AGA Technical Review on Gastrointestinal Evaluation of Iron Deficiency Anemia

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Iron deficiency anemia (IDA) is the commonest cause of anemia in the United States and worldwide. In the United States, it has been estimated that some 5%–11% of women and 1%–4% of men are iron deficient, and approximately 5% and 2%, respectively, have IDA.[1] Although the cause of IDA may include inadequate iron intake or absorption, which are common in children and premenopausal women, IDA in adult men and postmenopausal women is often the result of chronic occult gastrointestinal bleeding.

Although iron homeostasis is complicated, a basic understanding of its biology is important in the context of IDA (see Fleming,[2] Ganz and Nemeth,[3] Camaschella,[4] and Anderson and Frazer[5] for review). In brief, non-heme iron is absorbed primarily in the proximal small intestine (the absorption of heme iron is poorly understood), although active absorption is via the divalent metal transporter-1, which is expressed in the proximal duodenum (Figure 1). It is well recognized that in some forms of gastric bypass in which the typical iron-absorbing segment of the duodenum is bypassed, iron malabsorption ensues.

The ferroportin/hepcidin axis is also critically important in iron homeostasis. Hepcidin, a 25-amino acid peptide produced by hepatocytes via complex regulatory mechanisms, is distributed via the circulation to its target sites, where it binds to its receptor, ferroportin. Ferroportin is highly expressed at the basolateral surface of duodenal enterocytes, where it acts as a cellular iron exporter. Increased levels of hepcidin limit membrane insertion of ferroportin, blocking iron exit, with iron-laden enterocytes sloughed during their natural cycle of epithelial renewal, serving as a primary mechanism for removal of excess iron. Therefore, when the body is iron replete, hepcidin concentrations are high and iron delivery to the circulation is reduced. In contrast, in the iron-deficiency state, hepcidin levels are low and there is active iron delivery to the circulation.

Important regulators of hepcidin, and therefore of systemic iron homeostasis, include plasma iron concentrations, body iron stores, infection and inflammation, and erythropoiesis. Disturbances in the regulation of hepcidin contribute to the pathogenesis of many iron disorders. For example, hepcidin deficiency causes iron overload in hereditary hemochromatosis and non-transfused β-thalassemia, whereas overproduction of hepcidin is associated with iron-restricted anemias seen in patients with chronic kidney disease, chronic inflammatory diseases, some cancers, and inherited iron-refractory IDA.

Under normal conditions, iron homeostasis is tightly regulated.[6,7] Typical daily elemental iron loss is 0.25–0.75 mg from iron lost via sloughing of intestinal epithelial cells and microscopic gastrointestinal bleeding. With daily blood loss of 0.5–1.5 mL/d, a stool weight of 150 g, and circulating hemoglobin of 15 g/dL, stool hemoglobin concentration is 0.5–1.5 mg/g. In aggregate, the average daily iron loss is approximately 1 mg (Figure 1), which is precisely balanced by the same amount of iron absorption. Because the absorptive capacity of the small intestine for iron can increase in response to iron depletion, iron deficiency results only when iron loss exceeds the absorptive capacity of the small bowel. It is critical to emphasize that iron absorption is not only complex as highlighted above, but is limited (see Abbaspour et al[8] and Camaschella[9] for review), so that iron depletion only occurs when intestinal absorptive capacity of iron is outstripped by iron loss.

The degree to which blood can be "hidden" in the gastrointestinal tract is emphasized by the observation that although instillation of 50–100 mL of blood into the stomach may produce melena, patients losing 100 mL of blood per day may have grossly normal-appearing stools.[10,11] This concept is consistent with the clinical observation that truly occult bleeding is a common cause of IDA.

Virtually any gastrointestinal tract lesion that causes a mucosal defect can bleed enough to lead to occult blood loss and therefore cause IDA. Indeed, the clinical spectrum of IDA is broad because many different lesions occurring in many different sites in the gastrointestinal tract are capable of bleeding in an occult manner.[11,12] Endoscopic evaluation of patients with IDA has shown that nearly two-thirds of patients will have lesions identified in the gastrointestinal tract that are believed to be capable of causing occult bleeding (Figure 2).[13] Although gastrointestinal tract malignancies, especially right-sided colonic cancers, have historically been considered to be the most common and important lesions identified during endoscopy, cancers have been identified in patients with IDA in all

parts of the gastrointestinal tract and, furthermore, the most common causes of occult bleeding in patients with IDA are inflammatory ulcerative upper gastrointestinal tract lesions (Figure 2).[13] Only a small proportion of patients will be found to have a lesion capable of occult bleeding and causing IDA in each the upper and lower gastrointestinal tract simultaneously[14] (Figures 2 and 3). Notwithstanding, because of the propensity for a variety of gastrointestinal tract lesions to bleed in an occult fashion, the standard of care for postmenopausal women and men with IDA is to evaluate the gastrointestinal tract in search of a bleeding lesion.[13]

Although the effectiveness of fecal occult blood tests (FOBTs) has been well validated for use in colon cancer populations, the use of FOBTs in other populations has been more controversial. In theory, because FOBTs detect occult bleeding, it is possible that they may be useful in detection of occult bleeding in patients with IDA.[15–23] In a systematic review of the use of FOBTs in patients with IDA, it was found that the sensitivity of FOBTs for presumptive causes of IDA detected at endoscopy was 0.58 (95% confidence interval [CI], 0.53–0.63), with a specificity of 0.84 (95% CI, 0.75–0.89).[23] Results were similar in both guaiac-based testing and fecal immunochemical testing. Given this poor sensitivity and specificity, the Panel did not believe that the result of an FOBT would substantially influence the decision as to whether to perform endoscopy or not, and it was decided not to specifically address the use of FOBT in the evaluation of IDA. This assessment should not preclude future consideration of the use of FOBT in an algorithm in certain populations of patients with IDA.

This technical review will not discuss the details of the presentation of anemia, but rather will focus on the diagnosis and evaluation of IDA. This review will also not address patients with overt gastrointestinal bleeding. In patients with IDA, blood loss is typically chronic and occult, and therefore rarely associated with overt bleeding or hemodynamic compromise, unless the lesion responsible for chronic occult bleeding begins bleeding aggressively. Indeed, a syndrome of acute on chronic gastrointestinal bleeding, in which patients known to have IDA spontaneously develop acute bleeding, has been recognized.[24] Recognition of this entity emphasizes the wide spectrum of lesions in many different locations in the gastrointestinal tract that can bleed, and that often present with highly variable clinical features.

Despite the publication of a number of observational studies focused on IDA, and the presence of several scholarly reviews, there remains a great deal of controversy about best practices in the evaluation and management of IDA. Although it is well-appreciated that occult gastrointestinal bleeding is likely to be responsible for IDA in postmenopausal woman and in men, and therefore endoscopy is warranted, best practices regarding the type of endoscopy and the appropriate evaluation for *Helicobacter pylori*, celiac disease, atrophic gastritis, and of the small bowel, are not well established.

Given a number of questions surrounding the most appropriate approach to the gastrointestinal evaluation of IDA, the American Gastroenterological Association Institute called for a technical review of the clinical spectrum of IDA, with a focus on optimal evaluation and management approaches. The main purpose was to critically review

studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and to generate summary evidence and estimates for the Guidelines Panel to develop evidence-based recommendations.

It should be noted that this technical review does not address evaluation of patients with iron deficiency without anemia. In addition, it does not specifically address the evaluation of patients with IDA and prominent gastrointestinal symptoms (eg, dysphagia, odynophagia, abdominal pain, diarrhea, change in bowel habit, and intermittent hematochezia). These patients should be evaluated as indicated based on their gastrointestinal symptoms. It should be emphasized that a careful history is fundamentally important in these patients because subtle symptoms are often present and should be sought after. The guideline addresses the gastrointestinal evaluation of IDA primarily in patients without dominant gastrointestinal tract symptomatology, who we have considered asymptomatic.

Although iron replacement therapy is an important consideration in IDA patients, the Review Panel believed that addressing the type of iron therapy and route of treatment (ie, oral vs intravenous administration) was outside the scope of this review. We look forward to future guidelines, perhaps in collaboration with hematological societies, to address this important issue.

