

AGA Clinical Practice Update on the Diagnosis and Management of Atrophic Gastritis: Expert Review.

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The Best Practice Advice statements presented herein were developed from a combination of available evidence from published literature and consensus-based expert opinion. No formal rating of the strength or quality of the evidence was carried out. These statements are meant to provide practical advice to clinicians practicing in the United States.

Atrophic gastritis is defined as the loss of gastric glands, with or without metaplasia, in the setting of chronic inflammation mainly due to *Helicobacter pylori* infection or autoimmunity. Regardless of the etiology, the diagnosis of atrophic gastritis should be confirmed by histopathology.

Providers should be aware that the presence of intestinal metaplasia on gastric histology almost invariably implies the diagnosis of atrophic gastritis. There should be a coordinated effort between gastroenterologists and pathologists to improve the consistency of documenting the extent and severity of atrophic gastritis, particularly if marked atrophy is present.

Providers should recognize typical endoscopic features of atrophic gastritis, which include pale appearance of gastric mucosa, increased visibility of vasculature due to thinning of the gastric mucosa, and loss of gastric folds, and, if with concomitant intestinal metaplasia, light blue crests and white opaque fields. Because these mucosal changes are often subtle, techniques to optimize evaluation of the gastric mucosa should be performed.

When endoscopic features of atrophic gastritis are present, providers should assess the extent endoscopically. Providers should obtain biopsies from the suspected atrophic/metaplastic areas for histopathological confirmation and risk stratification; at a minimum, biopsies from the body and antrum/incisura should be obtained and placed in separately labeled jars. Targeted biopsies should additionally be obtained from any other mucosal abnormalities.

In patients with histology compatible with autoimmune gastritis, providers should consider checking antiparietal cell antibodies and anti-intrinsic factor antibodies to assist with the diagnosis. Providers should also evaluate for anemia due to vitamin B-12 and iron deficiencies.

All individuals with atrophic gastritis should be assessed for *H pylori* infection. If positive, treatment of *H pylori* should be administered and successful eradication should be confirmed using non-serological testing modalities.

The optimal endoscopic surveillance interval for patients with atrophic gastritis is not well-defined and should be decided based on individual risk assessment and shared decision making. A surveillance endoscopy every 3 years should be considered in individuals with advanced atrophic gastritis, defined based on anatomic extent and histologic grade.

The optimal surveillance interval for individuals with autoimmune gastritis is unclear. Interval endoscopic surveillance should be considered based on individualized assessment and shared decision making.

Providers should recognize pernicious anemia as a late-stage manifestation of autoimmune gastritis that is characterized by vitamin B-12 deficiency and macrocytic anemia. Patients with a new diagnosis of pernicious anemia who have not had a recent endoscopy should undergo endoscopy with topographical biopsies to confirm corpus-predominant atrophic gastritis for risk stratification and to rule out prevalent gastric neoplasia, including neuroendocrine tumors.

Individuals with autoimmune gastritis should be screened for type 1 gastric neuroendocrine tumors with upper endoscopy. Small neuroendocrine tumors should be removed endoscopically, followed by surveillance endoscopy every 1–2 years, depending on the burden of neuroendocrine tumors.

Providers should evaluate for iron and vitamin B-12 deficiencies in patients with atrophic gastritis irrespective of etiology, especially if corpus-predominant. Likewise, in patients with unexplained iron

or vitamin B-12 deficiency, atrophic gastritis should be considered in the differential diagnosis and appropriate diagnostic evaluation pursued.

In patients with autoimmune gastritis, providers should recognize that concomitant autoimmune disorders, particularly autoimmune thyroid disease, are common. Screening for autoimmune thyroid disease should be performed.

