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AGA SECTION

American Gastroenterological Association Institute Guideline on the Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the absence of mucosal lesions. The guideline was developed by the AGA's Clinical Practice Guidelines Committee and approved by the AGA Governing Board.

Esophagogastroduodenoscopy (EGD) is commonly performed in the evaluation of patients with dyspepsia. The primary value of diagnostic EGD is the ability to obtain a tissue diagnosis of potentially symptom-producing lesions. In many cases, however, biopsies are obtained of mucosa without an obvious, anticipated pathologic or symptomatic correlate, such as either normal-appearing or nonspecifically abnormal tissue. Currently, there are no clinical standards or guidelines for the performance of such biopsies of normal-appearing mucosa. As a result, there is likely wide practice variation in whether or not such biopsies of normal-appearing mucosa are obtained. Additionally, how the results of such biopsies affect management is poorly understood. At the same time, although endoscopic biopsy itself is generally associated with a negligible rate of complications, it substantially increases the cost of the procedure by incurring a higher procedural fee and the attendant specimen processing and interpretation fees. The purpose of the current guideline is to establish evidence-based practicing standards for the performance of biopsies of normal-appearing mucosa in the upper gastrointestinal tract. This guideline focuses on adult patients (ie, older than 18 years of age) who are undergoing EGD with dyspepsia as the sole indication. Dyspepsia is defined according to the Rome III criteria, which include 1 or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning.[1] In addition, this guideline assumes no prior treatment for *Helicobacter pylori* (HP) infection.

The current guideline was developed utilizing a process outlined elsewhere.[2] Briefly, the AGA process for developing clinical practice guidelines incorporates the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[3] and best practices for generating trustworthy guidelines as outlined by the Institute of Medicine.[4] GRADE methodology was utilized to prepare the background information for the guideline and the technical review that accompanies it.[5] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review, authored by a multidisciplinary panel that included a gastrointestinal pathologist. In preparation for the formulation of the current guideline recommendations, the guideline panel and the authors of the Technical Review met face to face in January 2015 to systematically review the quality, quantity, and consistency of the available aggregate evidence and consider other factors relevant for the risk-to-benefit assessment of the eventual recommendations. Although critically important, it must be underscored that evidence quality was not the only factor considered in the formulation of the recommendations. Other considerations, wherever appropriate, included comparison of the benefits and harms of particular recommendation, economic value, and potential variations in patient preference. In addition, these guidelines are developed based primarily on evidence derived from Western populations. Certain non-Western populations might have sufficiently high risk for upper gastrointestinal abnormalities to warrant a risk-tailored management approach. Finally, the endoscopic biopsy itself was assumed to be associated with a negligible rate of complications. The definitions of relevant GRADE terminologies are provided in Tables 1 and 2.

A summary of the 8 guideline statements is provided in Table 3, along with the ratings of the strength of recommendations and evidence quality.

Abbreviations used in this paper: **AGA, American Gastroenterological Association; EGD, esophagogastroduodenoscopy; GE, gastroesophageal; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GVHD, graft-vs-host disease.**

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Table 1. Grading of Recommendations Assessment, Development and Evaluation Definitions on Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Esophagus

1. In patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends against obtaining routine biopsies of the normal-appearing esophagus or GE junction regardless of immune status. *(Strong recommendation, very low quality evidence)*.

Very-low-quality and indirect evidence indicated that routine biopsy of normal esophagus or gastroesophageal (GE) junction in patients with dyspepsia alone would have very low probability of diagnosing esophageal abnormalities or have little impact on clinical management. Specifically, although a number of microscopic changes in the esophageal mucosa can be seen in patients with gastroesophageal reflux disease (GERD), these findings have limited specificity to distinguish true GERD patients from those with functional heartburn or healthy controls. Such biopsy-based histologic changes are insufficiently validated to be used to guide clinical management. Low-quality evidence based on a single cohort study involving 86 patients with intestinal metaplasia of cardia diagnosed by biopsy of normal-appearing GE junction indicated that this histologic finding had no potential for malignant progression and was of unclear clinical importance. Although frequently encountered, this finding is also unreliably demonstrated in follow-up biopsies. Among patients with lymphocytic esophagitis, although a significant proportion might have normal-appearing esophagus, the proportion with dyspepsia as the sole symptom is extremely small. In addition, the prevalence of this condition is very low in the general population and likely similarly low in patients with dyspepsia. Among adult patients with eosinophilic esophagitis or esophageal cancer, the proportion with normal-appearing esophagus and dyspepsia as the sole symptom is very low.