Methods

The technical review and its accompanying guideline were conducted according to the GRADE framework.[25] The American Gastroenterological Association Clinical Guideline Committee selected the members of the Technical Review and Clinical Guideline Panels who were screened to minimize any conflict of interest. The technical review collected and evaluated pertinent literature concerning the diagnosis and endoscopic evaluation of IDA, as well as appropriate investigations for *H pylori*, celiac disease, atrophic gastritis, and of the small bowel. Using these data, the Clinical Guideline Panel produced the final set of recommendations, as described.[26]

Formulation of Clinical Questions

The Technical Review and Guideline Panel formulated the clinical questions using the PICO format, which frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcome(s). The Panel finalized 5 questions on the topic (Table 1).

When direct evidence to inform any of the PICO questions was not available, we identified indirect evidence. We aimed to define the prevalence of gastrointestinal neoplastic and/or malignant lesions, celiac disease and/or small intestinal villous atrophy, *H pylori* infection, and chronic atrophic autoimmune gastritis in patients with IDA. We aimed to define the diagnostic accuracy of ferritin cutoffs, as well as tissue transglutaminase (TTG) IgA antibodies to diagnose celiac disease in patients with IDA.

The Systematic Review Process

Before conducting any systematic review, we identified systematic reviews published on any of the PICO questions. If we could not identify any systematic review or the available systematic reviews had low methodological quality, we conducted a de novo systematic review for the PICO question. The systematic review is reported according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) proposal.[27,28] The Technical Review Panel developed a protocol to guide the systematic review a priori.

Literature Search Strategy

Under the guidance of the Technical Review Panel, an experienced medical librarian conducted a comprehensive search of the following databases from prespecified start dates to April 2019: MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, EMBASE Classic, EMBASE, and Wiley's Cochrane Library. The prespecified start dates of the date range of the search and the study designs of interest were determined by the Technical Review Panel for each PICO question separately. The search was limited to English and human studies. Controlled vocabulary and keywords were used to search for the studies. The final search strategies are available in Appendix 1. To assure comprehensiveness, the reference lists of previously published systematic reviews, clinical guidelines, and the included studies were searched to identify other relevant studies that may have been missed by the search strategy.

Eligibility Criteria

We aimed to include randomized controlled trials (RCT) and/or nonrandomized comparative studies of different diagnostic and/or intervention strategies for each of the PICO questions. When we could not identify any RCT or nonrandomized comparative studies, we tried to identify diagnostic test accuracy studies of the different diagnostic strategies. If none of the aforementioned study designs was available, we included single cohort and prevalence studies to inform rates of occurrence (ie, prevalence or incidence rates).

Except for PICO 1 (the diagnostic accuracy of ferritin for IDA), we aimed to include studies of patients with IDA without overt gastrointestinal bleeding. Due to the scarcity of data on asymptomatic patients and to account for the variability seen in clinical practice, we included studies regardless of FOBT, the severity of anemia, and the presence of symptoms. Studies that included patients with overt gastrointestinal bleeding were included only if they reported separate results for patients without overt bleeding.

For studies of celiac disease, we only included studies from the United States due to the variable prevalence of celiac disease between countries.[29] Except for studies from large databases, we only included studies that diagnosed celiac disease based on biopsies.

Study Selection and Data Extraction

The references identified by the search strategy were uploaded to *Rayyan*, a web-based platform for the initial steps of systematic reviews.[30] The title and abstract of each reference were reviewed by 2 blinded reviewers for inclusion. The full texts of eligible references were

reviewed then abstracted using Microsoft Excel sheets. The outcomes of interest for each PICO question are summarized (Table 1).

Data Synthesis

When comparative studies were available, we used the DerSimonian-Liard random-effects model to pool their relative risks.[31] To pool the proportions from prevalence studies, we used the double arcsine transformation with the inversevariance the fixed-effects model.[32] We used this approach to allow larger studies, which are more inclusive than smaller studies and less prone to selection bias, to have an appropriately larger effect on the pooled estimates. We used the I^2 statistic to quantify heterogeneity with a threshold of 50% for comparative relative effect estimates as an indicator of substantial heterogeneity.[33] We assessed for publication bias using funnel plot asymmetry tests if there was a sufficient number of studies with no significant heterogeneity.[34] The statistical analyses were conducted using the package *meta* 4.9–2 in R 3.5.3.[35,36]

Assessing the Quality of the Evidence

The risk of bias for the individual studies was assessed depending on the study design. RCTs and nonrandomized comparative studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and the Newcastle-Ottawa Scale, respectively.[37,38] For single cohort studies and studies of prevalence, we used the Joanna Briggs Institute tool for assessing risk of bias in prevalence studies.[39]

We used the GRADE approach to assess the certainty (quality) of evidence for the body of evidence from the systematic reviews and meta-analyses. In this approach, the evidence is graded for each outcome as very low, low, moderate, or high. Evidence derived from RCTs start at a high certainty of evidence, but then is rated down for risk of bias, inconsistency, indirectness, imprecision, and/or other factors. Evidence derived from observational studies starts at low certainty of evidence, but certainty in the evidence can be rated up for large magnitude of effect and/or the presence of dose–response relationship, where appropriate.[25]

Evidence to Decision Framework

As this technical review was conducted to inform clinical practice guidelines, in addition to the comprehensive critical evaluation of the available evidence on risk and benefits of the different interventions and diagnostic tests, we also considered information about patients' preferences and values, resource utilization, and cost-effectiveness when available. Because we were unable to identify evidence to support one evaluation and management approach over another, we performed simple modeling analyses to assess the utility of different ferritin thresholds, serologic tests or biopsy for celiac disease, and noninvasive tests or biopsy for *H pylori* using reimbursement data from the Centers for Medicare and Medicaid Services as a surrogate for the costs to compare them (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/index).

The Importance of Establishing an Accurate Diagnosis of Iron Deficiency Anemia

Quality of evidence and summary.—The certainty in the evidence with regard to the use of ferritin to make a diagnosis of iron deficiency is high, suggesting that this test be used to make the diagnosis of IDA. We used a commonly defined threshold of a hemoglobin level <13 g/dL in men and <12 g/dL in nonpregnant women for anemia. A ferritin level of 45 ng/mL was identified to have the optimal tradeoff between sensitivity and specificity for the diagnosis of IDA (Table 2).

Because anemia is a common clinical condition and its diagnosis can lead to invasive testing, it is essential to verify the presence of anemia as well as iron deficiency. Although different societies and organizations have proposed different cutoffs for anemia, here we have defined anemia as a hemoglobin level <13 g/dL in men and <12 g/dL in nonpregnant women.[40] There is also often considerable controversy about how best to make a diagnosis of IDA. The distinction between IDA and other types of anemia is important because a diagnosis of IDA often prompts further evaluation. Therefore, we aimed to define a threshold for a laboratory test, to be used to define IDA and initiate gastrointestinal tract workup. The gold standard test to make a diagnosis of IDA is bone marrow biopsy. However, this test is invasive, cumbersome, and not commonly performed to evaluate IDA. In contrast, several blood tests, including mean corpuscular volume, transferrin saturation, and ferritin, have been commonly used to diagnose IDA. Mean corpuscular volume, although obtained routinely, lacks both sensitivity and specificity for the diagnosis of IDA. Transferrin saturation is often difficult to use in clinical practice, largely because patients with chronic disease have falsely low transferrin levels and interpretation of iron saturation in this setting is imprecise. In contrast, ferritin, depending on its level, is both sensitive and specific.[41]

A false-negative ferritin level could label an iron-deficient anemic patient to be iron sufficient, leading to a delay in workup, including possibly missing an important gastrointestinal tract lesion. In contrast, a false-positive ferritin value would label an iron-sufficient anemic patient as having IDA and lead to unnecessary workup, which is costly and poses increased risk to the patient. We explored a ferritin threshold that minimizes false negatives without significantly increasing false positives.