Atrophic gastritis (AG) is a preneoplastic condition defined by replacement of appropriate gastric glandular structures with connective tissue (nonmetaplastic atrophy) or a different, non-native epithelium (metaplastic atrophy) on a background of chronic inflammation. 1 – 3 AG is considered the first of a multistep precancerous cascade, with more advanced stages including gastric intestinal metaplasia (IM), dysplasia, and ultimately gastric adenocarcinoma. 4 The 2 most common etiologies of AG are chronic infection with *Helicobacter pylori* and autoimmunity, with the former recognized as the dominant etiology. It is important for providers to recognize the broad spectrum of clinical manifestations of AG, which includes both gastric and extragastric manifestations. 5

The estimated prevalence of AG is up to 15% in US populations, and may be greater in specific populations with a higher baseline prevalence of *H pylori* or incidence of gastric adenocarcinoma, such as non-White racial/ethnic minority groups and early-generation immigrants from high-risk countries. 6 – 12 AG is typically asymptomatic and may go undiagnosed, or with nonspecific symptoms that may occur later in the course. 13 In addition, the inconsistent reporting of AG on histopathology contributes to the underdiagnosis of this condition. Based on a meta-analysis, the rate ratio of AG incidence in patients with vs without *H pylori* infection was 5.0 (95% confidence interval, 3.1–8.3) and AG incidence was very low (<1% annually) among *H pylori* –uninfected individuals, supporting the strong relationship between *H pylori* and AG. 10 Other risk factors for nonautoimmune AG include age, tobacco use, high-salt diet, and possibly chronic bile acid reflux. 14 , 15

Autoimmune gastritis (AIG) is significantly less common than *H pylori* –associated AG (HpAG). The prevalence has been estimated to approximate 0.5%–2%, although this might be an overestimation. 16 – 18 The prevalence increases with age and the presence of other autoimmune diseases (eg, autoimmune thyroid diseases and type 1 diabetes mellitus). 19 For example, it is estimated that up to one-third of patients with autoimmune thyroid disease have AIG. 20 Women have a higher prevalence of AIG compared to men. In marked contrast to HpAG, racial and ethnic variation is not prominent in AIG. 19 Pernicious anemia (PA)—a late-stage complication of AIG characterized by megaloblastic anemia due to vitamin B-12 deficiency 19 —is even rarer, with an estimated prevalence of 0.15%–1%. 18 , 21

The estimates for the risk of progression from AG to high-grade dysplasia or gastric adenocarcinoma vary widely and reflect the heterogeneity of study populations and study design. It is estimated that the risk of progression of AG to gastric adenocarcinoma ranges from 0.1 % to 0.3 % per year (similar to the estimated rate of malignant progression from nondysplastic Barrett's esophagus or low-risk colorectal adenomas), but may be higher, depending on AG severity, extent, concomitant IM, and other factors. 22 – 24 As a late-stage manifestation of AIG, the diagnosis of PA identifies patients who have had corpus-predominant AG for at least several years. One meta-analysis of 27 studies demonstrated a nearly 7-fold significantly higher relative risk of gastric cancer in patients with vs without PA; although most individual studies suggest a 2- to 4-fold higher risk. 25

Patients with chronic AG, particularly AIG given the corpus-predominant atrophy, are also at increased risk of type I NETs. 26 These tumors develop as a consequence of the parietal cell loss, which leads to reduced gastric acid secretion and downstream persistent hypergastrinemia, enterochromaffin-like cell (ECL) hyperplasia, and, in a small percentage, ECL dysplasia and gastric NETs. 27 Based on longitudinal cohort studies, the incidence rate of type I gastric NETs in patients with chronic AG is estimated as 0.4–0.7% per year, 26 , 28 with variability across the literature. 29 – 31

The pathogenesis of AG involves the interaction between environmental and genetic determinants to a varying extent depending on the primary trigger, namely H pylori infection vs autoimmunity. In some individuals, chronic H pylori gastritis can advance to atrophy (loss of gastric glands) with or without replacement by metaplastic epithelium. In AIG, autoantibodies against parietal cells and intrinsic factor along with T-cell-mediated destruction of the gastric oxyntic mucosa leads to the characteristic pattern of corpus-predominant atrophy with antral sparing that distinguishes AIG from HpAG. That said, overlap exists between these phenotypes, both related to pathogenesis (eg, molecular mimicry between H pylori antigens and the gastric H⁺/K⁺ ATPase has been proposed as a trigger for AIG 19 , 32) and clinical considerations. 19 Regardless of the etiology, the diagnosis of AG should be confirmed by histopathology (Figure 1A – H) (Best Practice Advice [BPA] 1).

