ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

Prevention of Esophageal Cancer

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G&H What factors predispose patients to squamous cell carcinoma and esophageal adenocarcinoma?

JC Squamous cell carcinoma (SCC) is much more common than esophageal adenocarcinoma (EA) in Africa and Asia, whereas EA is more common in the United States. The pathology of SCC primarily involves damaging influences on the esophageal mucosa. Nonmodifiable risk factors include age and male sex. Modifiable risk factors include tobacco use and, to a lesser extent, alcohol use. A diet that is high in processed foods is more likely to cause squamous cell injury, and there is some evidence that diets that are high in fruits and vegetables are somewhat protective against SCC.

In addition, any type of injury to the esophagus, such as caustic exposure (eg, lye), can dramatically increase the risk of SCC. Drinking excessively hot liquids also may increase risk. Decreased peristalsis, which likely leads to higher contact time between triggers and the esophagus, may increase the risk of cancer as well. For example, the lifetime risk of esophageal cancer—usually in the form of SCC—for patients with achalasia is approximately 3%. The presence of human papillomavirus (HPV) is a major risk factor as well.

The pathology of EA is likely more closely associated with gastroesophageal reflux disease (GERD). Age and male sex play roles; however, many of the risk factors for worsening reflux increase the risk of EA. Barrett esophagus will develop in approximately 5% to 15% of patients with GERD, and those patients have a 10-fold risk of esophageal cancer—invariably EA. Obesity is a major risk factor as well, but the mechanism whereby obesity increases the risk of EA is presumably from GERD, leading to Barrett esophagus and then to EA.

G&H What is known about the role of the oral and esophageal microbiomes in esophageal pathology?

JC Within the past 60 years, there has been a dramatic increase in the incidence of Barrett esophagus, EA, and other esophageal disorders such as eosinophilic esophagitis in the United States. There also has been a dramatic shift regarding how medicine has impacted the oral, esophageal, and gut microbiomes. These impacts include interventions to combat *Helicobacter pylori* colonization, antibiotic use in general, exposure to antibiotic residues in food, and widespread use of acid-suppressive medications.

Data regarding what constitutes a normal esophageal microbiome are relatively recent and limited owing to several challenging factors associated with how to distinguish esophageal microbiota from oral microbiota and how to culture these microorganisms. Nevertheless, the literature points to the existence of a native microbiome in the esophagus and differences between a healthy microbiome and that of a patient with reflux, EA, or eosinophilic esophagitis. An important question is whether the altered esophageal microbiome in a patient with EA or another disorder is the cause or effect. Another question is whether the oral microbiome can be used as a screening tool for assessment of the esophagus.

An emerging area of study involves modifying the oral and esophageal microbiomes to influence therapeutic outcomes. A prebiotic is currently on the market that is meant to alter the esophageal microbiome to reduce the risk of GERD. Microbiome-based technology is also being investigated as a potential screening modality for Barrett esophagus. This involves a breath test to detect volatile organic compounds, which presumably are microbiome-mediated.

G&H How can clinicians educate patients regarding lifestyle modification and risk management for the prevention of esophageal cancer?

JC In terms of SCC risk, tobacco and alcohol use certainly can be modified. For patients who have a family history of SCC, cessation of tobacco products is likely the single best action they can take. Moderation of alcohol use is typically recommended along with maintaining a diet that is higher in fresh fruits and vegetables and lower in processed foods. Drinking very hot beverages should be avoided, and vaccination against HPV is recommended.

In the setting of EA, reducing the risk of reflux is the main focus. In terms of lifestyle modification, the single largest factor is weight control. Other lifestyle factors often recommended for reflux prevention include avoidance of eating within 3 hours of lying down and raising the head of the bed slightly (~2 inches) to ameliorate nighttime symptoms.

A long list of trigger foods can be found in information on reflux prevention, but evidence is scant that empirically eliminating such foods makes a difference unless a patient's symptoms are specifically linked to a particular food or drink. Weight control and maintaining a healthy diet typically yield a better result than eliminating a long list of foods that may or may not contribute to reflux symptoms.

Adherence is often determined by the patient's level of risk and investment in symptom relief. Recommending that the patient focus on weight control, avoid meals within 3 hours of lying down, and raise the head of the bed may be more acceptable and easier for the patient to do than avoiding presumed trigger foods. Also, avoidance of trigger foods may create further problems if the patient follows through by accessing website testimonials claiming that certain foods are harmful despite a lack of evidence that avoiding those foods produces an appreciable difference in symptomatology.