We limited our search strategy to systematic reviews and meta-analyses (Appendix 1). The search identified 221 references, 217 of them were excluded based on title and abstract review, and only 1 met the inclusion criteria after reviewing the full texts.[41] This systematic review included 55 studies that evaluated different diagnostic methods, including mean corpuscular volume, transferrin saturation, and serum ferritin, and compared them with bone marrow biopsy. They extracted individual patient data to develop receiver operating characteristic curves and assessed diagnostic accuracy of the different tests at different thresholds. The study had low risk of bias based on the AMSTAR 2 tool. The key finding of this study was that ferritin had the highest likelihood ratio for the diagnosis of IDA.[41]

We examined the evidence surrounding ferritin cutoffs and IDA. Although ferritin levels from 0 to 100 ng/mL have been examined in the setting of IDA, we focused on clinically relevant levels—15 ng/mL and 45 ng/mL. At a level of 15 ng/mL, with bone marrow biopsy being the reference standard, the likelihood ratio for having IDA is 11.1[41] and the

sensitivity was 0.59 (95% CI, 0.55–0.62), with a specificity of 0.99 (95% CI, 0.89–0.99) (Appendix 2). A ferritin level of 45 ng/mL has a sensitivity and specificity for IDA of 0.85 (95% CI, 0.82–0.87) and 0.92 (95% CI, 0.91–0.94), respectively. Further, given the varied prevalence of IDA found across different populations within the United States, we modeled the performance of these cutoffs in typical populations of patients[42] (Appendix 2, Table 3). In each prevalence setting, we found there to be substantially more false negatives when a ferritin level <15 ng/mL was used, with only a modest gain in the reduction of false positives. For example, in a scenario in which the prevalence of IDA among 1000 anemic patients was 20%, using a ferritin of cutoff of 15 ng/mL would miss 48 patients with IDA or approximately one-quarter of all patients with true IDA (Tables 2 and 3). Increasing the cutoff from 15 ng/mL to 45 ng/mL would substantially reduce the false-negative rate, but also increases the number of false positives, which will lead to unnecessary endoscopies; however, this latter increase is expected to result in only a small number of severe complications downstream (eg, <1 perforation in a population of 1 million men and premenopausal women). This is likely to be offset by a substantial reduction in the number of missed colon and gastrointestinal cancers (Table 3). The data, however, point out that optimizing ferritin cutoff levels to increase sensitivity has limitations. Nonetheless, the evidence favors a cutoff value of 45 ng/mL to make an accurate diagnosis of IDA.

We also emphasize several caveats to the use of ferritin in clinical practice. First, patients with certain underlying conditions, particularly inflammatory diseases, may have falsely high ferritin levels because ferritin is an acute phase reactant.[43] For example, this has specifically confounded evaluation of IDA in patients with inflammatory bowel disease. In fact, some experts have proposed assessment of the degree of inflammation by using C-reactive protein to assess the degree of inflammation.[44] Although this approach is theoretically attractive in patients with mixed IDA and anemia of chronic disease—which can be a diagnostic dilemma, the Review Panel thought that additional testing beyond that recommended here would likely inadvertently complicate the evaluation process. Ferritin levels may also be difficult to interpret in patients with chronic kidney disease who have been often frequently transfused and may also have underlying inflammation. Additionally, ferritin levels cannot be reliably used to diagnose total iron stores in patients who have received recent blood transfusion or who are on oral or intravenous iron replacement therapy. In aggregate, it should be emphasized that before subjecting a patient to invasive procedures, the diagnosis of IDA should be as definitive as possible.

Bidirectional Endoscopy in Patients With Iron Deficiency Anemia

Quality of evidence and summary.—We identified moderate-quality indirect evidence supporting bidirectional endoscopy in patients with IDA, specifically multiple descriptive studies reporting the finding of endoscopic lesions in patients with IDA. Therefore, in patients with no obvious other source of chronic blood loss, available evidence suggests that the benefits of identifying an important lesion with bidirectional endoscopy outweighs the small risks associated with invasive testing (Table 4). Finally, in patients who have gastrointestinal symptoms, evaluation should be site-directed.

Because the presence of IDA in postmenopausal women (for the purposes of this discussion, postmenopausal refers to the ceasing of menstruation) or men is a sine quo non for occult gastrointestinal bleeding, endoscopic evaluation is a cornerstone of the evaluation of IDA. Bidirectional endoscopy refers to esophagogastroduodenoscopy (EGD) and colonoscopy. The prevalence of gastrointestinal culprit lesions varies depending on many factors, including age, underlying risk factors, and the presence of gastrointestinal symptoms (specific symptoms, eg, unintentional weight loss, anorexia, abdominal pain, heartburn, and/or change in stool character). To guide our recommendations, we aimed to assess the benefits and harms of bidirectional endoscopy. Because we could not identify any study, randomized or nonrandomized, that compared bidirectional endoscopy with observation or oral iron therapy alone in patients with IDA in any population group, we identified the following indirect evidence to assist the Panel in making decisions: we identified systematic reviews that evaluated the benefits of screening colonoscopy to no endoscopic evaluation[45,46]; we identified observational cohort and cross-sectional studies to assess the frequency (or "diagnostic yield") of finding gastrointestinal tract lesions, and most importantly malignancy, during bidirectional endoscopy in patients with IDA[15–20,42,47–66]; we identified studies that evaluated the rates of complications of gastrointestinal endoscopy[67–72]; and we used the available epidemiologic reports to model the expected benefit and harm of bidirectional endoscopy for the different age/sex groups (Table 4).[73,74]

Clinical Variables Important in Evaluation

Gastrointestinal symptoms in patients with IDA might[15,16,51] or might not[75,76] help direct gastrointestinal tract evaluation toward specific pathology. It is generally considered to be a best practice to consider gastrointestinal tract symptoms in the evaluation process—and it is essential that a careful history be taken. Endoscopy should generally be directed at the site of symptoms, which is desirable to minimize both risk and cost (see Figure 3). Because dual lesions are rare, identification of an obvious abnormality consistent with bleeding, such as a mass lesion, large ulceration, or severe inflammation that is a likely cause of the symptoms, makes further evaluation unnecessary. It should be emphasized that clinical judgment is important in assessing whether a specific lesion accounts for occult bleeding resulting in IDA. For example, it is highly unlikely that trivial gastrointestinal tract lesions bleed enough to cause IDA.[12] Although the choice of sequence of procedures (colonoscopy followed by upper endoscopy or vice versa) varies based on local practice, both procedures, if necessary, should be performed on the same day. If the patient has upper gastrointestinal tract symptoms, EGD should be performed initially. In the patient in whom EGD is performed initially and clearly identifies a bleeding lesion, there is some controversy about whether colonoscopy should or should not be performed. In this scenario, whether or not to perform colonoscopic evaluation should be individualized based on the risk and benefit of the procedure, and will depend on variables such as the risk that the patient may have an underlying colorectal cancer.

History and clinical signs should be used to help direct investigation toward localization of a putative bleeding site. A history of peptic ulcer disease increases the likelihood that this may explain the IDA. A history of liver disease raises the possibility of bleeding associated with

portal hypertension, including portal hypertensive gastropathy. A history of inflammatory bowel disease suggests bleeding from gastrointestinal tract ulceration. Ingestion of aspirin or other nonsteroidal anti-inflammatory drugs makes bleeding from ulceration more likely. Abdominal pain raises the possibility of an ulcerative process, other mucosal injury, or perhaps obstruction. Pain, anorexia, and/or weight loss point to malignancy. History is also critical in ascertaining whether an extra-intestinal site may be the source of gastrointestinal bleeding, especially from the nasopharynx or pulmonary system.

Physical examination may provide valuable information as to the cause of bleeding. Cutaneous signs (spider angiomata, Dupuytren's contractures) or other evidence of liver disease (splenomegaly, ascites, caput) suggest the possibility of portal hypertension. Acanthosis nigricans may reflect underlying cancer (particularly gastric cancer); cutaneous telangiectasias of skin and/or mucous membranes and lips raises the possibility of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu); pigmented lip lesions are seen with Peutz-Jeghers syndrome; cutaneous tumors suggest neurofibromatosis; and purpura is consistent with vascular disease (Henloch-Schönlein purpura or polyarteritis nodosa).

Evidence Supporting Bidirectional Endoscopy in Postmenopausal Women and Men

We focused on the outcome of identifying malignancy as an outcome, which is the most important clinical finding in most patients with IDA and is a critical concern in this setting. Although we could not identify any direct evidence from comparative studies using bidirectional endoscopy in men and postmenopausal with IDA, high-quality indirect evidence from screening trials (RCTs and nonrandomized studies) demonstrates substantial mortality reduction even in a setting with substantially lower baseline risk for colon cancer than found in IDA.[45,46] This provides at least moderate certainty in the evidence of benefit in the endoscopic evaluation for IDA.

We searched the literature for studies that reported the prevalence of gastrointestinal tract neoplasms in patients with IDA published in or after 1990. Our search strategy identified 922 references, 772 of them were excluded by reviewing the titles and abstract, and only 24 studies met the inclusion criteria after reviewing the full texts. Sixteen studies (9632 patients) reported the diagnostic yield of bidirectional endoscopy in men and postmenopausal women with IDA (Figure 4). Bidirectional endoscopy detected 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 largely men and postmenopausal women with IDA.[15,20,47–49,51–56,60–62,65,66]

It should be emphasized that this estimate is likely an overestimation due to the inclusion of some symptomatic patients in the reported cohorts (high risk of bias), which makes the exact baseline risk for malignancy in IDA uncertain in this risk group. Based on the available data, we have high certainty in the evidence that the risk of malignancy is many fold higher (up to 100-fold) than an average risk screening population of similar age.

