The FirsT TesT
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AGA Perspectives

The FIRST TEST

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By the time you receive this issue of *AGA Perspectives*, the deadline for abstracts for DDW® 2013 will be nigh (Dec. 1 as always); the results of the first new GI fellowship match schedule will be available on Dec. 5. After many years of GI fellowship applications due Dec. 1 with interviews held in the new year and Match Day occurring in June, this year marks a new timeline. Ryan Madanick reviews the process and new dates, which facilitate residents having more time to decide upon subspeciality training. However, at the same time, there are downsides to completing the process in the last year of the internal medicine residency for both applicants and especially the GI fellowship training programs.

In the past year, we have focused issues of *AGA Perspectives* on colorectal cancer and liver diseases. Most recently, articles on intestinal conditions predominated. In this issue, we start at the top debating which method is best to evaluate the esophagus in a patient with dysphagia. Gregory Ginsburg argues that endoscopy is an appropriate approach, while David Katzka upholds the longer-standing role for barium radiology in assessing swallowing disorders. In my own practice, a lot depends on the individual situation as to which test I choose to order, but let’s see what other readers think. William Brugge assesses the role of confocal microscopy in Barrett’s esophagus asking, Is this a new diagnostic tool or a new toy?

In recognition of November being Stomach Cancer Awareness Month, we feature Benjamin Wong and Victoria Tan who discuss management of gastric cancer in the Asia-Pacific region. Douglas Morgan examines the changing epidemiology of gastric cancer in the Americas. His colleague, Pelayo Correa, reviews the relationship of intestinal metaplasia with gastric cancer. Gastric cancer remains the second largest cancer killer worldwide in spite of advances in treating *Helicobacter pylori* and endoscopic interventions. Further advances in prevention, detection and treatment are needed.

Please note the upcoming deadlines for AGA Research Awards between now and March 2013 (Page 15). As always, I hope our readers will be inspired to advocate for more support for biomedical research in digestive disease through donations, letters to government representatives and other pathways. Such support is most important to our livelihoods and to those patients we wish to help. As the year draws to an end, please consider making a donation to the AGA Research Foundation by visiting www.gastro.org/aga-foundation/contribute. Lastly, don’t forget that the AGA-ASGE Clinical Congress is being held in San Diego for the first time and is a joint effort of both societies.

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**Note From the Editor**

Sheila E. Crowe, MD, AGAF
EDITOR

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We welcome member feedback on all of the perspectives presented in this issue. Send your letters and comments to communications@gastro.org and include “AGA Perspectives” in the subject line.

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Which should be the first test for diagnosing dysphagia: endoscopy or barium swallow?
Endoscopy Should Be the First Test for Dysphagia

Dysphagia implies difficulty with swallowing. Patients may experience dysphagia with solids and/or liquids and at different localizations, invoking sensory, motor and/or structural disorders.

Oropharyngeal dysphagia occurs when there is dysfunction of the coordinated transfer from the mouth to the esophagus. Patients with oropharyngeal dysphagia describe symptoms of choking or cough on swallowing. The differential diagnosis for oropharyngeal dysphagia includes an array of central and peripheral neuromotor disorders. Poor dentition and progressive dementia may also be contributors. Other considerations include laryngopharyngeal malignancies, prior radiation therapy and xerostomia. Endoscopy with inspection of the laryngopharynx is indicated to exclude benign and neoplastic disease of the laryngopharynx and upper esophagus. Proximal esophageal rings, webs and extrinsic compression from a number of sources can mimic the symptoms of oropharyngeal transfer dysphagia. A cine-swallowing study performed by a speech pathologist is the most useful diagnostic test in the evaluation of oropharyngeal dysphagia. It affirms the suspected clinical condition (albeit, not the etiology), assesses risk of aspiration, and can direct management with food selection and swallowing therapy. Many patients with explained or unexplained oropharyngeal dysphagia

CONTINUED ON PAGE 6

Embrace the Dark Side (of the Reading Room): The Case for Barium Swallow

The use of the endoscope for evaluation of upper gastrointestinal disorders has clearly revolutionized the practice and understanding of gastroenterology. As a means of defining intraluminal esophageal abnormalities, there is no debate amongst physicians over its often-superior performance when compared to other forms of testing. On the other hand, the seasoned esophagologist realizes that the information one needs to elucidate the cause of dysphagia is far more than being able to diagnose an intraluminal abnormality. Information better obtained on a barium study includes motility, sensation and anatomic disorders resulting from intramural and extramural compression, as examples below will demonstrate.

Motility disorders of the esophagus as a cause of dysphagia are primarily diagnosed by barium esophagography. For example, in achalasia, the ability to diagnose esophageal dilation in subtle cases is poor with the endoscope when compared to barium radiography. Similarly, finding the characteristic pop of the lower esophageal sphincter in achalasia lacks sensitivity and specificity when compared to the accuracy of seeing an incomplete opening on a contrast study. I am amazed at how many patients diagnosed with early or incomplete forms of achalasia have been endoscoped on multiple occasions but have never had esophagography. Other manifestations of motor disorders such as diffuse

CONTINUED ON PAGE 7
benefit symptomatically with dilation using a 14 mm taper-tipped wire-guided dilating catheter performed at diagnostic or confirmatory endoscopy. Esophageal dysphagia is attributed to structural and/or functional sources. Sources of structural esophageal dysphagia include those conditions affecting the surface and/or caliber of the esophagus. Mucosal-based conditions that may cause dysphagia include esophagitis and neoplasia. Esophagitis from any cause may promote dysphagia due to surface distortion (inflammatory edema, furrowing erosion, excavating ulceration) or due to inflammation-induced esophageal spasm. While esophagitis attributed to gastroesophageal reflux is most common, other considerations include eosinophilic, infectious and medication-induced esophagitis. While Barrett’s esophagus is associated with reflux, it in and of itself is not considered a source of dysphagia. However, esophageal adenocarcinoma arising from Barrett’s mucosa and esophageal squamous cell carcinoma may present with dysphagia. While indirect imaging with barium swallow may suggest specific mucosal-based disease, definitive diagnosis and hence, directed therapy, comes only with direct endoscopic imaging and tissue sampling for histo-pathology. Swift and accurate diagnosis of a source of esophagitis directs therapy in an expeditious manner. Esophageal carcinomas are notoriously lethal. Survival is dependent on tumor stage at diagnosis. Early diagnosis is associated with improved survival. Moreover, endoscopic mucosal resection, as an alternative to operative esophageal resection, is a viable option for curative therapy in patients with mucosal-based (T1a) adenocarcinoma and squamous cell carcinoma. Endoscopy is necessary for the early diagnosis of esophageal cancer.

