

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia



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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the gastrointestinal evaluation of iron deficiency anemia (IDA). The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that provides a detailed synthesis of the evidence from which these recommendations were formulated.¹ For a better understanding of this guideline, we recommend reading the accompanying technical review. The technical review, guideline, and clinical decision support tool are available on the AGA website (www.gastro.org) free of cost.

Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding. Members of the Guideline Panel and Technical Review Panel were selected by the AGA Clinical Guidelines Committee Chair after careful consideration of all relevant conflict of interests and in accordance with the National Academy of Medicine (formerly the Institute of Medicine) standards for trustworthy guidelines. The guideline and accompanying technical review underwent independent peer review and were disseminated broadly during the 30-day open public comment period; comments were collated by the AGA staff and were reviewed and carefully considered by the Guideline Panel and technical review teams, respectively. All comments were addressed in an internal response document or incorporated as revisions to the final documents. In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guideline Committee meeting for new information. The next update for these guidelines is anticipated 3 years from publication (2023).

Anemia is a common diagnosis in both men and women, and iron deficiency is the most common cause of anemia worldwide. In the United States in 1999–2000, 2% of men aged 16–69 years, 12% of women aged 12–49 years, and 9% of women aged 50–69 years were iron deficient, and 4% of women aged 20–49 years and 3% of women aged 50–69 years had IDA.² The overall prevalence of IDA in North America in 2010 was estimated at 2.9%.³ The etiology of

IDA can include suboptimal oral intake, poor absorption of oral iron, and/or chronic blood loss from gastrointestinal and other sources. Gastrointestinal malignancy is the most serious potential cause, although other etiologies, such as peptic ulcer disease, celiac disease, inflammatory bowel disease, or other gastrointestinal tract lesions, can be detected and treated, potentially improving quality of life and patient-important outcomes.

Normal total body iron content varies between 3000 and 4000 mg, the majority of which is found in red blood cells (ie, in hemoglobin); a smaller amount of iron is found in storage compartments, including hepatic macrophages, resident bone marrow cells, and others. Iron is also bound to transferrin and other proteins, such as myoglobin, or in its storage forms as ferritin or hemosiderin. Most dietary iron absorption occurs in the duodenum and proximal jejunum. About 1–2 mg of iron is lost daily through desquamation of skin and enteric cells or through minor blood loss, which in normal individuals is balanced through intestinal absorption of dietary iron. Excess iron loss can occur through gastrointestinal bleeding, urinary losses, shedding of skin cells, or other sources of blood loss (eg, menstrual bleeding). In most adults without an obvious source of blood loss, evaluation of the gastrointestinal tract for a source of chronic blood loss or a malabsorptive process is indicated.

There is significant practice variability in the initial gastrointestinal evaluation of IDA, with uncertainty about the proper diagnostic criteria for iron deficiency in patients with anemia, the type and sequence of diagnostic evaluation with endoscopy or noninvasive testing, the utility of investigations, such as routine gastric biopsies to detect *Helicobacter pylori* infection or autoimmune atrophic gastritis,

Abbreviations used in this paper: AGA, American Gastroenterological Association; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IDA, iron deficiency anemia; PICO, population, intervention, comparator, outcome.

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and the need for routine duodenal biopsies to detect celiac disease. In addition, the proper diagnostic evaluation likely differs according to the underlying risk of serious gastrointestinal diseases, such as malignancy, in men and women of different ages. The aim of this guideline is to outline an evidence-based approach to the initial diagnosis and evaluation of this commonly encountered clinical condition.

Scope

In developing this guideline, the Panel prioritized clinical questions focused on the diagnosis of IDA as well as the initial gastrointestinal evaluation of chronic IDA. The target audience for this guideline includes health care professionals (primary care providers, gastroenterologists, and other specialists), policy makers, and patients. This guideline does not provide recommendations for evaluation of patients with refractory IDA despite appropriate initial evaluation and iron supplementation or recurrent IDA after initial iron repletion, due to the lack of robust evidence in the medical literature in these clinical scenarios. In patients with refractory IDA, consultation with hematology may be appropriate. In addition, management of obscure gastrointestinal bleeding, defined as persistent or recurrent bleeding of unknown origin after an appropriate endoscopic evaluation, is outside the intended scope of this guideline.