Because of time constraints regarding patient education in the office setting, providers need to make themselves aware of high-quality patient education tools and resources that can be referred to patients. For example, the gastroenterology service at Stanford University has a nutrition webinar series that discusses dietary interventions for reflux. Patients can view this series at a time that is convenient for them. There are also numerous websites that list dietary instructions for reflux that can be referred to patients.

G&H Who should be screened for esophageal cancer?

JC Several medical societies have formulated recommendations regarding screening for precursors of esophageal cancer. The general focus of these initiatives has been patients at high risk. Noted demographic characteristics include age older than 50 years, male sex, and a long-standing history of reflux. Some recommendations also include White race, higher body mass index, and family history. A major challenge to wider uptake of screening is that the main screening test is endoscopy. This test carries a fair amount of cost, and patient concerns include taking time off from work to undergo the procedure and having to undergo general anesthesia. Less-invasive and cost-efficient modalities are needed.

It has been proposed that a cost-efficient way to identify patients with Barrett esophagus is to enter patient profiles into a dedicated surveillance system. Current population estimates regarding Barrett esophagus suggest a prevalence of approximately 3 million individuals in the United States. Most of these cases are undiagnosed. In addition, this strategy does not include a significant number of at-risk patients, as most of the cases of esophageal cancer in the United States are not in patients who have a confirmed diagnosis of Barrett esophagus.

G&H What challenges persist regarding endoscopic screening for esophageal cancer, and how are they being overcome?

JC All in all, screening guidelines and modalities for esophageal cancer are currently suboptimal. One of the challenges in relation to society guidelines and their at-risk demographic is that 40% of cases of EA have no reported prolonged history of abnormal reflux. In addition, limiting screening to older White men is not acceptable given what is known about health care disparities regarding race and sex. Further, most of the current guidelines are based on expert opinion and weak data. A very different approach will likely emerge within the next several decades.

A number of nonendoscopic tests that may be less expensive and may have wider appeal are currently under study. One modality is Cytosponge (Medtronic), which

is a sponge on a string that is swallowed and retracted to obtain esophageal tissue. As mentioned, a volatile organic compound test, which is essentially a breath test, is being investigated to screen for Barrett esophagus. Several blood-based biomarkers are also being investigated.

G&H What is the role of image-enhanced endoscopy in esophageal cancer screening, diagnosis, and prevention?

JC Image-enhanced endoscopy has more benefits than white-light endoscopy for esophageal cancer screening. Many of the subtle signs are much easier to see with narrow-band imaging, chromoendoscopy, or confocal endomicroscopy. Endoscope manufacturers are now including narrow-band imaging or similar image-enhancing technology that makes visualization of mucosal and vascular changes much more efficient. Confocal endomicroscopy and stain-based enhancement, however, are more challenging to incorporate within general practice. A learning curve is associated with them, and their use significantly increases the length of the procedure. Use of these modalities is best reserved for tertiary Barrett esophagus screening sites or in patients in whom Barrett esophagus has been established and dysplastic change is being assessed. Enhancements that can be incorporated in existing procedures such as narrow-band imaging, on the other hand, do not take significant amounts of extra time and are now standard with current endoscopic technology.

G&H What is the role of artificial intelligence in esophageal cancer screening, diagnosis, and prevention?

JC This is a fascinating area that is in its early phases. Given that both SCC precursors and Barrett esophagus

have characteristic mucosal changes, artificial intelligence (AI) can likely play a key role in detection. Volumetric laser endomicroscopy is one of the technologies that has been developed over the past several years. This technology involves a laser scan of the affected area that highlights sections that look different based on an algorithm. Several international studies are also specifically looking at AI use in detecting esophageal cancer precursors. For example, investigators entered more than 12,000 separate images into a deep neural network in a recently published Chinese study. They found that the rate of detection with the AI modality was as good as that of expert endoscopists specializing in esophageal cancer screening and much better than that of novices. AI is not ready for prime time yet, but it will likely play a key role in esophageal cancer diagnostics within the next 10 years.

Disclosures
Dr Clarke has served as a consultant for Alnylam, ISOThrive, Medtronic, Pfizer, Regeneron, and Sanofi.

Suggested Reading

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