ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Clinical Prediction and Screening for Barrett Esophagus

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G&H What is the prevalence of Barrett esophagus in the general population?

JR It is difficult to know with certainty how common Barrett esophagus is in the general US population because this condition can only be diagnosed if a patient undergoes upper endoscopy, and the majority of patients with Barrett esophagus do not have any substantial symptoms that would prompt such a procedure. In 2 population-based studies in Sweden and Italy in which persons were invited to undergo upper endoscopy regardless of clinical indication, Barrett esophagus was confirmed by biopsy in 1% to 2%. However, the prevalence of Barrett esophagus varies quite a bit depending on patient demographics, including age and sex. In a study of men undergoing colonoscopy for colorectal cancer screening who were invited to also undergo upper endoscopy, my colleagues and I found Barrett esophagus in 8.5%. Other researchers have reported similar findings in older men undergoing colonoscopy. Barrett esophagus is more common in persons with symptoms of gastroesophageal reflux disease (GERD), with studies reporting prevalences between 5% and 15%.

G&H What are the most common risk factors for Barrett esophagus?

JR GERD symptoms, which are reported by roughly 20% of Americans, are an important risk factor for Barrett esophagus. Other important and common risk factors include male sex, older age, white race, abdominal obesity, and tobacco consumption. In contrast, *Helicobacter pylori* infection is associated with a decreased risk of Barrett esophagus. The paradox, however, is that the vast majority of patients with any of these risk factors do not have Barrett esophagus and will never develop esophageal cancer.

G&H How often does Barrett esophagus progress to cancer, and what are the risk factors for this progression?

JR Over the past decade, we have learned that the risk of progression to cancer is considerably lower than originally believed. The most recent highest-quality evidence suggests that the risk of progression in patients with nondysplastic Barrett esophagus is approximately 0.1% to 0.3% per year. Or, as I tell my patients, there is approximately a 98% chance that they will not develop esophageal cancer over the next 10 years. Those are fairly good odds.

The most important risk factor for progression to cancer is the presence of high-grade dysplasia on biopsy. Other risk factors include the length of the Barrett esophagus segment and possibly the control of reflux, abdominal obesity, male sex, and tobacco consumption. The use of aspirin might prevent progression, but this is not clear, as is the dose that would be necessary to do so. Therefore, as with any other patient, it is important to recommend that patients with Barrett esophagus abstain from tobacco use, eat a healthy diet, and exercise with the goal of maintaining a normal weight. In addition, it is reasonable to try to maximally control GERD symptoms of these patients. It is also reasonable to assess their cardiovascular risk and recommend daily baby aspirin use if appropriate.

G&H How is Barrett esophagus usually detected?

JR In the United States, the diagnosis of Barrett esophagus requires endoscopic visualization of columnar mucosa residing in the esophagus as well as histologic confirmation of specialized intestinal metaplasia from esophageal biopsies. Narrow-band imaging during endoscopy can make the squamocolumnar junction more apparent than white-light imaging. Specialized histology stains are generally not required if the slides are reviewed by a pathologist competent in gastrointestinal (GI) diseases.

G&H What are the screening guidelines for Barrett esophagus?

JR There are a number of GI specialty guidelines regarding screening for Barrett esophagus. For instance, the American Gastroenterology Association (AGA) guidelines from 2011 suggest screening persons with GERD who have multiple additional risk factors. Similarly, the 2012 guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) recommend that screening be considered in persons with multiple risk factors. The British Society of Gastroenterology (BSG) guidelines published in 2013 recommend that screening be considered in persons with chronic GERD and at least 3 of the following risk factors: age greater than 50 years, white race, male sex, and obesity. The guidelines also suggest requiring fewer risk factors if there is a family history of Barrett esophagus or esophageal cancer. It was not until 2012 that any non-GI specialty group issued guidelines on this topic. The American College of Physicians (ACP) recommends Barrett esophagus screening in men over the age of 50 years with GERD symptoms for at least 5 years who also have additional risk factors (hiatal hernia, nocturnal GERD symptoms, obesity, and tobacco use).

G&H How effective and practical are these guidelines for identifying Barrett esophagus?

JR It is not yet clear how effective these recommendations are for identifying patients with Barrett esophagus. From a practical standpoint, the guidelines from the AGA and the ASGE do not provide specific enough information regarding which individual and combinations of risk factors should prompt screening and at what thresholds. The BSG and the ACP guidelines are more specific and, therefore, easier to implement in theory. However, I am not aware of any studies estimating the sensitivity and specificity of the guidelines for predicting the presence of Barrett esophagus or for the subsequent development of esophageal adenocarcinoma.

It is important to note that none of the guidelines suggest screening persons without GERD symptoms even though we know that a slight majority of persons with esophageal adenocarcinoma deny ever having had significant GERD symptoms. Therefore, any screening program that focuses on GERD symptoms is destined to miss the majority of persons in whom esophageal adenocarcinoma will develop. It might then make sense to also screen, for instance, older white men with abdominal obesity who are smokers but do not have GERD symptoms.

That being said, it is not even clear whether we should screen a patient with GERD who is at very high risk for esophageal adenocarcinoma because we do not have any randomized controlled data showing that screening for esophageal adenocarcinoma can improve life expectancy. Even in the observational studies conducted thus far, it is not clear that screening improves outcomes. The vast majority of patients with Barrett esophagus die from other causes, particularly cardiovascular causes, as would be expected given the shared risk factors of obesity, smoking, and age. Knowledge of the presence of Barrett esophagus has been associated with a slight decrease in quality of life in some studies, and repeated endoscopic surveillance carries a financial cost to society and a burden to the patient. If screening and surveillance were reasonably effective at reducing mortality, then the disadvantages of screening would not be a major concern; however, as already mentioned, it is not clear that screening is effective.