Intrinsic or extrinsic strictures produce dysphagia by compromising esophageal caliber. This differential includes acquired or congenital rings, webs, inflammatory (peptic, eosinophilic), and neoplastic (mucosal, submucosal or extrinsic) stenoses. Based on clinical history, endoscopy may be planned with fluoroscopic guidance and/or small-caliber endoscopes to ensure safe and effective execution of diagnosis and initiation of therapy with dilation.

Functional esophageal dysphagia is attributable to primary (achalasia, scleroderma) and secondary (reflux-induced spasm, paraneoplastic) esophageal dysmotility and its sequelae (diverticula) as well as globus sensation. While endoscopy and barium swallow may be considered as complementary in the evaluation of functional esophageal dysphagia, endoscopy will be required in all cases to exclude mucosal-based disease.

The clinical history is capable of discriminating oropharyngeal from esophageal dysphagia in most patients. Physical exam may detect cutaneous or connective tissue findings to suggest systemic conditions like scleroderma and pemphigus, for example. Laboratory testing is more or less supportive and may be considered to assess anemia, peripheral eosinophilia and autoimmune markers in selected cases.

Both endoscopy and barium swallow are routinely safe and widely available. Barium swallow is contraindicated in patients with suspected complete or near complete esophageal obstruction and those with suspected food bolus impactions and foreign object ingestions. It should be acknowledged that the barium swallow exposes patients to ionizing radiation, delays definitive diagnosis in most patients and increases the cost of evaluation of dysphagia, owing to the need for eventual endoscopy in nearly all patients who undergo barium swallow as the first test. It is worth noting that contrast radiography is a dying field. Largely replaced by endoscopy and cross-sectional imaging, formal training in barium swallow execution and interpretation has contracted. As such, the expertise in performing and interpreting barium swallow is apt to be variable. It is fairly common for a radiologist’s interpretation of a barium swallow exam to conclude with the following intonation: “clinical correlation required, consider endoscopy.” The parallels between barium enema and colonoscopy are prescient — why use indirect imaging when direct imaging is accessible?

The notion of obtaining routine contrast radiography in advance of endoscopy for the evaluation of dysphagia is a relic, I think, from a past when our endoscopic forbearers were forced — with limited training — into use with the thick, rather dimly lit, fiber optic instruments of their day. However, the modern endoscopist and endoscopes have evolved beyond this necessity. Slim-caliber, well-illuminated video endoscopy advanced under direct visualization by highly trained practitioners does not routinely benefit from a pre-procedure directional road map. One notable exception is when clinical history suggests the possibility of an esophageal leak or fistula. In these instances, judicious use of pre-procedure contrast radiography performed by an informed radiologist is valuable in planning endoscopic therapy.

The bottom line is that for the vast majority of patients presenting to the gastroenterologist with dysphagia, endoscopy is safe and provides the most accurate and proficient means of diagnosis and initiation of management. Nearly all patients with dysphagia who undergo barium swallow as a first test will require endoscopy. If the barium swallow is abnormal, endoscopy will be required to confirm or corroborate the suggested diagnosis and/or initiate therapy. If the barium swallow is normal, endoscopy will be required to further the investigation for a causation and/or provide reassurance to patient and physician alike.
esophageal spasm as seen in the corkscrew esophagus, hypoperistalsis such as seen in end-stage GERD, scleroderma or other smooth-muscle myopathies are also far better appreciated on radiographic imaging. The power of a barium study to diagnose functional dysphagia is formidable. In patients who have symptomatic dysphagia, the finding of a normal endoscopy is not helpful. A test that is needed is one that demonstrates the mismatch between marked symptoms and normal motility function, and anatomic structure of the esophagus. By administration of a liquid (barium) and a solid (barium tablet), one has the ability to ask the patient if he or she had the sensation of one or both of these substances sticking in the esophagus and corroborating whether this is seen on imaging. I have found that, with the patient telling me the pill and/or barium are sitting in their chest long after both of these ingestants have entered their stomach on imaging, I have been able to secure this diagnosis. The only other test that can achieve this is solid- or liquid-phase esophageal scintigraphy, which is offered in only a few centers.

Barium esophagography also is more accurate at diagnosing subtle strictures and evaluating distensibility. In stricturing disorders such as gastroesophageal reflux, eosinophilic esophagitis, radiation in injury or lichen planus, I have found countless times subtle strictures seen on radiography but not on endoscopy. These studies also demonstrate better the length of these strictures, such as in small-caliber esophagus, and may even provide information on the distensibility of the esophagus when measuring minimum and maximum diameter. This has been valuable to help explain the dysphagia encountered in patients with eosinophilic esophagitis and a “normal” esophagus on endoscopy, and in those with a Schatzki ring, commonly missed on endoscopy. Another advantage of starting with a barium study is the ability to perform video esophagography with or without a speech therapist at the time. Both clinical and experimental data demonstrate that the ability to localize the point of functional and/or anatomic obstruction in a patient with dysphagia is difficult. As a result, it is not uncommon that the source of dysphagia is upper esophagus or even pharyngeal. For example, a cricopharyngeal bar or a Zenker’s diverticulum are best (and more safely!) diagnosed on video esophagography. Similarly, upper esophageal lesions such as webs or lichen planus are easily missed on endoscopy if this area is not carefully examined, which is often not the case during routine endoscopy for dysphagia.