Methods

The guideline was developed as described previously.⁴ Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices as outlined by the National Academy of Medicine, formerly Institute of Medicine.⁵ As described in detail in the technical review accompanying this guideline, clinically relevant questions for diagnosis and management of IDA were identified and framed using the PICO format, which defines a specific population (P), intervention (I), comparator (C), and outcome (O). Using the GRADE framework, recommendations are formulated based on the strength of the available evidence (Table 1), risks and benefits of different management pathways, patient preferences and values, and resource use (Table 2).⁴ Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review.¹ The Guideline Panel and the authors of the technical review met

face-to-face on April 30, 2019 and via teleconference on October 7, 2019 to discuss the findings from the technical review and develop the recommendations. All recommendations were based on consensus among the Guideline Panel members and voting was not performed. After the meeting, the Guideline Panel independently finalized the recommendations in this guideline document. The recommendations, quality of evidence, and strength of recommendations are summarized in Table 3.

Recommendations

In patients with anemia, the AGA recommends using a cutoff of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency. Strong recommendation, high-quality evidence.

Comment: In patients with inflammatory conditions or chronic kidney disease, other laboratory tests such as C-reactive protein, transferrin saturation, or soluble transferrin saturation, may be needed in conjunction with ferritin to diagnose iron deficiency anemia.

In adults with anemia, defined as hemoglobin <13 g/dL in men and <12 g/dL in nonpregnant women,⁶ determining whether the anemia is due to iron deficiency is an important step to guide appropriate diagnostic evaluation, as the evaluation of anemia without iron deficiency will differ substantially. Serum ferritin is the most commonly used test for diagnosing iron deficiency, with proposed cutoff values ranging from 15 to 100 ng/mL. Studies that use bone marrow biopsy as the gold standard for diagnosis of iron deficiency have defined the sensitivity and specificity of ferritin levels at different cutoff values. The choice of an optimal cutoff value involves a tradeoff between sensitivity and specificity at different ferritin levels. Therefore, the Technical Review Panel aimed to determine the optimal cutoff value of ferritin that would identify most patients who truly have iron deficiency (eg, maximizing sensitivity), while also providing an acceptable false-positive rate (eg, acceptable specificity) so as to best define the appropriate population in which evaluation is warranted. Optimizing the threshold ferritin level with high sensitivity will detect the great majority of patients who are truly iron deficient, minimize delays in diagnostic workup, and minimize the number of patients in whom serious underlying etiologies, such as gastrointestinal malignancy,

Table 1. Grading of Recommendations Assessment, Development and Evaluation Definitions for Quality of Evidence (or Certainty of Evidence)

| Quality of evidence | Definition |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 may 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 |

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

| 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. |
| 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 may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision. |

In some patients, such as those with chronic inflammatory conditions or chronic kidney disease, ferritin levels may not accurately reflect body iron stores. In these situations, other clinical tests, such as the serum iron, transferrin saturation, soluble transferrin receptor, or C-reactive protein, may be useful adjunctive tests to assist in the diagnosis of iron deficiency. We did not specifically address threshold ferritin values to diagnose iron deficiency in non-anemic patients. In addition, some patients with or without iron deficiency may have gastrointestinal symptoms that would necessitate endoscopic evaluation regardless of the diagnosis of iron deficiency.

The overall quality of evidence for this recommendation was rated as high. The underlying studies are potentially at risk for bias because of the patient populations included, which did not clearly differentiate between symptomatic and asymptomatic patients.

In asymptomatic postmenopausal women and men with iron-deficiency anemia, the AGA recommends bidirectional endoscopy over no endoscopy. Strong recommendation, moderate-quality evidence.

The AGA recommends bidirectional endoscopy, including both esophagogastroduodenoscopy and colonoscopy, over no endoscopy to evaluate asymptomatic postmenopausal women and men with IDA. Bidirectional endoscopy should be performed at the same setting in these patients. This recommendation does not apply to patients who may have gastrointestinal symptoms; these patients should be evaluated by integrating the symptoms into the clinical picture. In addition, this recommendation assumes there is no other unequivocal explanation for IDA, particularly in young men, after a thorough history and physical examination. Underlying etiologies, such as frequent blood donation, nutritional deficiencies (eg, vegan or vegetarian diet), nongastrointestinal blood loss, and malabsorption syndromes should be considered and evaluated as indicated.