In conclusion, in postmenopausal women and men with IDA, the Technical Review Panel identified evidence supporting bidirectional endoscopy over no endoscopy. This assumes that there is no other obvious source of chronic blood loss. Additionally, in patients with

IDA who also have gastrointestinal symptoms, evaluation should be site-directed. For patients in whom a definitive source of bleeding is identified in either the upper or lower gastrointestinal tract during initial endoscopic evaluation (see above and Rockey[13]), other portions of the gastrointestinal tract need not be routinely or obligatorily evaluated.

Should Bidirectional Endoscopy Be Performed in Premenopausal Women?

Quality of evidence and summary.—We identified moderate-quality indirect evidence supporting bidirectional endoscopy in premenopausal women with IDA, including descriptive studies reporting the finding of endoscopic lesions in patients with IDA. Therefore, in patients with no obvious other source of chronic blood loss (in particular, in women without abnormal menses), available evidence suggests that the benefit of bidirectional endoscopy outweighs the risk of no endoscopy (Table 5). In patients who have gastrointestinal symptoms, evaluation should be site-directed. Because there is very little evidence in younger premenopausal women, in the judgment of the Panel, the risk of endoscopy should be considered carefully.

IDA is commonly identified in premenopausal (defined as having menstruation) women. On one hand, blood loss through childbirth and menstruation may explain IDA in many patients (a careful history exploring menorrhagia and other gynecologic disorders that may be a potential source of abnormal blood loss is important). On the other hand, evidence suggests that this group of patients may harbor gastrointestinal tract lesions consistent with chronic occult bleeding leading to IDA.[16–19,50,57,58] Although we could not identify any direct evidence from comparative studies using bidirectional endoscopy in asymptomatic premenopausal women with IDA, high-quality indirect evidence from screening trials (RCTs and nonrandomized studies) demonstrate substantial mortality reduction, provided that the baseline risk for colon cancer does not fall substantially below established thresholds (ie, 0.6/1000 for 50-year-old woman at average risk without IDA).[45,46] This provides at least moderate certainty in the evidence of benefit in the endoscopic evaluation for IDA in premenopausal women. It should be noted that the benefit of endoscopy in IDA is likely to be diminished in younger patients and, therefore, the harms of endoscopy will likely outweigh the benefits at some age threshold.

We focused on the outcome of identifying malignancy as an outcome, which is critical for decision making in this setting. Our search strategy identified 9 studies (910 patients) that reported the diagnostic yield of bidirectional endoscopy in premenopausal women.[16–19,42,49,50,57,58] Bidirectional endoscopy detected lower gastrointestinal malignancy in 0.9% (95% CI, 0.3–1.9) and upper gastrointestinal malignancy in 0.2% (95% CI, 0.0–0.9) of premenopausal women with IDA (Figure 5). This estimate is likely an overestimation due to the inclusion of symptomatic women in the reported cohorts (high risk of bias). In addition, the number of studies identifying upper gastrointestinal tract malignancies was limited; together, these factors make it difficult to determine the precise baseline risk for malignancy in IDA in this risk group. Nonetheless, we are confident that the risk is substantially higher than the 0.6/1000 (0.06%) rate of malignancy expected in a 50-year-old woman at average risk without IDA—particularly in the mid to upper age range of premenopausal women. No reliable data are available with

which to further define this age threshold. Finally, in younger women with IDA, patient preferences regarding the risks and benefits of endoscopic evaluation should be considered carefully.

In conclusion, in asymptomatic premenopausal women, the currently available evidence suggests that bidirectional endoscopy provides benefit compared with no endoscopy. This approach assumes that there is no obvious other source of chronic blood loss, which is a particularly difficult assessment in many premenopausal women. The Panel also found evidence that suggests that in patients with IDA who also have gastrointestinal symptoms, evaluation should be site-directed.

Are Routine Gastric Biopsies for Helicobacter pylori *Indicated in Patients With Iron Deficiency Anemia?*

Quality of evidence and summary.—We identified low-quality evidence supporting noninvasive testing for *H pylori* in patients with IDA. Available evidence suggests that *H pylori* may cause IDA in select populations, in particular in pediatric populations. However, the role of *H pylori* as a causal factor for IDA in the majority of adult men and postmenopausal women is unclear. Therefore, given the associated cost of gastric biopsy and weak evidence to support the effectiveness of eradicating *H pylori* in adult patients with IDA, the Review Panel concluded that routine gastric biopsy and histologic assessment to detect *H pylori* is unlikely to be cost-effective (Table 6). A strategy of noninvasive testing for patients with negative colonoscopy and EGD appeared to be associated with reasonable benefit and less cost.

In addition to causing peptic ulcer disease and increasing the risk of gastric malignancies, *H pylori* causes atrophic gastritis and hypochlorhydria, which can lead to poor iron absorption and thus IDA. Observational studies have shown an association between iron deficiency and *H pylori* infection.[77] British guidelines have previously recommended testing and treating for *H pylori* in patients with recurrent IDA and negative bidirectional endoscopy.[78] Nonetheless, it should be emphasized that the role of *H pylori* as a causal agent in IDA is controversial.

We searched the literature for RCTs that evaluated the benefit of treating *H pylori* in patients with IDA. Our search identified 167 references, 32 of them were retrieved for full-text review based on title and abstract screening, and only 3 of them met the inclusion criteria[79–81] (Figure 6). To assist the Panel in decision making, we also identified systematic reviews of the prevalence of *H pylori* in the United States and the diagnostic accuracy of the different noninvasive tests for *H pylori* compared with gastric biopsies.[82–84]

We first evaluated testing strategies to evaluate for *H pylori*, including the accuracy and cost of various diagnostic approaches, focused on noninvasive tests (Appendix 3). At a fixed specificity of 90%, the urea breath test ^{13}C had the greatest sensitivity to detect active *H pylori* infection, followed by serologic testing and lastly stool antigen testing.[83] The estimated overall prevalence of *H pylori* in the United States is 35.6% (95% CI, 30.0%–41.1%).[82,84] In a hypothetical population of 1,000,000 adult patients, we estimated that 32,900 patients will have IDA. Of those, about 11,712 patients will have *H pylori* infection

based on the overall prevalence of *H pylori* in the United States. The use of urea breath testing to diagnose *H pylori* instead of obtaining biopsies routinely during endoscopy will lead to the accurate diagnosis of 3418 *H pylori*–infected patients and 142 *H pylori*–infected patients will be missed. False positives will lead to the treatment of 451 noninfected patients. Hence, an approach that starts by performing bidirectional endoscopy without routine gastric biopsies for the evaluation of asymptomatic IDA then testing for *H pylori* using urea breath testing for patients with negative bidirectional endoscopy will lead to missing 147 cases of *H pyl*ori (of 3560 based on 35.6% prevalence). Those missed cases can be diagnosed by repeating endoscopy with biopsies if an alternative source of IDA is not identified. Such an approach would lead to a major decrease in cost compared with obtaining biopsies routinely in the first bidirectional endoscopy encounter, with negligible risk (Appendix 3). Although not reported here, the cost of using alternative noninvasive tests with comparable diagnostic accuracy, such as *H pylori* stool antigen testing, is less than the cost of using urea breath testing. Hence, we believe that the use of the available noninvasive tests, which have comparable diagnostic accuracy, will still lead to a major decrease in the cost compared with obtaining biopsies routinely. It is important to note that the calculated costs that we are reporting include assumptions that we reported for transparency. For example, the costs were obtained from the Centers for Medicare and Medicaid Services data and we assumed that the biopsies were placed in a single specimen container. They also did not include other assumptions that may be of importance, such as the burden on the patient from taking time off or needing transportation to perform the required procedures and tests.