G&H Are there any other tools for predicting the presence of Barrett esophagus?

JR My colleagues and I developed a model for predicting the presence of Barrett esophagus using well-known risk factors in a cohort of men undergoing colonoscopy for colorectal cancer screening who were invited to undergo simultaneous upper endoscopy. In our study, among the 822 men who underwent upper endoscopy—19% of whom had at least weekly GERD symptoms—Barrett esophagus was found in 8.5%. Using age, pack-years of cigarette use, the ratio of the circumference of the waist to the hips, and the presence of at least weekly heartburn or regurgitation, we created the Michigan Barrett Esophagus Prediction Tool (M-BERET), which identified patients who had Barrett esophagus more accurately than GERD symptoms alone.

In addition, Aaron Thrift and colleagues recently developed a model for predicting Barrett esophagus among Australians with GERD. This model used sex, age, smoking, body mass index, education, and acid-reducing medication use. To develop the model, the researchers compared patients with Barrett esophagus to patients with erosive esophagitis and validated it in a separate cohort of patients with Barrett esophagus or GERD symptoms.

G&H What are the advantages and disadvantages of these models?

JR The M-BERET can identify persons without substantial GERD symptoms who may be at risk for Barrett esophagus and esophageal adenocarcinoma. Both the M-BERET and the Thrift model can identify which persons with GERD are at risk for Barrett esophagus and esophageal adenocarcinoma more specifically than just relying on the frequency and duration of GERD symptoms. The hope is that models such as ours and the Thrift model can help physicians communicate the risk of Barrett esophagus and, subsequently, the risk of esophageal adenocarcinoma to patients and help guide the selection of which patients should be screened so that expensive endoscopic resources can be efficiently directed toward the persons who can gain the most.

The main disadvantage with these models is that, in their current form, they have only a modest ability to predict which patients have Barrett esophagus. Although the Thrift model has been validated in a separate cohort, the M-BERET has not yet been, so my colleagues and I are planning studies to do so as well as to improve the model.

G&H How practical are these models to use?

JR I think that the M-BERET is very practical; my colleagues and I developed it with the idea that it had to be quick to complete or it would never be used. The model, which is available online at http://mberet.umms.med.umich.edu, requires the patient's age and sex and then has 6 questions about GERD and smoking. Probably the most time-consuming step is measuring the circumferences of the patient's waist and hips. The user then clicks a button, and an estimated probability of the presence of Barrett esophagus is displayed for that patient.

Ultimately, the ideal setting to use such a model may be in the endoscopy unit for persons who are referred for colonoscopy. A nurse or medical assistant could complete the questions and measurements in the preparation area, and if the risk of Barrett esophagus were calculated to be above a certain threshold, then the patient could be offered an upper endoscopy at the same time as the colonoscopy. However, such an arrangement is not currently possible in most endoscopy units because of payor issues.

G&H Are there any tools designed specifically for predicting the progression of Barrett esophagus to cancer?

JR A number of groups are working to improve the ability to predict which patients with Barrett esophagus will actually progress to cancer. A recent study demonstrated that circulating peptides related to obesity are associated with progression to cancer. Some of the most promising biomarkers appear to be related to aneuploidy or increased tetraploidy in the chromosomes of Barrett cells. There has also been promising work on methylated genes or binding to specific lectins. However, none of the molecular biomarkers have yet been fully validated. Most likely, it would not be possible to perform these tests in a community hospital laboratory, so they would end up becoming send-out tests if they were proven useful. It is also important not to forget about simple clinical risk factors.

One set of biomarkers is already clinically available and being marketed—a set of fluorescent in-situ hybridization probes from cytology brushings. Those markers have been shown to be associated with dysplasia found on biopsy, so they might decrease the sampling error rate for dysplasia. However, to my knowledge, these biomarkers have not yet been validated in terms of adding any additional benefit for predicting progression to cancer rather than simply relying on a standard biopsy regimen.

G&H Are there any important upcoming or ongoing studies in this area?

JR My colleagues and I, as well as other groups of researchers, are planning studies to improve and validate tools for predicting the presence of Barrett esophagus. Prospective longitudinal studies are also needed to validate biomarkers for predicting progression to cancer, but these studies would have to be very large and, thus, very expensive. There is also exciting research on a device called a cytosponge, in which a capsule on a tether is swallowed by a patient who is awake; the sponge is released inside the stomach and then pulled out, collecting esophageal tissue for specialized testing. Finally, many groups of researchers are trying to perfect novel imaging technologies that may identify areas of dysplasia more accurately than white-light endoscopy.

Dr Rubenstein has no relevant conflicts of interest to disclose.

Suggested Reading

Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus [published online October 28, 2013]. *Gut*. doi:10.1136/gutjnl-2013-305372.

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

Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2012;157(11):808-816.

Thrift AP, Kendall BJ, Pandeya N, Vaughan TL, Whiteman DC; Study of Digestive Health. A clinical risk prediction model for Barrett esophagus. *Cancer Prev Res (Phila)*. 2012;5(9):1115-1123.

Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2008;103(3):788-797.