The Technical Review Panel identified no comparative studies of the outcomes of bidirectional endoscopy vs simple clinical observation or empiric oral iron therapy alone in any patient population. Therefore, the Guideline Panel relied on indirect evidence in formulating this recommendation. Evidence was derived from observational cohort and cross-sectional studies of the frequency of gastrointestinal findings in patients with IDA, randomized studies of endoscopic screening for colorectal cancer, and studies evaluating the risks of complications after endoscopic procedures. Pooled estimates from 18 studies on the diagnostic yield of bidirectional endoscopy in postmenopausal women and men with IDA showed detection of lower gastrointestinal malignancy in 8.9% (95% CI, 8.3%–9.5%) and upper gastrointestinal malignancy in 2.0% (95% CI, 1.7%–2.3%) of individuals.¹ These studies likely overestimate the underlying prevalence of malignancy because of referral bias and inclusion of symptomatic as well as asymptomatic patients. However, the overall evidence strongly suggests that the underlying risk of malignancy is several-fold higher than in an asymptomatic colorectal cancer screening cohort. As a

might be missed. However, there are potential downsides or harms associated with evaluation of IDA, including adverse events from endoscopic procedures and higher health care utilization and cost. Therefore, the chosen threshold level also needs to have adequate specificity to minimize the number of false-positive diagnoses.

As outlined in the technical review, based on a systematic review of 55 studies, a ferritin threshold value of <45 ng/mL has a sensitivity for iron deficiency of 85% (95% confidence interval [CI], 82%–87%) with a specificity of 92% (95% CI, 91%–94%).⁷ In contrast, a ferritin value of <15 ng/mL has a sensitivity of only 59% (95% CI, 55%–62%) and specificity of 99% (95% CI, 89%–99%). A ferritin threshold value of <45 ng/mL was believed to maximize sensitivity for the diagnosis of IDA with an acceptable number of false-positive diagnoses. The tradeoff between higher sensitivity and lower specificity using a threshold of 45 ng/mL instead of 15 ng/mL was believed to provide an acceptable balance of benefits of fewer missed diagnoses compared with potential harms of additional diagnostic evaluations.

comparison, a recent meta-analysis found a prevalence of colorectal cancer of 0.8% (95% CI, 0.4%–0.7%) in individuals age 50 years and older.⁸

High-quality evidence from randomized controlled trials of flexible sigmoidoscopy^{9,10} showed that endoscopic screening reduces colorectal cancer incidence and mortality. Indirectly, this suggests that detection of colorectal cancer through endoscopic evaluation of patients with IDA is important, particularly with the ongoing advances in therapy for colorectal cancer and subsequent improvements in survival. Although data on the stage distribution of gastrointestinal tract malignancy in patients with IDA are lacking, it is plausible that overall stage distribution will be somewhat later than in an asymptomatic screening cohort, potentially attenuating the benefits of earlier diagnosis seen in screening populations. There is no comparable direct evidence applicable to screening for upper gastrointestinal malignancy. Nevertheless, detection of colorectal or upper gastrointestinal cancer is a patient-important outcome regardless of its impact on mortality.

Bidirectional endoscopy is invasive, but the overall risk of complications is small for both upper endoscopy and colonoscopy.^{11–16} In men and women older than 50 years, screening colonoscopy is already recommended in patients regardless of the presence of anemia, and the added risk of an upper endoscopy is likely minimal. Overall, the high prevalence of gastrointestinal malignancy in IDA suggests that endoscopic evaluation will lead to detection of malignancy with potential for improvement in cancer outcomes, particularly for colorectal cancer. Lastly, other potential etiologies, such as erosive esophagitis, peptic ulcer disease, celiac disease, and inflammatory bowel disease, may be detected by bidirectional endoscopy. The benefits of detection of gastrointestinal disorders and malignancy in this patient population were thought to outweigh the small risks of bidirectional endoscopy.

The overall quality of evidence for this recommendation was moderate, and its rating was downgraded for indirectness due to availability of only observational studies of the diagnostic yield of bidirectional endoscopy and differences in patient population compared to the randomized trials of screening flexible sigmoidoscopy. Studies of diagnostic yield of bidirectional endoscopy are at risk of bias due to potential referral bias.

In asymptomatic premenopausal women with iron deficiency anemia, the AGA suggests bidirectional endoscopy over iron replacement therapy only. *Conditional recommendation, moderate-quality evidence.*

Comment: Patients who place a high value on avoiding the small risk of endoscopy, particularly those who are young and might have other plausible reasons for iron deficiency anemia, and a low value on the very small risk of missing a gastrointestinal malignancy would reasonably select an initial course of iron replacement therapy and no initial bidirectional endoscopy.