Two of the 3 RCTs that we identified and pooled were in pediatric populations. Iron replacement combined with treatment of *H pylori* was associated with more rapid iron repletion compared with iron replacement alone. Patients who received *H pylori* treatment had a mean improvement in hemoglobin that was 2.2 g/dL (95% CI, 1.3–3.0) and ferritin was 23.2 ng/mL (95% CI, 12.2–34.3) more than the improvement with iron replacement alone (3 studies, 113 patients). The certainty of evidence was rated as low due to increased risk of bias (lack of allocation concealment) and imprecision (small sample size). Further, we recognize that data used in pediatric populations might not be generalizable to adults, also reducing the certainty of evidence. Finally, prior systematic reviews and meta-analyses found that the treatment of *H pylori* may be associated with decreased risk of gastric cancer.[85,86]

In summary, although the bulk of the evidence indicating that identification and eradication of *H pylori* leads to more rapid iron repletion, these data are largely in pediatric age groups, which might not be generalizable to adult populations and, therefore, the quality of the evidence was judged to be low. We also found that noninvasive indirect testing for *H pylori* has excellent diagnostic accuracy and an approach that utilizes such indirect testing is associated with minimizing the costs of testing. Therefore, in asymptomatic patients with IDA, the Technical Review Panel concluded that there was not enough evidence to support routine random gastric biopsy and testing may be considered in patients with negative bidirectional endoscopy using noninvasive testing methods for *H pylori* followed by treatment if positive over no testing.

The Role of Routine Gastric Biopsies for Autoimmune Atrophic Gastritis in Patients With Iron Deficiency Anemia

Quality of evidence and summary.—Although emerging evidence suggests an association between atrophic gastritis and IDA, the evidence that supports that the identification of atrophic gastritis followed by specific treatment leads to improvement of IDA is weak. Given the lack of evidence, the Review Panel concluded that there is insufficient evidence of benefit for routine gastric biopsy to diagnose atrophic gastritis, that is, the potential harms and additional cost of biopsy are likely to outweigh potential benefit (Table 7).

Autoimmune atrophic gastritis is associated with destruction of parietal cells in the gastric corpus, which leads to hypo- or achlorhydria, which can interfere with iron absorption and lead to IDA. Observational studies of patients suspected to have autoimmune gastritis or pernicious anemia have shown a pooled gastric cancer incidence of 0.27% per person-year.[87] However, there was insufficient comparative evidence to support the benefit of surveillance endoscopy. Autoimmune gastritis presents as IDA in young patients and vitamin B-12 deficiency (pernicious anemia) in older patients. Making a diagnosis of autoimmune atrophic gastritis requires separate biopsies of the gastric antrum and corpus and can be supported by the presence of hypo- or achlorhydria, hypergastrinemia, anti-parietal cells antibodies, and/or anti-intrinsic factor antibodies. It is notable that autoimmune atrophic gastritis has no specific treatment. However, observational studies have raised the possibility of increased risk of gastric adenocarcinoma and carcinoid tumors in patients with atrophic gastritis.[88] Guidelines published by The European Society of Gastrointestinal Endoscopy recommend considering endoscopic follow-up every 3–5 years in such patients, although the effectiveness of such an approach remains highly uncertain.[89]

No comparative evidence to illustrate the benefits vs harms of identifying atrophic gastritis in IDA was found. As a fall back, we identified 6 studies composed of 567 patients that reported the frequency of finding autoimmune atrophic gastritis in IDA patients. The pooled prevalence was 10.1% (95% CI, 7.6%–12.8%). Although establishing a diagnosis of autoimmune atrophic gastritis may prevent further evaluation and may direct iron repletion therapy in the patient with established atrophic gastritis, the certainty of evidence that the benefits of identifying atrophic gastritis outweighs the harms was very low due to indirectness of evidence, high risk of bias (selection bias), and inconsistency (different inclusion criteria and workup approach).[51,90–94]

In conclusion, in patients with IDA, the Review Panel did not find enough evidence that benefits of random gastric biopsies or noninvasive testing to diagnose atrophic body gastritis would outweigh potential harms.

What Is the Utility of Routine Small Bowel Biopsies for Celiac Disease in Patients With Iron Deficiency Anemia?

Quality of evidence and summary.—Although celiac disease is a well-known cause of IDA and it is generally accepted that making a diagnosis of celiac disease in patients presenting with IDA is likely to be important, evidence supporting routine use of small

bowel biopsy during EGD is sparse. Rather, the evidence suggests that performing serologic testing as an initial approach in those with clinically suspected celiac disease is more cost-effective (Table 8).

Celiac disease, which causes injury to the small bowel, is a well-known cause of IDA. The mechanism appears to be at least 2-fold, including both occult bleeding[95] and malabsorption of iron. Therefore, great emphasis has been placed on the diagnosis of celiac disease, particularly in populations at high risk for it. It is currently common practice to obtain routine "screening" small bowel biopsies during bidirectional endoscopy (in patients without an obvious source of occult gastrointestinal bleeding).

Prior published guidelines recommend routine small bowel biopsies in patients with IDA regardless of the status of celiac disease serologic tests.[96] Previous studies using the Clinical Outcomes Research Initiative database emphasize the common use of small bowel biopsies; these were performed in 10%–38% of anemic patients in general and 50%–93% of patients with iron deficiency without anemia.[97,98]

We searched the literature for comparative studies (randomized trials or nonrandomized observational studies) that assessed the benefits of routine small bowel biopsy compared with noninvasive testing or not testing for celiac disease in asymptomatic patients with IDA. However, our search did not identify any study that met the inclusion criteria. Hence, we searched for studies that evaluated the frequency of finding celiac disease in patients with IDA, and studies of the diagnostic accuracy of noninvasive testing for celiac disease to use them as indirect evidence to assist the Clinical Guideline Panel in making a decision.

The search strategy identified 825 references. We excluded 644 references based on title and abstract review. After reviewing the full texts, we included 11 studies the reported the frequency of finding celiac disease in IDA patients in the United States, and a systematic review that reported the diagnostic accuracy of noninvasive testing for celiac disease. We focused on studies from the United States due to the variable prevalence of celiac disease between countries.[29]

Of the 11 studies identified, 7 assessed the prevalence of celiac disease in IDA patients based on small bowel biopsies, 2 studies based on serologic testing, and 2 studies of pathologic databases. The pooled diagnostic yield of random duodenal biopsies to assess for celiac sprue-like histologic changes in patients with IDA in the United States was low at 1.15% (95% CI, 0.89%–1.44%). The studies included data from 7993 patients and certainty of evidence was very low due to increased risk of bias (mainly selection bias) and serious imprecision[16–18,76,99–105] (Figure 7).

We identified a systematic review conducted by the Southern California Evidence–based Practice Center, which assessed the diagnostic accuracy of serologic testing for celiac disease.[106] Serologic testing with TTG IgA antibodies has a pooled sensitivity of 0.93 (95% CI, 0.90–0.95) and pooled specificity of 0.98 (95% CI, 0.96–0.99).

To further inform the Panel, we examined 3 strategies that utilized small bowel biopsy and serologic testing in a theoretical population of asymptomatic IDA patients. We focused on

each of these approaches because they are in widespread use, and serologic assessment to detect celiac disease has gained considerable interest among experts and clinicians.[107] The first strategy assumes that the endoscopist performs routine small bowel biopsies in every patient with IDA. The second strategy starts by obtaining TTG IgA in every patient, followed by obtaining small bowel biopsies for those who test positive. In this strategy, patients who test negative and have negative bidirectional endoscopy receive oral iron replacement therapy, which will be expected to fail in patients with celiac disease due to malabsorption (false-negative TTG IgA). Those patients who fail iron replacement therapy would end up undergoing repeat endoscopy with biopsies. The third strategy accounts for a common scenario found in practice in which the patient presents for diagnostic endoscopy with no prior celiac testing. In this strategy, evaluation begins with performing diagnostic bidirectional endoscopy in every patient, followed by obtaining TTG IgA for every patient. Those who test positive will end up having a second endoscopy with biopsies to confirm the diagnosis, and those who test negative will receive iron replacement therapy. Similar to the second strategy, those who fail iron replacement therapy will undergo repeat endoscopy with small bowel biopsies to assess for celiac disease. The strategy in which initial serologic testing is performed in all patients appears to be the most cost-saving, while a strategy in which routine small bowel biopsies are obtained is associated with the highest cost (Appendix 4). Similar to the calculations we reported in the case of *H pylori*, it is important to note that the calculations reported here also include assumptions, which we have reported for transparency, and they might miss some assumptions, such as the patient burden from missing work and transportation. The costs were derived from the Centers for Medicare and Medicaid Services publicly available data and we assumed that all of the obtained biopsies were placed in a single specimen container.

The approach of using noninvasive serologic testing is also supported by a recent study[107] that showed that the cumulative incidence of celiac disease diagnosis in patients with negative celiac serologic testing followed for a mean of 8.8 years was extremely low (0.06%; 95% CI, 0.01%–0.11%).