AG is a slow process, in which, after years of mucosal inflammation, gastric glands gradually decrease in size and may disappear completely. The glands may be replaced with connective tissue (nonmetaplastic atrophy, usually referred to as atrophy) or with a different type of epithelium (metaplastic atrophy, ie, IM or pseudopyloric metaplasia). IM is the most frequently diagnosed histopathologic manifestation of AG.

In HpAG, atrophic changes arise initially in the incisura and the antrocorpal transitional mucosa as small foci with loss of glands and IM. Over time, these foci coalesce to form larger patches of atrophic/metaplastic mucosa along the lesser curvature and the antrum, and eventually spread to the corpus/fundus, followed by the loss of gastric acidity. In AIG, the typical histologic manifestation is corpus-predominant AG, with destruction of individual oxyntic glands by lymphocytes. 33 In both conditions, there may be progressive loss of oxyntic glands, and increasingly prominent pseudopyloric and IM. ECL hyperplasia and type 1 gastric NETs can develop, indicating a state of hypergastrinemia. 34 , 35 If antral atrophy is seen in AIG, concomitant HpAG should be considered. If the anatomic location of the biopsies is uncertain, special stains (eg, gastrin [antrum], pepsinogen I [corpus]) may discriminate between antral mucosa and pseudopyloric metaplasia, which can be avoided if the biopsy specimens from the corpus and antrum/incisura are placed in separate specimen jars following the updated Sydney protocol (discussed below).

In clinical practice, the ability to report AG depends on presentation of antral and corpus biopsy specimens in separate jars, and correct orientation of the specimens during the paraffin-embedding process. Of note, gastric IM is readily identified irrespective of mucosal thickness of the biopsy specimen and orientation.

Severity and topographic distribution of atrophic lesions are well-established determinants of gastric cancer risk. These prognosticators are incorporated in 2 classification systems for risk assessment: Operative Link for Gastritis Assessment (OLGA) and Operative Link for Gastric Intestinal Metaplasia Assessment (OLGIM) (see Supplementary Figure 1A and B for details). 36 , 37 Both OLGA and OLGIM are advocated by international guidelines for risk stratification of individuals diagnosed with precancerous gastric mucosal changes 38 , 39 ; however, reporting of OLGA/OLGIM stage has not gained a foothold in clinical practice in the United States. Barriers to routine incorporation in practice should be identified and addressed. At the very least, providers should be aware that the presence of IM on gastric histology almost invariably implies the diagnosis of AG, and the presence of extensive atrophy and metaplasia are associated with an increased cancer risk. 40 There should be a coordinated effort between gastroenterologists and pathologists to improve the consistency of documenting AG severity and extent, particularly if marked atrophy is present (BPA 2).

The endoscopic appearance of AG may be subtle. Endoscopists should perform a high-quality examination following a systematic approach in order to maximize diagnostic yield. First, endoscopists should ensure excellent mucosal visualization, which necessitates adequate air insufflation and mucosal cleansing, and should spend sufficient time carefully examining the gastric mucosa. 41 , 42 Defoaming and mucolytic agents, such as simethicone and 1 % N-acetylcysteine, may be considered because water irrigation alone may be insufficient for mucosal washing. 43 – 45

The entire gastric lumen should be examined for the overall appearance of the mucosa, including the color and texture, appearance of submucosal blood vessels, and the architecture of the gastric rugae, followed by targeted examinations of focal abnormalities using high-definition white-light endoscopy (HD-WLE) or image-enhanced techniques, such as narrow-band imaging (NBI). Photographic documentation should be obtained to cover the cardia and fundus, lesser and greater curvature of corpus and antrum, incisura angularis, and pylorus (Figure 2).