The AGA suggests bidirectional endoscopy over iron replacement therapy alone for asymptomatic

premenopausal women with IDA. This recommendation assumes that there is no other unequivocal explanation for IDA, particularly in younger women, after a thorough history and physical examination. Similar to postmenopausal women and men, etiologies such as frequent blood donation; other sources of blood loss, including menstrual blood loss, malabsorption syndromes; and nutritional deficiencies should be considered and investigated as indicated. Women with gastrointestinal symptoms should be evaluated as appropriate. In these patients, bidirectional endoscopy should be performed in the same setting.

In the technical review, no randomized studies comparing bidirectional endoscopy with iron replacement therapy in this patient population were identified, and the Guideline Panel relied on observational studies of the diagnostic yield of endoscopic evaluation and the harms of endoscopic evaluation to formulate this recommendation. Pooled evidence from 10 studies showed detection of lower gastrointestinal malignancy in 0.9% (95% CI, 0.3%–1.9%) and upper gastrointestinal malignancy in 0.2% (95% CI, 0%–0.9%) of premenopausal women with IDA. These are likely overestimates of the underlying prevalence of malignancy due to inclusion of symptomatic patients in the study cohorts. As a comparison, a recent meta-analysis found a prevalence of colorectal cancer of 0.1% (95% CI, 0%–0.1%) in individuals younger than 50 years, but did not estimate incidence separately for men and women.⁸ It should also be noted that the incidence of colorectal cancer has increased in younger cohorts recently.¹⁷ We did not find reliable data to define the risk of gastrointestinal malignancy in premenopausal women at different ages or with different degrees of anemia, but the prevalence of either upper or lower gastrointestinal malignancy will decrease with decreasing age in this population.

The risks of bidirectional endoscopy are likely to be small in this patient population and probably vary with patient age. Although data on endoscopy complications are limited in younger individuals, the risk of serious complications of screening and surveillance colonoscopy increases with age.^{11–13} Women in the younger age groups are likely at very low risk of endoscopic complications.

Given the lack of direct data on both the prevalence of gastrointestinal malignancy and endoscopic complications in premenopausal women, it is difficult to estimate the balance of the risks compared with the potential benefits of bidirectional endoscopy. In particular, there are insufficient data to suggest a specific age or ferritin cutoff for premenopausal women who might reasonably select iron supplementation and monitoring before bidirectional endoscopy. However, particularly at younger ages, the benefit of endoscopy to detect the extremely rare gastrointestinal malignancies is likely diminished compared with the risks. Evidence that more clearly weighs benefits and harms of bidirectional endoscopy in this situation is lacking. In addition, the role of fecal occult blood testing to determine need for endoscopy in this situation is not well studied. Therefore, clinicians should discuss the tradeoff between the very small risks of a missed gastrointestinal malignancy if bidirectional endoscopy is deferred vs the small risks of endoscopy in this patient population, and shared decision making on the value of endoscopy

Table 3. Executive Summary Table of Recommendations

| Recommendation | Strength of recommendation | Quality of evidence |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------|
| In patients with anemia, the AGA recommends using a cutoff of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency. Comment: In patients with inflammatory conditions or chronic kidney disease, other laboratory tests such as C-reactive protein, transferrin saturation, or soluble transferrin saturation, may be needed in conjunction with ferritin to diagnose iron deficiency anemia. | Strong | High |
| In asymptomatic postmenopausal women and men with iron deficiency anemia, the AGA recommends bidirectional endoscopy over no endoscopy. | Strong | Moderate |
| In asymptomatic premenopausal women with iron deficiency anemia, the AGA suggests bidirectional endoscopy over iron replacement therapy only. Comment: Patients who place a high value on avoiding the small risk of endoscopy, particularly those who are young and might have other plausible reasons for IDA, and a low value on the very small risk of missing a gastrointestinal malignancy would reasonably select an initial course of iron replacement therapy and no initial bidirectional endoscopy. | Conditional | Moderate |
| In patients with iron deficiency anemia without other identifiable etiology after bidirectional endoscopy, the AGA suggests noninvasive testing for <i>Helicobacter pylori</i> , followed by treatment if positive, over no testing. | Conditional | Low |
| In patients with iron-deficiency anemia, the AGA suggests against the use of routine gastric biopsies to diagnose atrophic gastritis. | Conditional | Very Low |
| In asymptomatic adult patients with iron deficiency anemia and plausible celiac disease, the AGA suggests initial serologic testing, followed by small bowel biopsy only if positive, over routine small bowel biopsies. Comment: Celiac disease is a well-recognized cause of iron deficiency anemia, even in asymptomatic patients, and, therefore it must be considered in the differential diagnosis of iron deficiency anemia. | Conditional | Very Low |
| In uncomplicated asymptomatic patients with iron deficiency anemia and negative bidirectional endoscopy, the AGA suggests a trial of initial iron supplementation over the routine use of video capsule endoscopy. Comment: Caution needs to be applied in patients with comorbid conditions where the identification of small bowel pathology will change medical management, such as the use of anticoagulation and/or antiplatelet therapy. | Conditional | Very low |