Barium esophagography helps plan and makes safer the ultimate need for endoscopy. In patients in whom achalasia has already been diagnosed by esophagography, only one endoscopy is needed, at which time therapeutic maneuvers such as injection of botulinum toxin or pneumatic dilation may be performed. Endoscopic ultrasound may also be scheduled simultaneously for staging of cancer, better evaluation of submucosal lesions or the need to rule out secondary causes of achalasia. For multiple or complex strictures, advanced planning such as need for fluoroscopy or anesthesia assistance may be implemented. For proximal unexpected lesions, as mentioned, such as a Zenker’s diverticulum or tight proximal stricture from lichen planus, perforation may be better avoided.

Finally, the performance of barium studies is also a wonderful chance for transfer of knowledge between colleagues. I cannot tell you how much esophagology I have learned by talking to the radiologists. Even more underrated is how much I have learned from going over studies with speech and swallowing therapists. It is incredible how much they know about oropharyngeal function and in contrast how little we do know, but should. Indeed, my consultative skills have improved markedly in the questions I ask and the advice I receive from these interactions.

Alas, in an era of highly technical radiologic advances, a good barium esophagographer is often labeled as seemingly irrelevant and, as a result, often unavailable to perform at the level of expertise needed by a gastroenterologist seeking to determine a cause of dysphagia. It is not our job to woe the passing of these radiologists. With our interest and encouragement, I feel there are still a plethora of radiologists willing to engage in such noble and time-tested imaging if we continue to support and work with them. It may even be our role to help radiology departments appreciate these skills, and insurance companies financially compensate such technically difficult yet ostensibly primitive diagnostic testing when compared to cross-sectional imaging.

Thus, there are times, even for a president of ASGE, when it is important to turn from the light (of the scope) and be drawn to and embrace the dark side (of the reading room).
November is Stomach Cancer Awareness Month. We have chosen to focus several articles on gastric cancer. In this two-part feature, Douglas Morgan, MD, MPH, takes a panoramic look at the changing epidemiology of gastric cancer in the Americas. Pelayo Correa, MD, gives an overview of intestinal metaplasia and its relationship to gastric cancer.

Gastric Cancer in the Americas

In global terms, with nearly one million incident cases annually, gastric cancer is the second leading cause of cancer mortality and the leading cause of infection-associated cancer mortality.\(^1\)\(^2\) It is projected to rise from 14th into the top 10 in all-cause mortality in the near term, primarily due to growing and aging populations in the high-incidence areas. Gastric cancer demonstrates marked geographic variability, both regionally and within countries. The high incidence areas include eastern Asia (China, Japan, Korea), western Latin America, and parts of Europe and the Middle East. The gender burden is relatively consistent (2:1, males to females), wherein estrogen may play a protective role.\(^3\)
H. pylori as a biomarker for the changing western microbiome

*Helicobacter pylori* (H. pylori) is the most common chronic bacterial infection, colonizing about one half of the world, with important roles as pathogen and human microbiome component.1,4 The biologic costs from chronic colonization and inflammation include an increased risk for noncardia gastric adenocarcinoma, leading the World Health Organization to classify H. pylori as a class I carcinogen. In contrast, recent observations suggest that as an important part of the human microbiome, H. pylori may be a beneficial commensal early in life. Its absence serves as a biomarker of the dramatic changes in the human microbiome in western societies in the last 50 years. Studies indicate that H. pylori infection is inversely related to the atopic diseases such as childhood asthma, atopic dermatitis and eosinophilic esophagitis. By modulation of immune responses, H. pylori and components of the human microbiome may be beneficial early in life and in transition to pathogen in the adult years.

Racial differences in North America

In the U.S., the overall gastric cancer incidence and mortality rates are modest, but are comparable to those of esophageal cancer. In 2012, 21,320 incident cases (males, 13,020; females, 8,300) and 10,540 deaths related to gastric cancer are expected, compared with esophageal cancer (17,460 new cases, 15,070 deaths), respectively.5 Significantly higher rates are observed among African Americans and Asian Americans (see figure). The overall decline in gastric cancer incidence over the past 50 years parallels the decrease in prevalent H. pylori infection, although large racial differences certainly persist in adults: 28 percent in whites versus 54 percent in African Americans.6 Interestingly, a rising incidence of gastric cancer has been observed among young white males in the U.S. over the past several decades.7

H. pylori in Latin America

At national and international scientific meetings in Latin America, there is considerable interest in H. pylori, dyspepsia and gastric cancer, as they reflect the daily patient care reality. H. pylori is highly prevalent in adults in most regions. In a recent large H. pylori eradication trial in the community setting in six countries (Mexico, Honduras, Nicaragua, Costa Rica, Colombia, Chile), the overall prevalence was 79 percent, with a cytotoxin-associated gene A prevalence of 84 percent in the study group.8 Interestingly, chronic dyspepsia, as assessed with the Rome III criteria and questionnaire, is also highly prevalent (26 percent) in the community setting. This is echoed among specialists, as the care of dyspeptic patients is commonplace in Latin America and among Hispanic immigrants in the U.S.

The altitude enigma in Latin America

Gastric cancer has a wide geographic variability within Latin America. In general terms, higher rates are observed in western Latin America along the Pacific coast, contrasting with lower rates in the Caribbean, Amazonia and Atlantic coastal regions. Country-wide standardized annual incidence rates range from 23 to 31 in males. The highest mortality rates are noted in the mountainous regions, which follow the Pacific from Mexico to Chile, and include the Sierra Madre in Mexico, the Cordillera de Centroamérica in Central America and the Andes in South America. This is amply demonstrated in Colombia, where there is a clear correlation between gastric cancer mortality and altitude. Altitude is likely a surrogate for clustering of host genetic risk factors, H. pylori virulent strains, diet and environmental factors.

In conclusion

Gastric cancer is a leading cause of cancer mortality in many regions in the Americas; its burden will increase due to the growing and aging populations. The marked geographic variability offers the opportunity for accelerated scientific discovery and focused prevention programs.