Providers should recognize that HpAG and AIG have different patterns of gastric mucosa involvement. In the former, the atrophy typically initiates in the gastric antrum and expands proximally, and may involve the entire stomach in severe cases. In 1969, Kimura and Takemoto proposed a classification system for AG based on the extent of the atrophic border. 46 In this system, gastric atrophy is categorized as closed (C) or open (O) type, each with a grade based on the extent of atrophic border (Supplementary Figure 2). Multiple reports have consistently demonstrated that severe or extensive atrophy (O2–O3 types) has significantly higher cumulative risk of gastric cancer compared with mild atrophy (C1–C2 types) 47 – 49 ; these findings are concordant with those based on OLGA/OLGIM systems described above. In AIG, because of the destruction of parietal cells by autoantibodies, the areas of atrophy primarily involve the gastric corpus and fundus with characteristic sparing of the antrum. In the early phase of the AIG, the mucosal changes are usually subtle except for nonspecific erythema, and the diagnosis of AIG can be missed without taking biopsies. 17 With progressive loss of parietal cells, the mucosa of the entire gastric body appears atrophic.

Compared to conventional WLE, HD-WLE offers significantly improved sensitivity for identifying premalignant mucosal changes (Figure 2). 50 – 52 Atrophic mucosa typically has a pale appearance, with increased visibility of submucosal blood vessels due to thinning of the gastric mucosa and loss of gastric folds (BPA 3). Frequently, a border of atrophic mucosa can be identified (Figure 2). In a Swedish study, the sensitivity and specificity of absence of rugal folds for moderate to severe AG in the gastric corpus were 67 % and 85 %, respectively. 53 A combination of magnifying endoscopy and chromoendoscopy or image-enhanced techniques (eg, NBI) provides more detailed evaluation of gastric mucosa and microvascular architecture. Although magnifying endoscopy is not routinely available in the United States, the near-focus function of the newer-generation HD endoscopes, which are available in the United States, does provide better differentiation of mucosal abnormalities compared to the older-generation HD-WLE 54 (Figure 2).

Because IM is an indicator of AG, providers should similarly be able to recognize endoscopic features of IM (BPA 3). Compared to AG, IM can be more reliably identified using HD-WLE, with the sensitivity further improved with image-enhancing technology, such as NBI. 52 , 55 , 56 Relevant to US practice, prospective multicenter study using HD-WLE with NBI showed a sensitivity and specificity of 87% and 97% for the diagnosis of IM and 92% and 99% for the diagnosis of dysplasia, even without using magnifying endoscopy. 57 On HD-WLE, the areas with IM typically appear mildly nodular with ridged or tubulovillous mucosal patterns. 52 , 57 The “light blue crest” (LBC) sign, defined as fine, blue-white lines on the crests of the epithelial surface (Figure 2G), is characteristic for IM, with sensitivity and specificity approximately 90%, and positive and negative likelihood ratio 8.98 and 0.12, respectively, based on one meta-analysis. 58 , 59 The so-called white opaque fields (or “white opaque substance”) (Figure 2D), which is the result of microscopic lipid droplets that accumulate in the mucosa of gastric tumors and IM, is also a useful marker for IM, with high specificity (100%; 95% confidence interval, 85%–100%) and limited sensitivity (50%; 95% confidence interval, 40%–50%) in 1 study. 60

In the United States, the diagnosis of AG requires histopathologic confirmation. Because of the higher risk in patients with extensive AG vs AG limited to the antrum, providers should follow the updated Sydney protocol for obtaining topographical biopsies. 3 This protocol has close to 100% sensitivity in identifying *H pylori* colonization as well. 61 The protocol requires 5 gastric biopsies, which should be placed in separately labeled jars 3 : 2 from the antrum along the lesser and greater curvature, within 2–3 cm of the pylorus; 2 from the gastric corpus (including 1 from the lesser curvature at 4 cm proximal to the incisura angularis and the other from the middle portion of the

greater curvature of the gastric body at 8 cm from the cardia), and 1 from the incisura angularis. Because AG/IM frequently involves the incisura angularis, providers should not skip this site when obtaining biopsies. 62 – 64 If the cost incurred by separating each of these sites is a concern, at a minimum the biopsies should be placed in 2 separate specimen jars labeled antrum/incisura and body. Targeted biopsies should be obtained from any visible mucosal abnormalities and placed in appropriately labeled specimen jars (BPA 4).