is needed. For example, women who place high value on avoiding the small risks of endoscopy and low value on the very small risk of missing a gastrointestinal malignancy may reasonably elect to pursue initial iron therapy over bidirectional endoscopy, particularly if they are young and have other plausible etiologies of the IDA. Further research is needed to define the risk of gastrointestinal malignancy as well as the diagnostic yield and adverse event rate from endoscopic procedures in this patient population.

The overall quality of evidence for this recommendation was rated as moderate due to indirectness and the availability of observational evidence only. Although there is modest benefit for detecting gastrointestinal malignancy, particularly in older premenopausal women, there is also a small risk of harm from endoscopic procedures. The balance between benefits and harms is dependent on age and other clinical considerations, and individualized decision making is needed.

In patients with iron deficiency anemia without other identifiable etiology after bidirectional endoscopy, the AGA suggests noninvasive testing for *H pylori*, followed by treatment if positive, over no testing. Conditional recommendation, low-quality evidence.

The AGA suggests noninvasive testing for *H pylori*, followed by treatment if positive, over no testing. *H pylori* can cause peptic ulcer disease and is graded as a class I carcinogen by the World Health Organization due to its association with gastric adenocarcinoma.¹⁸ *H pylori* infection is also associated with atrophic gastritis and hypochlorhydria, which can decrease iron absorption. An association between *H pylori* infection and iron deficiency has been demonstrated in observational studies.¹⁹ Therefore, it has been hypothesized that treatment of *H pylori* infection may lead to improvement in iron deficiency.

Based on the technical review, pooled analysis of 3 randomized controlled trials showed greater improvement in mean hemoglobin in patients tested and treated for *H pylori* in conjunction with iron replacement compared with those who received iron replacement alone (mean difference, 2.2 g/dL greater improvement in hemoglobin; 95% CI, 1.3–3 g/dL).¹ In these studies, the mean improvement in ferritin was 23.2 ng/mL (95% CI, 12.2–34.3 ng/mL) greater in the *H pylori* treatment with iron replacement therapy group compared with those who received iron replacement alone. Two of these 3 randomized controlled trials were conducted in children. Therefore, testing for *H pylori*, with treatment if positive, may assist in resolution of iron

deficiency. In addition, detecting and treating *H pylori* will likely have benefits beyond resolution of iron deficiency, such as decreasing the incidence of gastric cancer.²⁰

Given the benefit of identifying and treating *H pylori*, the Technical Review Panel examined different strategies for detecting this infection. Multiple methods for *H pylori* testing exist, including gastric biopsy and noninvasive tests such as serology, *H pylori* stool antigen testing, and urea breath testing.¹ Compared with a strategy of routine gastric biopsies in all patients, the overall cost savings of a strategy of urea breath testing after negative bidirectional endoscopy was substantial. The short-term harms of delayed diagnosis of *H pylori* in those with false-negative noninvasive testing were believed to be minimal. Therefore, a noninvasive testing strategy for *H pylori* after negative bidirectional endoscopy was believed to provide sufficient sensitivity and specificity with cost savings and few short-term harms, and is recommended over a strategy of routine gastric biopsies at the time of bidirectional endoscopy.

The quality of evidence for this recommendation was rated as low and was downgraded due to risk of bias, as the randomized controlled trials were not blinded. In addition, the randomized controlled trials included children primarily and evidence for benefits in adults is indirect. Lastly, there was serious imprecision in the effect estimates due to small sample size.