REFERENCES


Gastric Cancer Incidence Rates1,5

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*Includes Alaska natives **Includes Pacific Islanders
Gastric cancer incidence in the Americas is characterized by marked contrasts. In the Andean region, it is directly proportional to the altitude above sea level: the so-called altitude enigma. The disease carries a very poor prognosis, with five-year survival rates below 20 percent, mostly driven by late diagnosis because the disease is asymptomatic in the early phases. Early diagnosis campaigns in Japan result in five-year survival rates above 90 percent. The clinical disease is preceded by a series of well-characterized changes in the gastric mucosa: the so-called precancerous cascade consisting of subsequent lesions of atrophy (gland loss), intestinal metaplasia (first “complete” and later “incomplete”) and dysplasia. These changes take place over several decades, providing an ample window of opportunity for prevention. Given the contrasting incidence rates, prevention strategies should focus on populations at high cancer risk. Intestinal metaplasia represents the best marker of cancer risk. It is frequently mentioned by pathologists in their reports on gastric biopsies. An algorithm for the management of patients with intestinal metaplasia has been proposed, calling for endoscopic surveillance of patients in whom the metaplasia is extensive and/or of the incomplete type.1-3

In general, the prevalence of precancerous lesions and their risk of progression to gastric adenocarcinoma correlate with the background incidence of gastric cancer in the population. This applies both to racial and ethnic groups, as well as specific geographic regions. The rate of progression is modest in affluent western countries, but may be elevated in higher incidence regions. In a study conducted with the large histo-pathology registry in the Netherlands from 1991 to 2004, the rates of progression to adenocarcinoma over a five-year period were 0.1 percent, 0.25 percent, 0.6 percent and 6 percent, respectively for chronic atrophic gastritis, intestinal metaplasia, low-grade dysplasia and high-grade dysplasia. Notably, in the Colombia cohorts followed by Correa, et al., the dynamic flow of progression and regression between these precancerous lesions is observed. In addition, the challenges of gastric mucosal sampling are highlighted.4

In the higher risk patient, gastric biopsies for topographic mapping to rule out precancerous and advanced lesions are indicated. This may further delineate cancer risk and the need for surveillance. In practical terms, the optimal approach is two to four biopsies from the corpus, incisura and antrum, with greater and lesser curve sampling of the antrum and corpus. Irregular areas of the mucosa should also be biopsied to rule out dysplasia, early gastric cancer or other pathology. Higher risk extensive intestinal metaplasia is defined by the presence of intestinal metaplasia in at least two areas of the stomach (antrum, incisura, corpus), whereas limited intestinal metaplasia is confined to one site.5

The specific histo-pathologic subtypes of intestinal metaplasia may also help define risk and the need for surveillance. Complete intestinal metaplasia is defined by the presence of small intestinal type mucosa with goblet cells, a brush border and eosinophilic enteroctyes. In patients with complete intestinal metaplasia limited to one biopsy site, the risk for progression is modest. Incomplete intestinal metaplasia is defined by the presence of epithelium with multiple mucus vacuoles and absence of a brush border with higher cancer risk.4

In summary, with respect to the histo-pathologic diagnosis, extensive intestinal metaplasia based upon gastric biopsy mapping and/or incomplete intestinal metaplasia with the presence of colonic epithelium may warrant endoscopic surveillance with gastric mapping. The interval may range from two to three years depending upon the severity of the lesions. New guidelines support this approach, in parallel with prospective studies. In addition, Helicobacter pylori eradication is indicated in general.1

Lastly, we comment that the evolution of novel imaging technologies for detection of precancerous lesions and neoplasia detection may aid in early detection. Examples include chromoendoscopy, narrow-band imaging and autoluminescence imaging. These technologies are now being used throughout the gastrointestinal tract, primarily being driven by programs in Japan for the detection of early gastric cancer. Similarly, the need for better approaches to the treatment of early gastric cancer has led to the development of advanced endoscopic resection techniques, such as endoscopic mucosal resection and endoscopic submucosal dissection, also now in common use beyond the stomach. The use of advanced imaging modalities is limited to specialized centers in Latin America to date.
Sub-Saharan Africa is at a turning point. A new generation, raised with cell phones and the Internet, is changing age-old social paradigms and political realities across the continent. Medicine in Africa is changing too. Patients are better informed, available therapies are broadening, and there is an urgent need for large numbers of well-trained health-care providers. More than ever, American gastroenterologists can make a difference in Africa.

Gastroenterology is at the forefront of Africa’s needs and opportunities. By some estimates, GI complaints account for up to 50 percent of patient visits, and GI illnesses are leading causes of mortality. Consider the following scenarios:

- A nine-month old infant presents with diarrhea and lethargy. You perform a venous cut-down and begin an intravenous saline infusion. When you round several hours later, you discover that the IV became dislodged, and she died.
- A 36-year-old man presents with bleeding esophageal varices. An African endoscopist, trained by visiting Americans, successfully ligates the varices. Antiviral therapy for hepatitis B is advised, but the patient is unable to afford the medication. Four years later, he is diagnosed with hepatocellular carcinoma.
- A woman dies of esophageal squamous cell carcinoma, the leading cause of cancer death in her region. Her oldest son undergoes screening upper endoscopy with chromoendoscopy, and is found to have esophageal squamous dysplasia that is treated endoscopically.

Each of these true stories reflects the toll of preventable illness as well as the opportunities for progress that exist across sub-Saharan Africa.

There is a critical need for trained health-care professionals in sub-Saharan Africa, including gastroenterologists. Besides seeing referrals and performing endoscopic procedures, African GI and liver specialists play a key role in training and creating health-care policy. However, most countries have few trained gastroenterologists. This shortage limits training opportunities for young physicians. Training in America or Europe is often an inadequate solution, as it is difficult for trainees to return to their home countries after settling in the developed world, and training in high-resource environments addresses a different spectrum of disease.

Initiatives are underway in many African countries to train gastroenterologists. Foremost among these are residency and fellowship programs at both national and mission hospitals. The World Gastroenterology Organization (WGO) has training centers in South Africa, Morocco and Egypt. Gastrointestinal endoscopy and device companies also play an important role by providing donations and loaning equipment and supplies to facilitate training. There are many opportunities for American gastroenterologists and hepatologists to teach in these settings.

The AGA has supported the creation of a postgraduate training program in gastroenterology and hepatology at Korle Bu Teaching Hospital in Accra, Ghana. The first fellows will begin training in September 2013. Short-term visiting professors are needed to teach in this program and in annual GI endoscopy workshops facilitated by AGA, WGO and industry partners. AGA members from seven states have joined colleagues from Africa and Europe to conduct these workshops, training endoscopists from six West African nations in therapeutic techniques such as variceal band ligation.