Serum pepsinogens (PGs) reflect both the functional and morphologic status of the gastric mucosa and are useful markers of extensive atrophy. 65 Chief and mucous neck cells in the gastric corpus and fundic glands secrete both PG I and PG II, while PG II (but not PG I) is also produced by pyloric glands and Brunner's glands. At least in regions with high gastric cancer incidence (with most studies from East Asia), PG I levels ($<70 \mu\text{g/L}$) and low PG I:II ratio (<3.0) demonstrate a high sensitivity and specificity for severe corpus atrophy. 66 However, PG testing is not available for routine clinical use in the United States.

In patients with histology compatible with AIG, providers should check parietal cell antibodies (PCAs) and intrinsic factor antibodies (IFA) to assist with the diagnosis (BPA 5). PCA is the most sensitive serum biomarker for AIG, but false positives are not uncommon, as PCA can be elevated in H pylori infection and other autoimmune diseases. 19 , 67 IFA has low sensitivity ($<30\%$ in many studies) but high specificity, and is more often positive later in the disease course. 32 , 68 Autoantibody positivity might also predate clinical presentation of AIG, particularly in individuals with other autoimmune disorders. 19 , 69

The vast majority of patients with AG have evidence of current or prior infection of H pylori . 70 , 71 Irrespective of etiology, patients with AG should be tested for H pylori and, if positive, H pylori should be eradicated. Subsequent non-serologic H pylori testing should be performed to confirm successful eradication (BPA 6). Normal gastric mucosa may be restored over time in some patients with AG after successful H pylori eradication, 72 although most patients may have passed a "point-of-no-return" in which the gastric mucosal damage cannot be reversed despite H pylori eradication. 73 For these patients, their risk remains elevated, particularly among those with extensive or moderate to severe atrophy (eg, OLGA/OLGIM III/IV), providing the clinical rationale for endoscopic surveillance even after successful H pylori eradication, a practice supported by international guidelines (Supplementary Table 1). Nevertheless, despite persistent signs of AG, H pylori eradication does still appear to reduce the risk of gastric cancer. 74

Overall, only a small minority of patients with AG will have neoplastic complications. There is a lack of prospective, randomized controlled trials to support the benefits of performing routine surveillance endoscopy for patients with AG, namely reduced gastric cancer–related morbidity and mortality. However, multiple observational studies consistently demonstrate a strong association between severe AG (based on histology, anatomic distribution, or OLGA/OLGIM III/IV stages) and increased risk of gastric adenocarcinoma; this provides the justification for endoscopic surveillance for these patients to increase the likelihood of detection of gastric cancer at an early stage when resection with curative intent is possible. 37 , 75 – 79 In addition to risk stratification for gastric neoplasia, endoscopic surveillance in patients with AG should also consider comorbidities, as well as patient values and priorities. 80 , 81 Providers should consider performing endoscopic surveillance every 3 years in patients with advanced AG. However, it should be recognized that optimal surveillance intervals remain to be determined, and shorter or longer intervals may be appropriate depending on individual risk assessment (BPA 7). An algorithm for clinical management of AG is shown in Figure 3 .

Additional risk factors that should be considered for informing surveillance intervals include the quality of baseline endoscopy, family history of gastric cancer, immigration history from geographic regions with high incidence of gastric cancer, persistent H pylori infection, smoking history and dietary factors, among others. 80 , 82 This risk stratification-based approach is overall consistent with current guidelines from different professional societies on surveillance for chronic AG and GIM (Supplementary Table 1).

The optimal surveillance strategy for individuals with AIG is unclear (BPA 8). The current European Society for Gastrointestinal Endoscopy guidelines advocate performing surveillance endoscopy at 3–5 years in patients with AIG. 38 In patients with PA, observational studies suggest that the risk of gastric adenocarcinoma might be highest within the first year of diagnosis. Reflective of this, the American Society of Gastrointestinal Endoscopy advocates that an upper endoscopy be performed within 6 months of the diagnosis of PA. 83 The development of upper gastrointestinal symptoms in patients with PA should also prompt diagnostic endoscopy (BPA 9).