In patients with iron deficiency anemia, the AGA suggests against the use of routine gastric biopsies to diagnose atrophic gastritis. *Conditional recommendation, very-low-quality evidence.*

The AGA suggests against the use of routine gastric biopsies to diagnose autoimmune atrophic gastritis in patients with IDA. Atrophic gastritis can be associated with long-standing *H pylori* infection or can be autoimmune in etiology. Atrophic gastritis associated with *H pylori* is characterized by antral-predominant or pangastritis, with atrophy involving the antrum and potentially extending to the corpus. In autoimmune atrophic gastritis, the atrophic process is restricted to the gastric corpus, with metaplasia of the gastric body and fundus. Autoimmune atrophic gastritis leads to hypochlorhydria or achlorhydria due to destruction of parietal cells in the gastric body, potentially interfering with absorption of oral iron and subsequent IDA. In its later stages, this condition may also lead to vitamin B-12 deficiency. The diagnosis of autoimmune atrophic gastritis rests on biopsy analysis of the gastric antrum and corpus, although it can be suggested by the presence of hypochlorhydria or achlorhydria, elevated gastrin levels, and anti-parietal cell or anti-intrinsic factor antibodies. Some have suggested that a serologic panel, including gastrin levels and antibodies against *H pylori*, parietal cells, and intrinsic factor, can identify patients with potential autoimmune atrophic gastritis who might benefit from endoscopy and gastric biopsies. No proven therapy for this condition is available.

The Technical Review Panel identified 6 studies that reported the prevalence of autoimmune atrophic gastritis in

patients with IDA. The estimated pooled prevalence of this condition was 10.1% (95% CI, 7.6%–12.8%). However, available studies often did not differentiate atrophy due to *H pylori* infection from that due to autoimmune atrophic gastritis.¹ In addition, no evidence was found that earlier identification of autoimmune atrophic gastritis affects the clinical management of iron deficiency or long-term outcomes. Some observational studies have suggested that the risk of gastric adenocarcinoma and carcinoids may be elevated in this condition, although the degree of risk elevation is not clearly defined. The European Society of Gastrointestinal Endoscopy recommends considering endoscopic surveillance every 3–5 years, but this recommendation is based on low-level evidence.²¹

Given the lack of well-accepted management implications after a diagnosis of atrophic gastritis and insufficient evidence to demonstrate that earlier diagnosis improves patient outcomes, the use of routine gastric biopsies for this diagnosis is not supported. The use of a serologic panel to diagnose this condition would also be hindered by these concerns. The quality of evidence for this recommendation was rated as very low and was downgraded due to indirectness of the evidence, risk of bias, and inconsistency.

In asymptomatic adult patients with iron deficiency anemia and plausible celiac disease, the AGA suggests initial serologic testing, followed by small bowel biopsy only if positive, over routine small bowel biopsies. *Conditional recommendation, very-low-quality evidence.*

Comment: Celiac disease is a well-recognized cause of iron deficiency anemia, even in asymptomatic patients, and therefore it must be considered in the differential diagnosis of iron deficiency anemia.

The AGA suggests initial serologic testing, with small bowel biopsy only if positive, over routine small bowel biopsies in asymptomatic patients with IDA and plausible celiac disease. Patients with symptoms suggestive of celiac disease should be evaluated appropriately. Although celiac disease is a well-recognized cause of iron deficiency, consensus on the optimal diagnostic strategy in this clinical scenario is lacking. In the technical review, no randomized or observational studies were identified directly comparing routine small bowel biopsies in asymptomatic patients to targeted workup based on serologic testing and symptoms.¹ The Guideline Panel used studies on the prevalence of celiac disease in patients with IDA, the accuracy of noninvasive diagnostic testing in the general population, and the costs of small bowel biopsies and serologic testing in formulating this recommendation.

The Technical Review Panel compared different diagnostic strategies to identify celiac disease with sufficient sensitivity and specificity and accounting for potential harms and costs.¹ A strategy of serologic testing for celiac disease, followed by small bowel biopsies only if positive, would diagnose the large majority of patients with celiac disease with minimal short-term harm and overall cost-savings. This strategy was cost-saving compared with the

common practice of obtaining routine small bowel biopsies at the time of bidirectional endoscopy or a strategy of obtaining serologic testing after negative bidirectional endoscopy. Overall, the balance of expected benefits, harms, and costs was believed to favor initial serologic testing unless the prevalence of celiac disease is >5% in the population under consideration.