Our experience as visiting faculty in African settings has taught us these lessons:

- Be flexible and ready to adapt to the needs of learners and the resources at hand.
- Relationships are just as important as curriculum. Get to know your colleagues and students.
- Your effectiveness will increase with each return visit to the same location or program. Plan on returning.

Are you interested in teaching in sub-Saharan Africa? We know of opportunities in countries across the continent. In particular, we hope to include experienced gastroenterologists and hepatologists in a short-term teaching rotation for the AGA-sponsored training program in Accra, Ghana. If you have an interest in partnering with us, please contact Lewis Roberts (roberts.lewis@mayo.edu), Mark Topazian (topazian.mark@mayo.edu) or the AGA Institute International Committee (smegally@gastro.org).
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Conclusions of comparative efficacy and safety cannot be drawn from this information.

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- the healing of all grades of erosive esophagitis (EE) for up to 8 weeks
- maintaining healing of EE and relief of heartburn for up to 6 months
- the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

**CONTRAINdications**
DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use [see Adverse Reactions].

**WARNINGS AND PRECAUTIONS**

**Gastric Malignancy**
Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.

**Bone Fracture**
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to stated treatment guidelines [see Adverse Reactions].

**Hypomagnesemia**
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions].

**ADVERSE REACTIONS**

**Clinical Trials Experience**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions

The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 2.

**TABLE 2: INCIDENCE OF ADVERSE REACTIONS IN CONTROLLED STUDIES**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=896)</th>
<th>DEXILANT 30 mg (N=455)</th>
<th>DEXILANT 60 mg (N=2218)</th>
<th>DEXILANT Total (N=2621)</th>
<th>Lansoprazole 30 mg (N=1363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2.9</td>
<td>5.1</td>
<td>4.7</td>
<td>4.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3.5</td>
<td>3.5</td>
<td>4.0</td>
<td>4.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6</td>
<td>3.3</td>
<td>2.8</td>
<td>2.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>0.8</td>
<td>2.9</td>
<td>1.7</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.8</td>
<td>2.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.6</td>
<td>2.6</td>
<td>1.4</td>
<td>1.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Adverse Reactions Resulting in Discontinuation

In controlled clinical studies, the most common adverse reaction leading to discontinuation from DEXILANT therapy was diarrhea (0.7%).

**Other Adverse Reactions**

Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:

**Blood and Lymphatic System Disorders:** anemia, lymphadenopathy; **Cardiac Disorders:** angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia; **Ear and Labyrinth Disorders:** ear pain, tinnitus, vertigo; **Endocrine Disorders:** goiter; **Eye Disorders:** eye irritation, eye burning; **Gastrointestinal Disorders:** abdominal tenderness, abnormal feces, anal discomfort. Barrett’s esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypertrophy disorders, GERD, GI ulcer, perforation, hemorrhoids, hemosiderin, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching; **General Disorders and Administration Site Conditions:** adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, node, pain, pyrexia; **Hepatobiliary Disorders:** biliary colic, cholelithiasis, hepatomegaly; **Immune System Disorders:** hypersensitivity; **Infections and Infestations:** candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvovaginal infection; **Injury, Poisoning and Procedural Complications:** falls, fractures, joint sprains, overdose, procedural pain, sunburn; **Laboratory Investigations:** ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase; **Metabolism and Nutrition Disorders:** anorexia; **Musculoskeletal and Connective Tissue Disorders:** arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia; **Nervous System Disorders:** altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia; **Psychiatric Disorders:** abnormal dreams, anxiety, depression, insomnia, libido changes; **Reproductive and Urinary Disorders:** dysuria, micturition urgency; **Respiratory System and Breast Disorders:** dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder; **Skin and Subcutaneous Tissue Disorders:** acne, dermatitis, erythema, pruritus, rash, skin lesion, urticaria; **Vascular Disorders:** deep vein thrombosis, hot flush, hypertension

**Other adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT by the treating physician included:** anaphylaxis, auditory hallucination, B12-cell lymphoma, bursitis, cellulitis, chest pain, cholestasis, cholecystitis acute, dehydratation, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis. Other adverse reactions not observed with DEXILANT, but occurring with the racemate lansoprazole can be found in the lansoprazole prescribing information, ADVERSE REACTIONS section.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval of DEXILANT. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Blood and Lymphatic System Disorders:** autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura; **Ear and Labyrinth Disorders:** deafness; **Eye Disorders:** blurred vision; **Gastrointestinal Disorders:** oral edema, pancreatitis; **General Disorders and Administration Site Conditions:** facial edema; **Hepatobiliary Disorders:** drug-induced hepatitis; **Immune System Disorders:** anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); **Metabolism and Nutrition Disorders:** hypomagnesemia, hyponatremia; **Musculoskeletal System Disorders:** bone fracture; **Nervous System Disorders:** cerebrovascular accident, transient ischemic attack; **Reproductive and Urinary Disorders:** acute renal failure; **Respiratory, Thoracic and Mediastinal Disorders:** pharyngeal edema, throat tightness; **Skin and Subcutaneous Tissue Disorders:** generalized rash, leucocytoclastic vasculitis

**DRUG INTERACTIONS**

Drugs with pH-Dependent Absorption Pharmacokinetics

DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir.
DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

Warfarin
Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR [see Clinical Pharmacology]. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Tacrolimus
Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Clopidogrel
Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects
Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole [see Nonclinical Toxicology].

Nursing Mothers
It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in animal reproduction studies, caution should be exercised when DEXILANT is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of DEXILANT in pediatric patients (less than 18 years of age) have not been established.

Geriatric Use
In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between younger and older patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment
No dosage adjustment of DEXILANT is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole.

Hepatic Impairment
No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE
There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 60 mg include hot flashes, confusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Serum Gastrin Effects
The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In patients treated for more than 6 months, serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-Like Cell (ECL) Effects
There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed following ECL cell proliferation and formation of carcinoid tumors, especially in female rats [see Nonclinical Toxicology].