Besides the added cost of the biopsy, several other potential undesirable effects associated with obtaining biopsies of normal esophagus or GE junction were considered. Patients who are found to have intestinal metaplasia of the cardia might be regarded (albeit inappropriately) as having increased cancer risk, which can negatively affect their insurability. In addition, they might be unnecessarily placed in an endoscopic surveillance program, further adding to the cost of care. Given the lack of evidence to suggest a clear benefit, and the potential for increased cost and harm, a strong recommendation against obtaining routine biopsy of normal-appearing esophagus and GE junction was believed to be justified, despite the very-low-quality evidence. Nevertheless, in certain populations (eg, Iranian and Chinese) at high risk for squamous dysplasia, which could be associated with subtle mucosal changes, risk-tailored management considerations might be warranted.

The lack of any added benefit for tissue sampling of normal-appearing mucosa should be similar for immune-compromised patients for most disorders. Esophageal graft-vs-host disease (GVHD) and infections (eg, cytomegalovirus and *Candida*) are sometimes encountered in patients with a compromised immune system. However, low-quality evidence indicated that no patients had esophageal GVHD involvement without involvement elsewhere in gastrointestinal tract, and other luminal sites are more likely to yield positive biopsies for GVHD when suspected. In addition, absence of symptoms other than dyspepsia is extremely unlikely in infectious esophagitis and GVHD. Therefore, obtaining endoscopic biopsy of a normal-appearing esophagus in an immunocompromised patient with dyspepsia alone would have no added value.

Table 2. Grading of Recommendations Assessment, Development and Evaluation Definitions on Strength of Recommendation

	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids might well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Table 3. Summary of Statements

Anatomic location	Statement	Strength of recommendations	Quality of evidence
Esophagus	1. In patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends against obtaining routine biopsies of the normal-appearing esophagus or GE junction regardless of immune status	Strong	Very low
Stomach	2. In immunocompetent patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of HP infection if the HP infection status is unknown.	Strong	Moderate
	3. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of HP infection if the HP infection status is unknown.	Strong	Very low
	4. When obtaining biopsies from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests following the 5-biopsy Sydney System with all specimens placed in the same jar.	Conditional	Moderate
	5. When biopsies are obtained from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests not obtaining automatic special staining of the specimens.	Conditional	Moderate
Duodenum	6. In patients undergoing EGD for dyspepsia as the sole indication, and in the absence of signs or symptoms associated with an increased risk of celiac disease, the AGA suggests not obtaining routine biopsies of the normal-appearing duodenum to detect celiac disease.	Conditional	Very low
	7. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA suggests obtaining routine biopsies of the normal-appearing duodenum for the detection of GVHD in post–allogeneic tissue transplantation patients and for opportunistic infections.	Conditional	Very low
	8. When biopsies are obtained from the normal-appearing duodenum, the AGA suggests not performing routine special staining of the specimens.	Conditional	Very low

Stomach

2. In immunocompetent patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of HP infection if the HP infection status is unknown. *(Strong recommendation, moderate quality evidence).*

Most clinically significant disorders found in the stomach are associated with endoscopically apparent mucosal abnormalities. HP infection can be present in the stomach even with a normal appearance on EGD, and finding HP is important for management decisions. Very-low-quality indirect evidence suggests that the prevalence of HP among patients with functional dyspepsia could be substantial. Moderate-quality randomized controlled trial data demonstrated that testing and eradicating HP led to significant symptomatic relief among patients with functional dyspepsia, which provides indirect evidence suggesting a similar benefit with performing routine gastric biopsies to detect HP in patients with functional dyspepsia. Furthermore, moderate- to low-quality evidence derived from a recent meta-analysis of observational data indicated that testing and treating HP was associated with a reduced incidence of gastric cancer. The magnitude of absolute risk reduction varied depending on patient characteristics (eg, country of origin, family history), but a clinically important level of benefit was present for all populations, including the Western populations. Consistent with these data, existing AGA guidelines generally support the test-and-treat approach to the management of dyspepsia.