Some special considerations may alter the balance of risks and harms for these different strategies. First, epidemiologic risk factors and clinical features will alter the clinician's suspicion of underlying celiac disease. For example, celiac disease is comparatively uncommon in individuals from minority groups in the United States or in East Asian countries (eg, Japan and China). Second, suspicion for celiac disease would be increased in patients with a positive family history, a personal history of autoimmune diseases such as type 1 diabetes, or gastrointestinal symptoms. The balance of benefits, harms, and costs would change in patients with higher-risk features. In these patients, routine small bowel biopsies may be a reasonable approach, and the diagnostic strategy should be approached with shared decision making. Next, small bowel biopsies should also be taken if the duodenum appears abnormal at the time of initial upper endoscopy. Finally, if the initial serologic testing was negative, the possibility of celiac disease should be reconsidered if iron deficiency persists despite an adequate trial of iron supplementation.

The overall quality of evidence was rated as very low due to potential selection bias in the studies examining the prevalence of celiac disease in IDA. It was also rated down for indirectness, as no comparative studies of the benefits and harms of the different diagnostic approaches were identified.

In uncomplicated asymptomatic patients with iron deficiency anemia and negative bidirectional endoscopy, the AGA suggests a trial of initial iron supplementation over the routine use of video capsule endoscopy. *Conditional recommendation, very-low-quality evidence.*

Comment: Caution needs to be applied in patients with comorbid conditions where the identification of small bowel pathology will change medical management, such as the use of anticoagulation and/or antiplatelet therapy.

In asymptomatic patients with IDA and negative bidirectional endoscopy, the AGA suggests a trial of initial iron supplementation over the routine use of small bowel video capsule endoscopy. No studies that directly compared small bowel investigation of any type with iron replacement therapy or clinical observation were identified, and no direct evidence that performing video capsule endoscopy reduces the risk of adverse outcomes was found. The Technical Review Panel considered studies of the diagnostic yield of small bowel evaluation in the absence of overt gastrointestinal bleeding in formulating this recommendation.

In the technical review, pooled analysis of 16 studies of the diagnostic yield of video capsule endoscopy found that small bowel malignancy was identified in 1.3% (95% CI, 0.8%–1.8%).¹ However, these studies were believed to be at very serious risk of bias due to the potential for referral bias and the inclusion of symptomatic patients. The diagnostic yield for malignancy in asymptomatic patients without overt gastrointestinal bleeding could not be determined from available evidence, and the diagnostic yield for other outcomes, such as inflammatory bowel disease, small bowel ulcers or erosions, and vascular lesions is also unknown. In addition, available studies did not include an appropriate gold standard to define the sensitivity and specificity of video capsule endoscopy. Finally, whether video capsule endoscopy leads to any change in clinical management in a clinically meaningful proportion of patients is unclear. Therefore, the evidence required to evaluate the benefits of video capsule endoscopy in IDA is not currently available.

Given the uncertainty about diagnostic yield and effect on overall clinical management in asymptomatic patients without overt gastrointestinal bleeding, as well as concerns about resource utilization, the routine use of video capsule endoscopy is not well supported. Evidence on use of fecal occult blood testing to determine need for endoscopic evaluation is lacking. A trial of adequate iron supplementation with further small bowel investigation only if iron deficiency persists may provide similar clinical outcomes, although no direct comparisons are available. Evidence on the utility of other methods of small bowel investigation, including computed tomography or magnetic resonance enterography, small bowel follow through, tagged red blood cell scintigraphy, push or deep enteroscopy, and angiography was also lacking, and did not allow for formal evidence synthesis.

This recommendation does not apply to patients who have symptoms suggestive of small bowel disease or at higher risk of small bowel pathology, such as patients with increased propensity for small bowel angioectasias, in whom diagnostic video capsule endoscopy might otherwise be indicated. Similarly, video capsule endoscopy may be indicated in select circumstances where identification of small bowel pathology may alter medical management. Examples include patients who use anticoagulation or antiplatelet medications, in whom identification of a bleeding lesion may be important for prognostic or management purposes. Likewise, patients with anemia refractory to adequate iron supplementation may be appropriate candidates for video capsule endoscopy. Also, as mentioned, this recommendation does not apply to hospitalized patients with acute or acute on chronic anemia who may warrant small bowel evaluation after negative bidirectional endoscopy due to the acute nature of anemia and potential need for transfusions.

The quality of evidence for this recommendation was rated as very low due to lack of properly designed comparative or outcomes studies, the possibility of selection or referral bias in the available studies of diagnostic yield,

and the lack of a reference standard in the studies of diagnostic yield of video capsule endoscopy.

Question: How should iron supplementation be managed?