In conclusion, based on the available evidence, in asymptomatic patients with IDA and clinically suspected celiac disease, the bulk of the evidence supports initial serologic testing (followed by small bowel biopsy only if positive) to routine small bowel biopsy. Patients who have symptoms or signs of celiac disease or who have other indicators of malabsorption should be managed based on the entirety of the clinical evidence and will likely still require small bowel biopsies due to the possibility of false-negative serologic testing.

After Negative Bidirectional Endoscopy, in Patients With Iron Deficiency Anemia, When Should Small Bowel Evaluation Be Performed?

Quality of evidence and summary.—Even though the use of capsule endoscopy to evaluate the small bowel has become commonplace in practice, there is little evidence supporting the routine use of capsule endoscopy to evaluate the small bowel in asymptomatic patients with IDA immediately after negative bidirectional endoscopy. Given the paucity of evidence in asymptomatic patients with IDA and negative bidirectional endoscopy, the Review Panel concluded that a trial of iron therapy before capsule endoscopy

is the most appropriate initial approach (Table 9). Capsule endoscopy may then be pursued in patients who fail to respond to iron replacement therapy.

The small bowel is a well-appreciated source of bleeding in patients with IDA. Small bowel tumors, ulcers, vascular ectasia (also arteriovenous malformation), and even Crohn's disease have all been reported.[13] Small bowel imaging (including computed tomography or magnetic resonance enterography), while ineffective at detecting angiodysplasia and superficial inflammation, is effective at detecting small bowel malignancy. Imaging may be considered initially if malignancy is suspected. Having said that, 2 major advances in small bowel investigation have begun to reshape the evaluation and management of patients with IDA; these include capsule endoscopy (CE) and balloon enteroscopy. Each has advantages and disadvantages, particularly with regard to the level of invasiveness (CE is noninvasive) and ability to administer therapy (therapy can be administered via balloon enteroscopy).

We searched the literature for studies that directly compared the small bowel investigation with iron replacement therapy alone (randomized trial or nonrandomized studies) but we were unable to identify any. To assist the Panel in making a recommendation, we identified studies that evaluated the frequency of finding small bowel neoplasia in IDA patients with negative bidirectional endoscopy and no overt gastrointestinal bleeding. We selected neoplasia as an outcome, as it is critically important as a diagnosis that should not be missed. The search strategy identified 532 references and 457 of them were excluded based on title and abstract screening. Of the remaining references, 16 studies composed of 2899 patients were included after reviewing the full-text articles. CE detected malignancy in 1.3% (95% CI, 0.8–1.8) of patients with IDA and negative bidirectional endoscopy (Figure 8). The certainty of evidence was very low due to high risk of bias (selection bias due to inclusion of symptomatic patients and patients referred to specialty centers for CE).[108–123] Additionally, in a recent study that followed 93 patients with IDA for more than 5 years, no small bowel malignancies were identified.[124] However, the comparative efficacy of CE in IDA remains undefined.

Although the studies published on CE and balloon enteroscopy in patients with IDA have demonstrated that a substantial number of patients will have putative bleeding lesions identified with these 2 modalities, it is difficult to draw meaningful conclusions from these studies because the patient populations studied are extremely heterogeneous and poorly described, there are no or poor definitions of putative bleeding lesions, there is lack of consistency in technique, and outcomes are generally not meaningful. Despite drawbacks, the data suggest that abnormalities are more commonly detected with CE (CE is highly effective at identifying vascular lesions and inflammatory changes, which may cause IDA) and balloon enteroscopy than with modalities, such as push enteroscopy or small bowel imaging studies.[13,116,120] Given the superior visualization ability of CE, the limited availability and the invasive nature of balloon enteroscopy, and the often incomplete evaluation of the small bowel with this examination, the Review Panel did not consider balloon enteroscopy as a viable first-line diagnostic possibility.

Push enteroscopy is widely available in clinical practice, and is often performed in patients with IDA and negative bidirectional endoscopy. However, there is a lack of data supporting

its use and additionally it provides an incomplete examination of the small bowel. Therefore, push enteroscopy should be not be considered a diagnostic modality to evaluate IDA. Given these considerations, capsule endoscopy is the preferred modality to evaluate the small bowel in patients with IDA.

In conclusion, in asymptomatic patients with IDA, there is insufficient evidence to support the routine use of CE after negative bidirectional endoscopy. Instead, the Technical Review Panel believed that CE should be considered a second-line diagnostic tool, best employed after a trial of iron therapy. Because available literature does not comment on the appropriate time course for a trial of iron therapy or the types of iron replacement therapy, the type and duration of iron therapy before investigation of the small bowel should be based on clinical judgment. It should also be noted that there may be circumstances where CE could be warranted as a first-line investigative approach, such as in those requiring ongoing antiplatelet or anticoagulation medications, or those requiring blood transfusion or with refractory IDA.

Future Directions

There is a great need for further evidence in this field. Although we have come to a number of specific conclusions based on the available data, we emphasize that a number of evidence gaps exist in the field. For example, we have not addressed iron deficiency without anemia. An important area has to do with investigation of the risks and benefits of gastrointestinal evaluation in premenopausal women and other patient subgroups; further research in these areas is necessary. In asymptomatic patients with negative bidirectional endoscopy the following issues remain: 1) whether *H pylori* testing in patients with IDA (and subsequent treatment) is indicated; 2) what is the role of atrophic gastritis in IDA? And what is the benefit, if any, of aggressive diagnostic evaluation for this disorder in patients with IDA? 3) what is the best approach to diagnose celiac disease in patients with IDA? Formal outcome studies and cost-effectiveness analyses of serology vs biopsy to detect celiac disease are needed; 4) the timing and need for routine small bowel investigation in asymptomatic IDA patients with negative bidirectional endoscopy is not clear, better evidence of the benefit of CE is required specifically in this population; 5) a better understanding of the natural history of IDA in patients with negative bidirectional endoscopy is needed; and finally, 6) once gastrointestinal evaluation is complete, when should patients be referred to hematology for further evaluation?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

CE	capsule endoscopy
CI	confidence interval
EGD	esophagogastroduodenoscopy
FOBT	fecal occult blood test
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDA	iron deficiency anemia
PICO	population, intervention, comparator, outcome
RCT	randomized controlled trial
TTG	tissue transglutaminase

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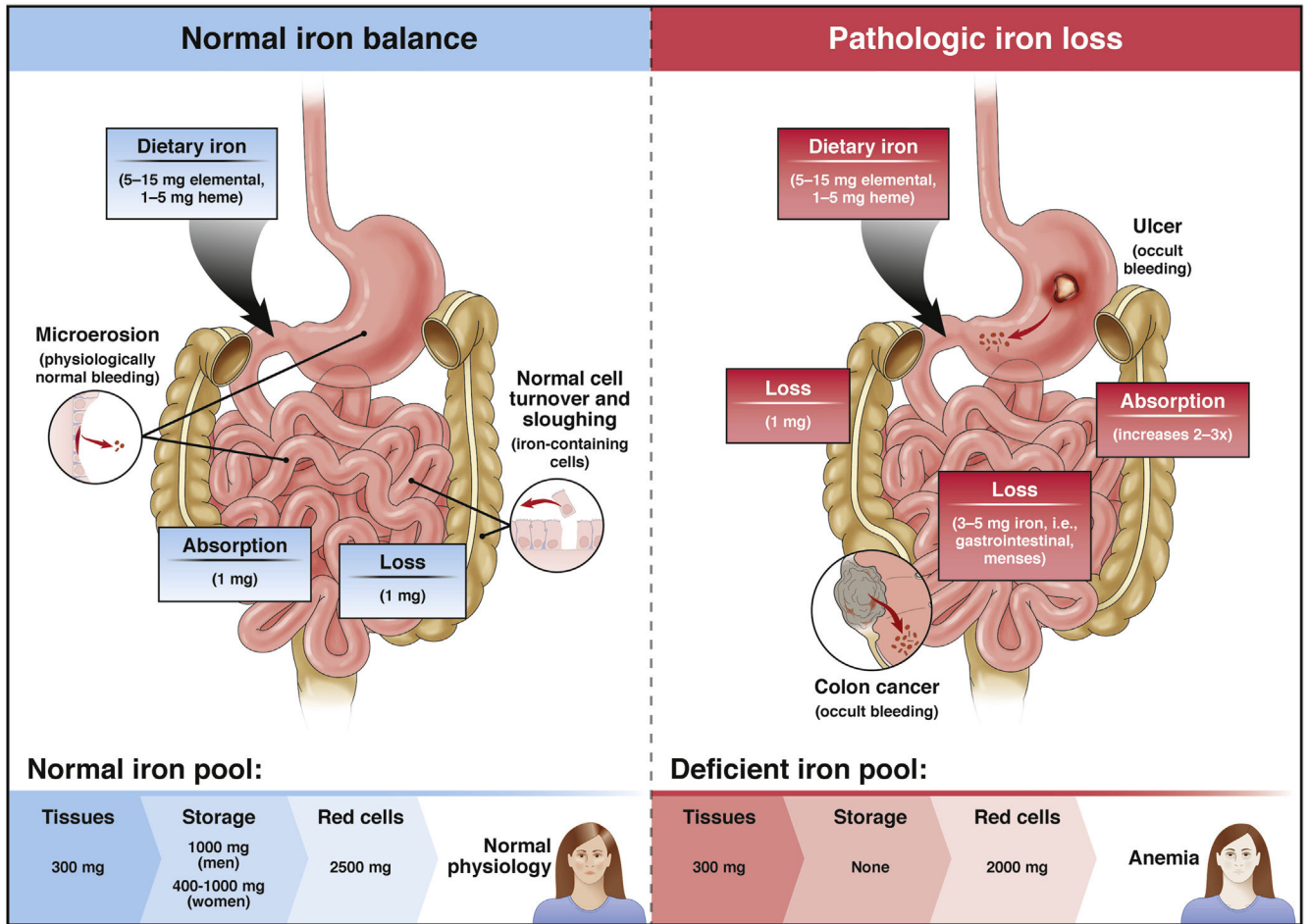
Figure 1.