Alternative non-endoscopic tests are available for the diagnosis of HP. However, a patient who is already undergoing an EGD would likely prefer not having to take additional time to undergo one of the alternative HP tests. Furthermore, the cost of these alternative tests would offset the cost of diagnosing HP infection endoscopically.

Despite the overall low quality of the evidence, there are substantial data, including those from randomized controlled trials, supporting a clinically important benefit to detecting and eradicating HP infection in patients with dyspepsia, both with respect to symptomatic relief and

gastric cancer risk reduction. A strong recommendation for obtaining routine biopsies for the detection of HP in patients with dyspepsia was justified. Notably, in patients whose HP infection status is already known, this recommendation would not apply, as the assumed benefit would not be present.

3. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of HP infection if the HP infection status is unknown. *(Strong recommendation, very low quality evidence)*.

There is no evidence from the literature to suggest that the risk-to-benefit consideration of testing and treating HP infection in patients presenting with dyspepsia would be different according to immune status. Furthermore, very-low-quality evidence based on small case series and anecdotal clinical experience raises the possibility that cytomegalovirus infection might be present in normal-appearing gastric mucosa in immunocompromised patients. Therefore, the strong recommendation for routine endoscopic biopsy of the gastric mucosa for the detection of HP infection was reiterated in the immunocompromised population, despite the very-low-quality evidence.

4. When obtaining biopsies from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests following the 5-biopsy Sydney System, with all specimens placed in the same jar. *(Conditional recommendation; moderate quality evidence)*.

The performance characteristics of endoscopic biopsy protocol for the detection of HP infection have been compared in a single study. The updated Sydney System protocol identified 100% of HP infections. The updated Sydney System protocol includes specimens from the lesser and greater curve of the antrum within 2−3 cm of the pylorus, from the lesser curvature of the corpus (4 cm proximal to the angularis), from the middle portion of the greater curvature of the corpus (8 cm from the cardia), and one from the incisura angularis (Figure 1). Although the same study noted that a 3-biopsy protocol (1 each from greater curvature of the corpus and antrum and 1 from incisura) also identified 100% of HP, equivalency of the 3- vs 5-biopsy protocol cannot be definitively established, as this study included only 20 HP-infected patients with unspecified acid-suppressive status. It is conceivable that the 5-biopsy Sydney System might increase the yield of HP detection compared with the 3-biopsy system among patients receiving acid-suppressive therapy. Given that the time and cost of specimen preparation and processing from the pathology standpoint are the same for a 3- vs 5-biopsy protocol, a conditional recommendation was made to follow the 5-biopsy protocol.

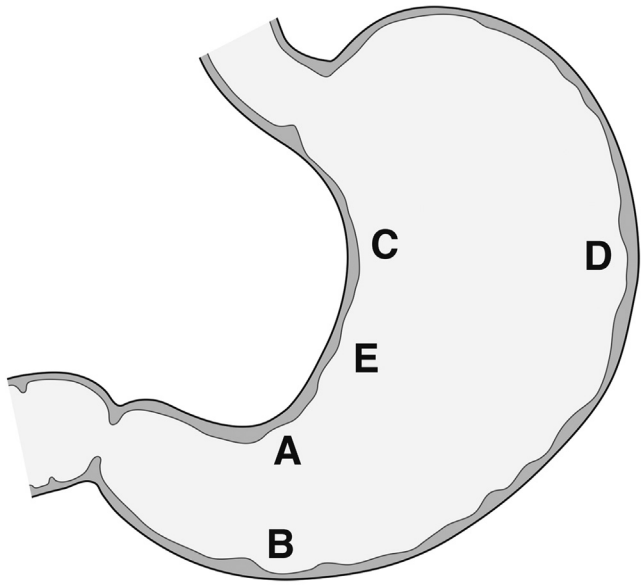

Figure 1. Locations of gastric biopsy recommended by the updated Sydney System. (*A*) Lesser curvature of the antrum; (*B*) greater curvature of the antrum; (*C*) lesser curvature of the body; (*D*) greater curvature of the body; and (*E*) incisura angularis. Adapted with permission from Dixon et al.[6]

Experienced gastrointestinal pathologists can determine the anatomic location of biopsy specimens sent from the stomach, which obviates the need for separating specimens into multiple jars. All gastric biopsy specimens sent for HP diagnosis should be submitted in a single jar as a means to limit costs without compromising accuracy or patient health outcomes.