Although the Technical Review Panel initially considered a PICO question on this topic, this question was ultimately determined to be outside the scope of this guideline. Although no formal recommendation is provided for this question, clinicians should recognize that several formulations of both oral and intravenous iron are available with varying costs and side effects. In most patients, an initial trial of oral iron supplementation should be given, as it is generally effective, available, inexpensive, and safe. There is no strong evidence that any of the available oral formulations is more effective or better tolerated than the others.²² However, gastrointestinal intolerance to oral iron supplements is common, and patients with malabsorption syndromes may have limited response. Historically, a daily dose of 150–200 mg of elemental iron has been recommended, but some studies suggest that lower dosing or every-other-day dosing may improve tolerability and absorption.^{23,24} Taking iron supplements with food or using enteric-coated formulations may improve tolerability but decrease absorption. Vitamin C co-administration is commonly recommended to improve oral absorption, although the evidence supporting this practice is limited.²⁵ A response (with improvements in hemoglobin concentration) to oral iron supplementation is typically evident within 1 month of treatment. If such a response is not seen, assessment for nonadherence (due to side effects or other reasons), malabsorption, or ongoing blood loss exceeding iron intake is needed.

Intravenous iron may be appropriate in selected patients, such as those with impaired absorption due to prior gastric surgery, with inflammatory bowel disease or chronic kidney disease, or in whom blood loss exceeds the ability to replete iron orally.²⁶ Consultation with a hematologist is often helpful when intravenous iron repletion is required.

Future Research Needs and Evidence Gaps

Several gaps in current knowledge were identified. In premenopausal women, better understanding of the prevalence of serious gastrointestinal lesions at different ages and severity of IDA, as well as the risks of bidirectional endoscopy, is needed to inform providers about the utility of endoscopic evaluation. The role of fecal occult blood testing to determine need for endoscopic evaluation also needs further investigation. The balance of benefits and harms of gastrointestinal evaluation also needs better definition in other patient subgroups, such as patients of different ages, with different degrees of IDA, or with other clinical risk factors. Larger well-designed studies in adults should further define the utility of testing and treating for *H pylori* infection either before or after bidirectional endoscopy.

Similarly, comparative outcome and cost-effectiveness studies of initial serologic testing for celiac disease vs routine small bowel biopsy are needed.

A large evidence gap is apparent regarding the outcomes and proper techniques of small bowel investigation in patients with negative bidirectional endoscopy. Well-designed studies of the diagnostic yield of video capsule endoscopy and comparative studies of outcomes of initial iron replacement vs small bowel investigation would guide future practice. In addition, there is little evidence about the role of fecal occult blood testing and the comparative efficacy of various methods of small bowel investigation, such as video capsule endoscopy, deep enteroscopy, or magnetic resonance/computed tomography enterography, in this clinical scenario. Future studies that define patient subgroups that are likely to benefit from small bowel investigation are clearly needed. Finally, further research on the utility of repeating the diagnostic evaluation in patients with persistent or recurrent IDA and negative prior evaluation is needed.

Discussion

These practice recommendations for the initial gastrointestinal evaluation of IDA were developed using the GRADE framework, with the goal of promoting high-quality and high-value care. IDA is extremely common worldwide, and a gastrointestinal cause should be considered in all patients without an obvious etiology. There are some meaningful differences between this guideline and the British Society of Gastroenterology guideline, which does not recommend bidirectional endoscopy for premenopausal women who do not have symptoms suggesting gastrointestinal disease, a strong family history of colorectal cancer, or age older than 50 years.²⁷ The British guidelines also suggest that the order of endoscopic evaluation in postmenopausal women and men should be determined by the presence of symptoms and local availability of endoscopy, and that either colonoscopy or computed tomography colonography may be used for colonic evaluation. In contrast, the AGA recommends bidirectional endoscopy as the mainstay for gastrointestinal evaluation, particularly in men and in postmenopausal women for whom no other unequivocal source of iron deficiency has been identified. The outcomes and value of bidirectional endoscopy in asymptomatic premenopausal women suggest a benefit of bidirectional endoscopy over no endoscopy, but particularly in younger women, individualized decision making to balance the potential benefits of detecting a serious gastrointestinal condition vs the potential harms of endoscopy is needed. Additional etiologies that should be considered and evaluated with noninvasive testing include *H pylori* infection and celiac disease. Although other small bowel etiologies are often considered in patients with negative bidirectional endoscopy, they are relatively rare, and an initial trial of iron replacement therapy rather than routine small bowel investigation is suggested.

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Conflicts of interest

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Access

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