Effect on Cardiac Repolarization
A study was conducted to assess the potential of DEXILANT to prolong the QT/QTc interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m2) basis of a 50 kg person of average height (1.46 m2 body surface area (BSA)) given the recommended human dose of lansoprazole 30 mg per day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see Clinical Pharmacology].

In rats, lansoprazole also increased the incidence of intestinal metaphasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day (4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day. 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice.

Lansoprazole treatment produced adenoma of rete testis in male mice receiving 15 mg/kg up to 25 mg/kg per day (5 to 80 times the recommended human lansoprazole dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

PATIENT COUNSELING INFORMATION

To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Patient Information Leaflet should be discussed with the patient.

Inform the patient to watch for signs of an allergic reaction as these could be serious and may require that DEXILANT be discontinued.
Advise the patient to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [see Warnings and Precautions].

Advise the patient to tell their health care provider if they take atazanavir, tacrolimus, warfarin and drugs that are affected by gastric pH changes [see Drug Interactions].

Advise the patient to follow the dosing instructions in the Patient Information Leaflet and inform the patient that:

- DEXILANT is available as a delayed release capsule.
- DEXILANT may be taken without regard to food.
- DEXILANT should be swallowed whole.
- Alternatively, DEXILANT capsules can be administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately. Granules should not be chewed.
  - Do not store for later use.

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Deerfield, IL 60015
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DEX006 R15, BS Revised: October 2011 L-LPD-1011-2
Gastric cancer is the fourth most common cancer worldwide, but the second leading cause of cancer deaths.\(^1\) Gastric cancer is a major public health burden in the Asia-Pacific region, but this burden varies due to the heterogeneity of the ethnic populations that form the backbone of this region. The risk of gastric cancer varies from high-risk areas in East Asia, including China, Japan and Korea, where the age-standardized incidence rate (ASR) is greater than 20 per 100,000, to low-risk areas such as Australia, India and Thailand where the ASR is just half of that. In Malaysia, Singapore and Taiwan, the risk of gastric cancer is intermediate between the highest- and lowest-risk areas.\(^2\) This pattern of risk explains the divergence in allocation of resources. In western populations, where the risk of gastric cancer tends to fall into the low-risk category, gastric cancer management has very much been focused on the management of advanced gastric cancer; this statement does not hold true for the highest-risk areas in the Asia-Pacific region where resources have focused on preventive strategies and management of early gastric cancer.

### Preventive strategies

It is widely accepted that gastric cancer, like colonic cancers, progresses through a cancer cascade.\(^3\) However, why certain individuals and families have a greater propensity to move along the cascade towards gastric cancer is most certainly a multi-factorial process, and arises from complex interactions between host factors, *Helicobacter pylori* (*H. pylori*) infection and environmental factors. These factors have long been considered targets for preventive programs to reduce the burden of gastric cancer development.

Diet high in salt and nitrates seem to confer the highest risks, with salt in particular demonstrating an ability to augment the effects of gastric carcinogens. A diet rich in fresh fruits and vegetables is associated with a reduced risk of gastric cancer. However, augmentation of the diet with ascorbic acid or use of multivitamins does not appear to confer the same protection.\(^4\) \(^5\) Despite these observations, sustained measurable alterations in diet sufficient to affect gastric cancer prevalence would be difficult to assess in a study population, particularly over the long lead times gastric cancer studies require.

However, *H. pylori* infection has proven to be a more interesting target in this region. Multiple studies have indicated that *H. pylori* infection is a necessary, but not a sufficient causal factor in the development of gastric cancer.\(^7\) This has led to gastric cancer prevention strategies focused on *H. pylori* eradication in the Asia-Pacific region, which sees some of the highest rates of *H. pylori* infection (between 31 to 92 percent in developed and developing countries, respectively) and gastric cancer prevalence rates.\(^8\) Unfortunately, despite four randomized placebo-controlled trials evaluating *H. pylori* screening and eradication on gastric cancer prevalence, all four did not show a significant reduction in gastric cancer development; however, there was a nonsignificant trend towards risk reduction for gastric cancer with *H. pylori* eradication.\(^9\) The strategy of population screening and treatment of *H. pylori* infection appears to be the strategy of choice in high gastric cancer risk populations, particularly in light of the suggestive population-based studies mentioned. However, unresolved issues include the optimal age of intervention, ethical considerations — including the induction of antibiotic resistance — and the costs to individual countries incurred by population-based screening programs.

### Management of early gastric cancers

Countries such as Japan and Korea are trailblazers in terms of the management of early gastric cancer, and this has primarily been driven by need. Given that these countries have some of the highest gastric cancer ASRs, Japan, Korea and Matsu Island in Taiwan have established population screening programs for early gastric cancer. Screening is done through barium meal (Japan), gastroscopy (Japan and Korea) and serum pepsinogen/gastroscopy (Taiwan).\(^7\) \(^9\) Studies from the Asia-Pacific region examining the techniques of endoscopic mucosal resection and endoscopic submucosal dissection have proven that with improving technical expertise, the outcome for patients with early gastric cancer is excellent — as high as 100 percent survival at five years in carefully selected patients.\(^10\) However, the detection of early gastric cancer is difficult and only systematic population screening has been shown to increase early detection and confer a survival advantage.\(^11\) \(^12\) Health economics modeling indicates that population endoscopic screening for early gastric cancer is cost effective in moderate- to high-risk populations,\(^13\) hence it may not be applicable to other countries.

### Management of advanced gastric cancer

In the management of advanced gastric cancer, the majority of the studies have been carried out in the West, as primarily, some 80 to 90 percent of gastric cancer in the West present late.\(^14\) The backbone of the management of advanced gastric cancer is chemotherapy, and despite little evolution over the last 15 years in chemotherapy regimes, we are entering an
exciting age with the introduction of biological agents. In Asia, the first-line treatment of advanced gastric cancer remains doublet chemotherapy, with preferred regimens including a platinum compound, usually cisplatinum in combination with 5-fluoro-uracil, capecitabine or S-1. Fluoro-pyrimidines show less toxicity in Asian populations, possibly owing to polymorphisms in genes encoding drug-metabolizing enzymes, translating into more options for advanced gastric cancer treatments in Asian populations. Unfortunately, in the Asia-Pacific region, access to oral fluoro-pyrimidines, including capecitabine and S-1 or the biologic agents is not routinely funded by the government. This severely limits the choices available to patients in this region of higher gastric cancer prevalence and where a majority of patients still present with advanced gastric cancer.

