew they had BE.

G&H What nonendoscopic testing methods for BE are currently available in the United States?

DL The only swallowable cell collection device and test for BE screening currently available on the US market are EsoCheck and EsoGuard (Lucid Diagnostics). A similar device, the Cytosponge (Medtronic), has been approved by the US Food and Drug Administration but is currently on a recall. Interestingly, the company that developed the EsoGuard test had evaluated a sponge-based method and found the EsoCheck device to be a better-tolerated,

more user-friendly, and quicker method. With EsoGuard, a well-trained health care practitioner can inflate the balloon in the stomach; it takes my nurse practitioner a minute and a half to obtain a cell sample. With the sponge method, the clinician has to wait for the capsule to dissolve in the stomach, and then pull the sponge all the way up the esophagus and into the oropharynx; this can cause patients to gag, which they do not like. I have been very happy with the EsoGuard test and have found it to be well received by my patients.

G&H How can EsoGuard be implemented by gastroenterologists and other clinicians in clinical practice?

DL As a rural surgeon, I am the area gastroenterologist as well, so I perform the screening colonoscopies. For every patient who comes to our center for a pre-colonoscopy office visit, we look at their medication list and their history, and we ask if they have ever in their lifetime had reflux or had to take an antacid for reflux issues. If the answer is yes, then we will educate them on how BE is the precursor to esophageal cancer, just like a colon polyp is a precursor to colon cancer. Patients with a history of reflux are offered an EsoGuard test at their pre-colonoscopy visit, and if positive, an EGD will be performed in the same setting as their screening colonoscopy. Patients benefit in that they receive both procedures and miss only 1 day of work, and they receive a single anesthetic, lessening their risk of complications. For the endoscopist, the EGD takes an extra 5 minutes to perform.

Other practices may have to implement EsoGuard differently. For the gastroenterologist who does not meet with patients prior to the day of their colonoscopy, for example, there needs to be another way to catch these patients and perform the EsoGuard test ahead of their scheduled procedure. That is why the ideal place for this test to be performed may be either in the family practice/internal medicine doctor's office or at an EsoGuard testing center, where patients can schedule the test for a time that is convenient for them. If such a screening strategy was in place and there was more direct-to-patient marketing of the EsoGuard test, then it is very likely that utilization of this test would increase and the incidence of EAC could decrease.

G&H Which groups of patients should be considered for nonendoscopic testing?

DL Other than people who have risk factors for BE and EAC, there are interesting data showing that firefighters have a higher risk of all cancers in general than the average population. The data showed an excess of digestive cancers in esophageal and colorectal sites in this group. The reason for the increased risk may not necessarily be because firefighters breathe in carcinogens but that they work in environments that produce reflux. Whether it is because firefighters tend to eat at odd times and carry heavy packs which increase intrabdominal pressure that cause reflux is not known. However, firefighters do have both exposure to carcinogens resulting in inhalant injury and the tendency to have more reflux. One would suspect that people who work around aerosolized chemicals like paints or in brake shops may also be at higher risk; however, I am not aware of any studies in those populations.

According to the AGA guidelines, risk factors for BE and EAC include a history of chronic GERD, male sex, non-Hispanic White race, age over 50 years, obesity, tobacco use, and family history of BE or EAC. A high percentage of our center's patient population in Arkansas has at least 2 or 3 of these risk factors, so I think everyone, male and female, should be screened. Since we began screening with EsoGuard, BE has been found in a high number of females as well as males. This finding is very concerning because currently the guidelines are focused on the male predominance of this disease, and that may not be accurate.

G&H What is the next step for patients with a positive nonendoscopic test result?

DL Patients with a positive result after an EsoGuard test should have a high-quality upper endoscopy performed by someone who treats BE with endoscopic eradication or who has an interest in BE. It is unfortunate that a significant number of patients are diagnosed with EAC within a year of their initial endoscopy that was negative. Did cancer develop that quickly or was it missed initially because the endoscopist did not take the time to perform a high-quality examination with both white light and chromoendoscopy, like narrow-band imaging, or obtain adequate biopsies? Did the endoscopist spend a minute per centimeter of columnar-lined esophagus inspecting for BE? It is important for the endoscopist to take the time to biopsy patients with a positive EsoGuard result.

In reviewing my data from the recent CLUE clinical utility study, I found that when the EsoGuard test was positive, I usually found goblet cells. Not all patients had a 1-cm segment to meet the current US definition of BE. They might have had a 2- or 3-mm segment of columnar-lined epithelium or an irregular Z-line, which when biopsied revealed goblet cells, which should not be there. Spechler and El-Serag recently published an article that questions the reliance on the 1-cm segment and highlights the need to start paying attention to the shorter segments because of the potential for a biopsy to remove cancer cells in those segments.