Iron homeostasis. The molecular regulation of iron homeostasis is complex, including interplay between divalent metal transporter-1 found in enterocytes in the proximal duodenum (*large arrow*), hepcidin, and ferroportin (see the text for details). Iron balance is tightly regulated under normal circumstances, with losses balanced by iron absorption. When iron losses through occult bleeding exceed the capacity to absorb iron, iron is depleted first from iron stores then from the red blood cell pool, ultimately leading to IDA. From Rockey,[11] modified with permission.
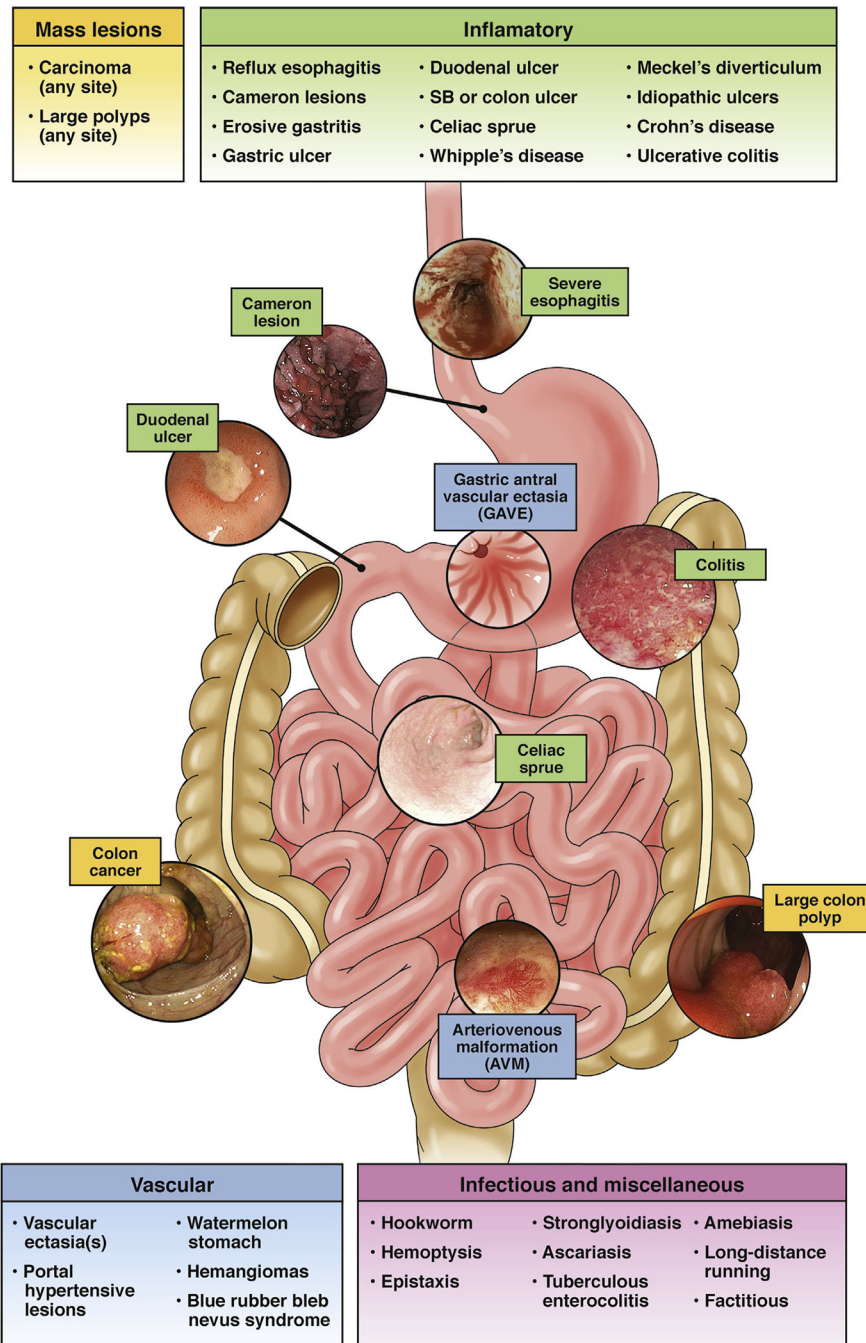
Figure 2.
Gastrointestinal tract lesions causing IDA. Virtually any gastrointestinal tract lesion can bleed in an occult fashion. Highlighted in *red* are the more common causes of occult gastrointestinal bleeding that lead to IDA. SB, small bowel.
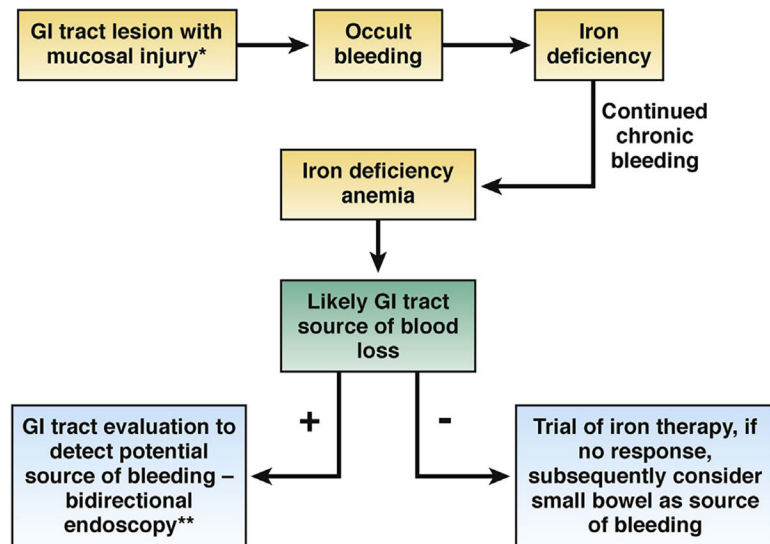
Figure 3.
The role of endoscopy in IDA. In patients who have gastrointestinal (GI) tract lesions, occult bleeding leads to IDA, which usually should be pursued with endoscopy. In asymptomatic patients, if initial bidirectional endoscopy fails to identify a lesion, best evidence suggests that a trial of iron therapy is the most appropriate management approach. If that fails to correct IDA, further evaluation is typically indicated. *See Figure 2 for typical lesions. **Bidirectional endoscopy at the same sitting is preferred over sequential endoscopy at separate times. Note, in patients with IDA and symptoms, endoscopy should be directed first at the source of symptoms. If endoscopy in that location (ie, upper or lower tract) is negative, the portion of the gastrointestinal tract (ie, upper or lower tract) not yet investigated should be examined.