Conclusion
The Asia-Pacific region is somewhat heterogeneous in its gastric cancer risk, and the unique specialization developed to manage gastric cancer reflects this. Due to the region’s relatively higher rates of gastric cancer, proportionately more interest and resources have been allocated to population screening and treatment for H. pylori, and towards the development and refinement of advanced endoscopic techniques for early gastric cancer. This, along with the availability of new biologics ushers in an exciting next phase in the management of gastric cancer in the Asia Pacific.

REFERENCES
The Timeline Shift in the Medical Subspecialties Match — A Wolf in Sheep’s Clothing?

GI fellowship candidates and programs will experience a major change in the Medical Specialties Matching Program. Beginning this year, internal medicine residents have until post-graduate year three (PGY-3) to apply and interview for fellowship programs. This change was put into effect to permit internal medicine residents to make a more informed decision about their career by expanding their opportunities for subspecialty experiences during residency before formally beginning the application process. Internal medicine residents now have greater opportunities to find faculty within GI to provide mentorship and write stronger letters of support for them, instead of scrambling around chaotically during their internship year. For those who needed extra time and could not apply until their PGY-3 year, this change means that they can continue training immediately following residency without needing to take a year off. In short, the new subspecialty Match timeline is intended to represent a significant benefit for our future colleagues.

The new timeline should also benefit GI fellowship programs by decreasing the number of fellows who experience “buyers’ remorse” about their subspecialty selection or specific track during their training. The extra year will give residents a better chance of selecting a field and a career pathway that fits best with their long-term goals. For programs with a research focus, candidates will be able to better explore their motivations to enter a research career without undue time pressure.

Nonetheless, many program directors have concerns about the new timeline. One major problem faced by programs involves the condensed interview cycle. Programs have just under four months, from July 15 until Nov. 14 (see figure), to review applications, invite and interview candidates, and submit their rank lists. This year, program directors had to compete with summer vacation schedules to ensure an adequate complement of faculty members to interview candidates. Combine vacation schedules with annual meetings of the AGA’s sister groups, and arranging dates for interviews becomes much more difficult. With fewer dates available for interviewing, strong candidates will surely be faced with overlapping dates or impossible travel schedules. Such conflicts may lead candidates to decline interviews they would have otherwise accepted or even to cancel their interviews at the last minute. Programs located in more isolated or seemingly less desirable areas of the country may find themselves in the unenviable situation of having to scramble just to fill their interview slots.

Further adding to program directors’ worries is the condensed period to apply for state licensure. Until this year, candidates who successfully matched into a fellowship position had more than a year to complete all of this paperwork. Starting this year, new fellows will have approximately six months to obtain their state licenses. Licensing may be a particular problem in states with notoriously slow processes (e.g., California, Texas) or for international medical graduates who may need to obtain visas and/or documentation of their education from other countries. This may skew fellowship applicant selection toward residents who already have a license in that state.

With these issues in mind, program directors and faculty need to be flexible, understanding, and even creative in their approach to the new subspecialty Match timeline. We should not assume that the cancellation of an interview indicates that other programs are taking fellows “outside the
Remembering Past AGA Presidents

The AGA reflects on the incredible achievements of Joseph B. Kirsner, MD, PhD, and John Thruston Farrar, MD, both who passed this summer.

Joseph B. Kirsner, MD, PhD

Renowned gastroenterologist Joseph B. Kirsner, MD, PhD, the Louis Block distinguished service professor of medicine at the University of Chicago, died from kidney failure at his home in Chicago on July 7. He was 102.

A former president of the AGA, Kirsner was a pioneer in the understanding and treatment of IBD, and a role model for physicians learning how to care for patients. He was a leader in understanding the immunology and genetics of IBD and was one of the first to show the increased risk of colon cancer in patients with ulcerative colitis. He received our society’s highest honor, the Julius Friedenwald Medal, in 1975.

When AGA announced his passing on Twitter, gastroenterologists posted tributes, calling him a “legend in IBD” and noting that “he was a model of intelligence and dedication.”

“Dr. Kirsner was one of the most important and influential leaders within gastroenterology, the AGA and the broader American medical community. With his passing, we honor his career and legacy as a clinician, mentor, researcher and inspirational figure,” said Loren Laine, MD, AGAF, president, AGA Institute.

Dr. Kirsner was committed to giving back to the field. He became a founding member of the AGA Research Foundation Legacy Society to support our mission of funding young researchers.

Read more about Dr. Kirsner’s life and achievements in the July 12 issue of AGA eDigest, accessible at http://bit.ly/NEtQyk.

John Thruston Farrar, MD

John Thruston Farrar, MD, an AGA past president, died on his 92nd birthday, June 26, at the Hospice House of Williamsburg.

He graduated from Princeton University and Washington University Medical School in St. Louis, MO, where he had grown up. After serving in the U.S. Army Medical Corps, he trained in Boston under the leading gastroenterologist at the time, Franz Ingelfinger, MD. He became one of the “Five Fingerlings,” an experience that influenced the rest of his career.

He taught at the Boston University School of Medicine and the Cornell University College of Medicine before moving to Richmond to become chair of the internal medicine department’s division of gastroenterology at the Medical College of Virginia (MCV) (now VCU Medical Center). He built a division known for its excellence by his ability to recruit some of the best physicians in the field. Throughout his career he trained a total of 51 residents/fellows.

From MCV he transferred to the McGuire Veterans Affairs Medical Center as chief of staff. After 11 years in that position, he was chosen as deputy to the undersecretary for health in the U.S. Department of Veterans Affairs in D.C. Before leaving the central office, he was acting undersecretary for health for more than a year.

Throughout his career he won many awards; the most prestigious was the AGA Julius Friedenwald Medal. He was a prolific writer and lecturer in the area, nationally and internationally, and served in numerous volunteer national positions. He was also editor of several medical journals, among them, the American Journal of Digestive Diseases.