Gastric NETs associated with AG represent approximately 80%–90% of all gastric NETs and are overwhelmingly categorized as type 1. 84 Small NETs are typically asymptomatic and often diagnosed incidentally. These usually appear as small to tiny nodules <10 mm and are most often found at the gastric corpus or fundus; they are typically well-differentiated with an indolent course. 85 – 88 Endoscopically, they present as polypoid lesions in slight yellow or red color on HD-WLE (Figure 2H – I). The prognosis is determined by the size, depth of invasion, and mitotic activity of the tumor. The rate of metastasis is <10% in gastric NETs ≤2 cm but approaches 20 % in NETs >2 cm. 89 Small gastric NETs <1 cm are generally amenable to endoscopic resection. The optimal interval for endoscopic surveillance has not been well defined. Providers should resect all small NETs <1 cm endoscopically, and should consider surveillance endoscopy every 1–2 years, depending on the burden of NETs (BPA 10). For gastric NETs >1–2 cm, providers should consider endoscopic ultrasound to assess depth of tumor invasion and presence of local metastasis to help guide further management. 90 Surgical resection is appropriate for NETs >2 cm, with invasion past the submucosa, or with evidence of lymph node metastasis. 89 , 90

Patients with corpus-predominant AG, irrespective of etiology, are at an increased risk of developing iron and vitamin B-12 deficiency due to reduced gastric acid secretion and intrinsic factor. Iron deficiency is common, with some series reporting this in up to 50% of patients with corpus-predominant AG, and often presents much earlier than the manifestation of B-12 deficiency. 19 Providers should therefore evaluate for iron and vitamin B-12 deficiency in patients with AG, especially if corpus-predominant; likewise, in patients with unexplained iron or vitamin B-12 deficiency, AG should be considered in the differential diagnosis and appropriate diagnostic evaluation pursued (BPA 11).

Providers should recognize that there is an established association between AIG and other autoimmune diseases, especially autoimmune thyroid disease, perhaps related to shared genetic susceptibility loci. 91 – 93 Screening for autoimmune thyroid disease should be considered in patients diagnosed with AIG. Providers should also have a low threshold to evaluate for other associated autoimmune diseases, including type 1 diabetes mellitus and Addison's disease, if the clinical picture is consistent 94 (BPA 12).

Providers should recognize AG as an important, albeit frequently underdiagnosed, condition with both gastric and extragastric manifestations. Patients with severe AG should be considered for endoscopic surveillance for the purpose of early gastric cancer detection and may require additional management considerations, including attention to micronutrient deficiencies, particularly iron and vitamin B-12 deficiencies. Coordinated efforts between gastroenterologists and pathologists are needed to improve the diagnosis and characterization of AG. In addition, collaborative efforts are also needed, particularly in the form of comparative clinical trials in US populations, in order to refine risk stratification algorithms and optimize surveillance strategies for patients with AG.

This Expert Review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Update Committee and external peer review through standard procedures of Gastroenterology .

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European Society of Gastrointestinal Endoscopy

Helicobacter pylori –associated atrophic gastritis

Operative Link for Gastric Intestinal Metaplasia Assessment

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Typical endoscopic appearance of chronic AG, IM, and gastric NET. Characteristic endoscopic features of chronic AG include pale appearance of mucosa, loss of gastric rugal folds, and prominence of submucosal blood vessels due to thinning of the atrophied gastric epithelium, as shown in (A) HD-WLE and (B) NBI. Changes representing IM are frequently found in chronic AG (C – G). On HD-WLE, the areas with IM typically appear mildly nodular (C). On magnifying NBI (D), characteristic signs of IM include the LBC (white arrowhead) and white opaque field (WOF,

yellow arrowhead) (or white opaque substance [WOS]). The LBC sign refers to the fine, blue-white lines on the crests of the epithelial surface, which correspond to histologic finding of the brush border (microvilli). The WOF (or WOS) is caused by light scattering at microscopic lipid droplets that accumulate in the mucosa of IM. Both LBC and WOF/WOS signs are best visualized using magnifying NBI. IM in the flat gastric mucosa is shown in (E) (nonmagnifying NBI image). (F, G) Magnified views of IM (white square [E]) with and without NBI, respectively, with abundant LBCs visible in (G). Note that areas of IM with LBC coexist with non-IM mucosa (right upper corner of [G]). (H) and (I) demonstrate endoscopic appearance of gastric NETs on HD-WLE (H) and near-focus NBI (I).

Algorithm for clinical management of AG.