G&H What approach is taken for patients with confirmed disease?

DL For all confirmed cases of BE, risk stratification should be performed. Our center uses TissueCypher (Castle Biosciences), which allows the physician to personalize care for each patient based on what their risk of progression is in the next 5 years. One of the problems with endoscopy is that it provides a still image of the patient's status; however, BE is not a static condition but a dynamic one that has movement. An example for patients is to have them imagine a field where on the left side is the normal esophagus, reflux esophagitis, nondysplastic BE, and then a fence. On the right side of that fence is low-grade dysplasia, high-grade dysplasia, and then a cliff called esophageal cancer. As long as the patient stays on the left side of the fence, they are safe. The physician will not know how fast a patient is moving toward that cliff (or from nondysplastic BE to low-grade dysplasia or high-grade dysplasia) until the patient has the second endoscopy. This is where TissueCypher can play an important role by providing an idea of whether the patient is running for the cliff (a high-risk score), or the patient is just hanging out in the field and not making any progress toward the fence or the cliff (a low-risk score). For disease surveillance in the future, it would be ideal if a nonendoscopic screening test such as EsoGuard could be used with a test like TissueCypher to risk stratify the cells. If the result is low-risk, an endoscopy is not needed, and rescreening with another EsoGuard or an endoscopy can be considered in 3 years. However, if the result is high-risk, then an endoscopy or endoscopic eradication is recommended. During a colonoscopy, every polyp is removed as part of colon cancer screening, which is partly why the risk of colon cancer in older adults has been decreasing. BE has the exact same malignant potential as a tubular adenoma of the colon. Although endoscopic eradication of BE from all patients would make a big dent in EAC risk, this strategy is cost prohibitive. However, knowing which patients were on the express line toward the cliff of EAC and eradicating BE in those patients could start making a difference.

G&H How can EsoGuard impact esophageal cancer?

DL The EsoCheck and EsoGuard system will allow gastroenterologists to screen more patients effectively. The only requirement for patients is to refrain from eating for 2 hours before the test. An EsoGuard testing center can be temporarily set up in a doctor's office or even at a mall or local business. The device manufacturer can provide gastroenterology practices with a nurse practitioner who can administer the test to a group of patients who require testing, relieving the physicians and staff of this responsibility. Having an impact on EAC has to start somewhere, and the development of more convenient ways to screen for BE is a good place to start.

G&H Could EsoGuard potentially be used as a diagnostic/biopsy method in the future?

DL EsoGuard will not replace conventional endoscopy similar to how Cologuard (Exact Sciences) is not meant to replace colonoscopy because a positive result indicates the presence of a polyp and the need for a colonoscopy. EsoGuard works the same way in that a positive result identifies the patients with BE who need an endoscopy. A negative result is helpful in that it can prevent gastroenterologists from performing unnecessary endoscopies.

G&H What might surprise gastroenterologists about EsoGuard?

DL Patients have been very receptive and accepting of the EsoGuard test, more than we anticipated, and that was surprising. Patients coming to our center for surgery or for other conditions have asked for the test after reading the Check Your Food Tube posters with EsoGuard's mascot Freddy the Food Tube who explains esophageal disease. Gastroenterologists will find that implementing the EsoCheck and EsoGuard system is not as difficult as they may think. The cell collection procedure can be performed without interrupting their day because basically any midlevel clinician can administer the EsoCheck device. The results can then help cherry-pick the best patients to surveil for BE with EGD. In my experience, a positive EsoGuard result indicates that there is something there, and the physician needs to pay attention.

Disclosures

Dr Lister is a consultant for Lucid Diagnostics, Castle Biosciences, Laborie, EndoGastric Solutions/Merit, and Implantica.

Suggested Reading

Muthusamy VR, Wani S, Gyawali CP, et al; CGIT Barrett's Esophagus Consensus Conference Participants. AGA Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: expert review. *Clin Gastroenterol Hepatol.* 2022;20(12):2696-2706.e1.

Pinkerton L, Bertke SJ, Yiin J, et al. Mortality in a cohort of US firefighters from San Francisco, Chicago and Philadelphia: an update. *Occup Environ Med.* 2020;77(2):84-93.

Qumseya B, Sultan S, Bain P, et al; ASGE Standards of Practice Committee; ASGE Standards of Practice Committee Chair. ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc.* 2019;90(3):335-359.e2.

Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and management of Barrett's esophagus: an updated ACG guideline. *Am J Gastroenterol.* 2022;117(4):559-587.

Spechler SJ, El-Serag HB. Why has screening and surveillance for Barrett's esophagus fallen short in stemming the rising incidence of esophageal adenocarcinoma? *Am J Gastroenterol.* 2023;118(4):590-592.