5. When biopsies are obtained from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests not obtaining automatic special staining of the specimens. *(Conditional recommendation; moderate quality evidence)*.

Moderate-quality data indicated that HP infection is almost always found in the context of chronic inflammation. With the 5-biopsy updated Sydney protocol, which acquires specimens from the antrum, incisura, and body, the majority of cases of HP infection can be identified by experienced pathologists on hematoxylyn and eosin (H&E) stains. Therefore, routine use of ancillary special staining of the specimen would have limited value and will increase the overall procedural cost. In instances in which HP infection is not identified on H&E staining in the presence of chronic gastritis, at the pathologists' discretion, immunohistochemistry or other special staining will be considered.

Duodenum

6. In patients undergoing EGD for dyspepsia as the sole indication, and in the absence of other signs or symptoms associated with an increased risk of celiac disease, the AGA suggests not obtaining routine biopsies of the normal-appearing duodenum to detect celiac disease. *(Conditional recommendation; very low quality evidence)*.

Celiac disease can be present in patients with endoscopically normal duodenum. Based on very-low-quality evidence, the prevalence of biopsy-proven celiac disease among patients with dyspepsia is not significantly different from that in the US general population in which screening for celiac disease is not recommended. In addition, one must consider the potential for false-positive biopsy diagnosis in this setting, particularly when only early-grade celiac changes (eg, Marsh I–II) are detected. Because this recommendation is primarily dependent on very-low-quality prevalence data, a conditional recommendation is warranted. As the possibility exists that the true prevalence of celiac disease among patients presenting with dyspepsia might be higher than what the current literature suggests, this recommendation might need to be updated when higher-quality evidence becomes available. Finally, biopsy of the normal-appearing duodenum might be appropriate in patients who are at high risk for celiac disease, as specified by a previous AGA guideline on the diagnosis and management of celiac disease.[7] If the suspicion for celiac disease is high, biopsies of the normal-appearing duodenum can be of value even if serologies (obtained while the patient is on a gluten-free diet) are negative.

7. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA suggests obtaining routine biopsies of the normal-appearing duodenum for the detection of GVHD in post-allogeneic tissue transplantation patients and for opportunistic infections. *(Conditional recommendation; very low quality evidence)*.

There are no published data on the prevalence of GVHD in immunocompromised patients with dyspepsia and normal-appearing duodenum. Nevertheless, the endoscopic appearance of GVHD can be subtle in some cases, suggesting a potential diagnostic role of endoscopic biopsy in normal-appearing mucosa. In addition, based on very limited data, routine biopsies of the normal-appearing duodenum in immunocompromised patients might increase slightly the diagnostic yield of EGD for opportunistic infections. The inclusion or exclusion of GVHD, as well as early diagnosis of opportunistic infections, would have a clear impact on clinical management. Therefore, routine biopsy of normal duodenum in immunocompromised patients with a clinical suspicion for GVHD or opportunistic infection might be a reasonable practice, but a conditional recommendation is warranted because the magnitude of the potential benefit is likely small.

8. When biopsies are obtained from the normal-appearing duodenum, the AGA suggests not performing routine special staining of the specimens. *(Conditional recommendation; very low quality evidence)*.

Diagnosis of duodenal disorders generally does not require special staining. CD3 (T-cell marker) immunohistochemistry stains have been utilized in a number of studies to highlight intraepithelial T cells for the purposes of counting intraepithelial lymphocyte to enterocyte ratios. However, studies using H&E counting methods show results similar to those obtained using CD3 stains. Therefore, routine use of special staining in this setting is not recommended, but at the discretion of experienced pathologists, advanced staining can be considered in certain rare situations (eg, CD3 immunohistochemistry in suspected celiac disease with normal villous architecture).

Summary

This set of actionable recommendations was developed under the framework of the GRADE methodology as well the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines. It provides evidence-based practicing standards for the performance of upper gastrointestinal biopsy of normal-appearing mucosa in the evaluation of patients with dyspepsia. These standards are intended to reduce practice variation and promote high-value care. It is important to recognize that there are areas of scientific uncertainty due to low-quality evidence or absence of evidence associated with a number of the recommendations. We would like to encourage future research to address these evidentiary limitations. Accordingly, the AGA will continue to monitor and assess new and potentially relevant evidence to determine whether updating of these recommendations is justified.

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Conflicts of interest
The members were required to complete disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland and pertinent disclosures are published with the report.