During his presidency of the AGA, he collaborated with the pharmaceutical industry to fund gastroenterology research. This was the beginning of the current multimillion dollar AGA/industry research scholar awards given yearly to young professionals conducting research in the field.

Read more about Dr. Farrar’s life and achievements in the Aug. 2 issue of AGA eDigest, which can be viewed at: http://bit.ly/PR7L2T.
Confocal Endomicroscopy in Barrett’s Esophagus: A New Tool or Toy?

The detection, diagnosis and staging of early neoplastic lesions and other digestive diseases are some of the principal aims of gastrointestinal endoscopy. High-definition white-light endoscopy (HD-WLE) is currently the standard of care, and under proper conditions, endoscopy can detect early gastrointestinal malignancy. When mucosal abnormalities are detected, they are usually biopsied or resected and submitted for histologic analysis. This current practice of histological analysis is associated with delays in diagnosis and management. Until recently, this time-honored and resource-intensive protocol had not been challenged. This tradition has now been brought into question with the recent development and novel application of confocal microscopy coupled with gastrointestinal endoscopy, termed confocal laser endomicroscopy (CLE).

Indications and considerations for use

The current indications for the use of CLE include clinical scenarios that require histologic sampling of the target mucosa. CLE imaging of the gastrointestinal mucosa enables endoscopists to obtain real-time histologic images as well as enhance the guidance of physical mucosal biopsies. The general indications for the use of CLE include the identification of premalignant mucosa and the rapid diagnosis of benign mucosal disease.

There are two manufacturers for CLE: 1) Pentax Medical (Tokyo, Japan) in joint partnership with Optiscan Pty. Ltd. (Notting Hill, Melbourne, Australia) and 2) Cellvizio, Mauna Kea Technologies (Paris, France). The Pentax confocal system obtains images via a confocal microscope integrated within the distal tip of an endoscope (eCLE), thus limiting its use to the alimentary tract. The Cellvizio system acquires confocal images via a fiber optic mini-probe that can be passed through the accessory channel of an endoscope (pCLE). This system, given its flexible design, allows use in the alimentary tract in addition to the biliary and pancreatic ducts, and targeted organs via endoscopic accessories (i.e., catheters and biopsy needles).

Contrast agents

A contrast agent is critical for endoscopic confocal imaging, and fluorescein is most commonly used. Once administered intravenously, there is a dramatic highlighting of vascular structures and the mucosa, lasting about 20 minutes. Although fluorescein sodium can be topically applied, it performs poorly for imaging deeper mucosal layers. Transient hypotension, nausea or injection-site erythema occurs in less than 1 percent of patients.

Clinical indications for CLE

The strongest indication for the use of CLE is in the detection of Barrett’s esophagus and associated dysplasia and neoplasia. CLE can readily detect the mucosal changes of Barrett’s epithelium. In contrast to the normal squamous mucosa (which appears as a bland array of elliptical cells), intestinal metaplasia appears as a villous-like epithelium (see figure below). One potential role of CLE might be to screen for Barrett’s esophagus in high-risk individuals (e.g., older males with chronic GERD) who will undergo endoscopy with biopsy. The accuracy of CLE in differentiating between esophagitis, Barrett’s and gastric epithelium is more than 90 percent. In a large study, Barrett’s esophagus and associated neoplasia could be predicted with a sensitivity of 98.1 percent and 92.9 percent, and a specificity of 94.1 percent and 98.4 percent, respectively (overall accuracy: 96.8 percent and 97.4 percent). The potential advantage of using CLE would be to decrease the dependence on biopsies in the diagnosis of Barrett’s esophagus. Unfortunately,
these cost savings might be offset by the cost of equipment and training.

CLE can also be used for the detection of early malignancy arising in patients with known Barrett’s esophagus. In this clinical scenario, patients with well-established Barrett’s esophagus who undergo surveillance endoscopy and CLE would be candidates for CLE. The role of CLE could be in the detection of dysplasia and the guidance of biopsies to suspicious sites. In a recent study, CLE-guided targeted biopsies of Barrett’s doubled the diagnostic yield of endoscopy for the detection of Barrett’s neoplasia from 17.2 percent to 33.7 percent. In addition to improving the yield of endoscopic biopsies, CLE could also reduce the need for routine surveillance biopsies in Barrett’s mucosa without evidence of dysplasia. Currently, there is a large prospective international multicenter study underway to assess the performance characteristics of eCLE in patients with Barrett’s and associated neoplasia (ClinicalTrials.gov Identifier: NCT01124214).

... confocal endoscopic microscopy holds great promise to aid the endoscopist in the diagnosis of Barrett’s esophagus and the early neoplasia associated with Barrett’s esophagus.

Probe-based CLE studies in Barrett’s esophagus

The use of CLE with a probe has great appeal because of its ease of use and ability to target small suspicious lesions arising in Barrett’s. The initial studies comparing the sensitivity of pCLE against histology in patients with Barrett’s esophagus were disappointing. However, pCLE criteria for the diagnosis of Barrett’s-associated neoplasia have been better developed and published. A two-fold increased sensitivity has been demonstrated (from 34 to 68 percent) in the detection of early neoplasia using CLE.

Recently, an international, multicenter, randomized, controlled trial compared pCLE with HD-WLE in 101 consecutive patients with Barrett’s esophagus. The authors investigated the comparative sensitivities of HD-WLE, narrow band imaging and pCLE. The combination of pCLE with HD-WLE significantly improved the diagnostic ability to detect Barrett’s-associated neoplasia over HD-WLE alone. The sensitivity and specificity for detecting neoplasia with HD-WLE were 34.2 percent and 92.7 percent compared to 68.3 percent and 87.8 percent with pCLE. Furthermore, pCLE detected many more neoplastic lesions than HD-WLE alone.

In summary, confocal endoscopic microscopy holds great promise to aid the endoscopist in the diagnosis of Barrett’s esophagus and the early neoplasia associated with Barrett’s esophagus. With the recent approval of a CPT code for confocal endomicroscopy, we will see increasing use of this new endoscopic imaging technique.
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