Left panel: Percentage of Men and Postmenopausal Women with IDA found to have Lower GI Malignancy

Study	Events	Total	%	95%-CI	Weight
Kim, 2017	1	128	0.78	[0.02; 4.28]	1.6%
Majid 2009	2	95	2.11	[0.26; 7.40]	1.2%
Yun 2011	5	206	2.43	[0.79; 5.57]	2.5%
Landy 2010	24	478	5.02	[3.24; 7.38]	5.8%
Ho 2005	8	148	5.41	[2.36; 10.37]	1.8%
Droogendijk 2011	17	287	5.92	[3.49; 9.31]	3.5%
James 2005	44	695	6.33	[4.64; 8.41]	8.5%
Stephens 2006	83	896	9.26	[7.45; 11.35]	10.9%
Bosch 2017	487	4552	10.70	[9.82; 11.63]	55.4%
Yates 2004	20	184	10.87	[6.77; 16.29]	2.2%
Rockey 1993	11	100	11.00	[5.62; 18.83]	1.2%
Nahon 2002	14	117	11.97	[6.70; 19.26]	1.4%
Cappurso 2004	13	98	13.27	[7.26; 21.62]	1.2%
Till 1997	13	89	14.61	[8.01; 23.68]	1.1%
Hardwick 1997	17	89	19.10	[11.54; 28.81]	1.1%
Niv 2005	10	48	20.83	[10.47; 34.99]	0.6%
Fixed effect model	**769**	**8210**	**8.88**	**[8.26; 9.52]**	**100.0%**

Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.0041$, $P < .01$

Right panel: Percentage of Men and Postmenopausal Women with IDA found to have Upper GI Malignancy

Study	Events	Total	%	95%-CI	Weight
Kim, 2017	0	128	0.00	[0.00; 2.84]	1.3%
Droogendijk 2011	3	287	1.05	[0.22; 3.02]	3.0%
Rockey 1993	1	100	1.00	[0.03; 5.45]	1.0%
Bosch 2017	83	4552	1.82	[1.45; 2.26]	47.2%
Stephens 2006	44	2318	1.90	[1.38; 2.54]	24.1%
Landy 2010	10	478	2.09	[1.01; 3.81]	5.0%
Till 1997	3	89	3.37	[0.70; 9.54]	0.9%
Yates 2004	7	184	3.80	[1.54; 7.68]	1.9%
James 2005	28	695	4.03	[2.69; 5.77]	7.2%
Majid 2009	4	95	4.21	[1.16; 10.43]	1.0%
Niv 2005	2	48	4.17	[0.51; 14.25]	0.5%
Cappurso 2004	5	98	5.10	[1.68; 11.51]	1.0%
Ho 2005	8	148	5.41	[2.36; 10.37]	1.5%
Nahon 2002	7	117	5.98	[2.44; 11.94]	1.2%
Yun 2011	16	206	7.77	[4.50; 12.31]	2.1%
Hardwick 1997	7	89	7.87	[3.22; 15.54]	0.9%
Fixed effect model	**228**	**9632**	**1.96**	**[1.67; 2.27]**	**100.0%**

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.0017$, $P < .01$

Figure 4.
Frequency of colorectal and upper gastrointestinal (GI) tract malignancy in men and postmenopausal women with IDA. *Forest plots* of studies reporting the frequency of colon cancer (*left*) and upper gastrointestinal tract cancer (*right*) in men and postmenopausal women with IDA are shown.

Study	Events	Total	Percentage	%	95%-CI	Weight
Ioannou, 2002	0	92		0.00	[0.00; 3.93]	10.1%
Annibale, 2003	0	40		0.00	[0.00; 8.81]	4.4%
Vannella, 2008	1	187		0.53	[0.01; 2.94]	20.5%
Nahon, 2002	1	124		0.81	[0.02; 4.41]	13.6%
Kepczyk, 1999	0	19		0.00	[0.00; 17.65]	2.1%
Park, 2006	1	108		0.93	[0.02; 5.05]	11.9%
Green, 2004	3	111		2.70	[0.56; 7.70]	12.2%
Bini, 1998	6	186		3.23	[1.19; 6.89]	20.4%
Fireman, 2006	2	43		4.65	[0.57; 15.81]	4.8%
Fixed effect model	**14**	**910**		**0.95**	**[0.30; 1.86]**	**100.0%**

Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.0006$, $P = .27$

Percentage of Premenopausal Women with IDA found to have Lower GI Malignancy

Study	Events	Total	Percentage	%	95%-CI	Weight
Vannella, 2008	0	187		0.00	[0.00; 1.95]	20.5%
Green, 2004	0	111		0.00	[0.00; 3.27]	12.2%
Park, 2006	0	108		0.00	[0.00; 3.36]	11.9%
Ioannou, 2002	0	92		0.00	[0.00; 3.93]	10.1%
Fireman, 2006	0	43		0.00	[0.00; 8.22]	4.8%
Kepczyk, 1999	0	19		0.00	[0.00; 17.65]	2.1%
Nahon, 2002	2	124		1.61	[0.20; 5.70]	13.6%
Bini, 1998	5	186		2.69	[0.88; 6.16]	20.4%
Annibale, 2003	1	40		2.50	[0.06; 13.16]	4.4%
Fixed effect model	**8**	**910**		**0.24**	**[0.00; 0.87]**	**100.0%**

Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.0014$, $P = .14$

Percentage of Premenopausal Women with IDA found to have Upper GI Malignancy

Figure 5.
Frequency of colorectal and upper gastrointestinal (GI) tract malignancy in premenopausal women with IDA. *Forest plots* of studies reporting the frequency of colon cancer (*left*) and upper gastrointestinal tract cancer (*right*) in premenopausal women with IDA are shown.

Study	Total	Hp Rx & Iron Mean	SD	Total	Iron only Mean	SD	Mean Difference	MD	95%-CI	Weight
Population = Pediatrics										
Choe, 1999	8	4.10	0.8246	7	0.90	0.7792		3.20	[2.39; 4.01]	29.1%
Vijayan, 2007	11	3.00	0.6620	11	1.10	0.9229		1.90	[1.23; 2.57]	31.8%
Random effects model	19			18				**2.53**	**[1.26; 3.80]**	**60.8%**
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.7005$, $P = .02$										
Test for effect in subgroup: $z = 3.89$ ($P < .01$)										
Population = Adults										
Chen, 2007	43	5.50	0.3050	43	3.90	0.3299		1.60	[1.47; 1.73]	39.2%
Random effects model	43			43				**1.60**	**[1.47; 1.73]**	**39.2%**
Heterogeneity: not applicable										
Test for effect in subgroup: $z = 23.35$ ($P < .01$)										
Random effects model	62			61				**2.16**	**[1.31; 3.01]**	**100.0%**
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.4777$, $P < .01$										
Test for overall effect: $z = 4.97$ ($P < .01$)										

-4 -2 0 2 4

Favors iron monotherapy   Favors iron/*H pylori* treatment

Change in Hemoglobin in Patients with IDA & *H pylori* Infection

Figure 6.

Iron treatment in patients with *H pylori* and IDA. Shown is a *forest plot* depicting the effectiveness of iron therapy in patients with *H pylori* and IDA. Hp Rx, *H pylori* treatment; MD, mean difference.

Study	Test	Celiac	IDA	%	95%-CI	Weight
Bini, 1998	Biopsy	0	175	0.00	[0.00; 2.09]	2.2%
Kepcyzk, 1999	Biopsy	0	19	0.00	[0.00; 17.65]	0.2%
Green, 2004	Biopsy	2	111	1.80	[0.22; 6.36]	1.4%
Gordon, 1994	Biopsy	5	170	2.94	[0.96; 6.73]	2.1%
Karnam, 2004	Biopsy	3	105	2.86	[0.59; 8.12]	1.3%
Kepcyzk, 1995	Biopsy	4	70	5.71	[1.58; 13.99]	0.9%
Grisolano, 2004	Biopsy	9	103	8.74	[4.07; 15.94]	1.3%
Abdalla, 2017	Serology	5	569	0.88	[0.29; 2.04]	7.1%
Murray, 2013	Serology	14	571	2.45	[1.35; 4.08]	7.1%
Pitman, 2019	Database	4	920	0.43	[0.12; 1.11]	11.5%
Carmack, 2010	Database	88	5180	1.70	[1.36; 2.09]	64.8%
Fixed effect model		**134**	**7993**	**1.15**	**[0.89; 1.44]**	**100.0%**

Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.0019$, $P < .01$

Percentage of IDA Patients with Celiac Disease

Figure 7.

Frequency of celiac disease in patients with IDA. Shown is a *forest plot* depicting the frequency with which celiac disease was detected in different studies of patients with IDA.

Study	Events	Total	Percentage	%	95%-CI	Weight
Muhammad, 2009	0	231		0.00	[0.00; 1.58]	8.0%
Tong, 2012	0	97		0.00	[0.00; 3.73]	3.4%
Goenka, 2011	0	96		0.00	[0.00; 3.77]	3.3%
Sealock, 2018	0	75		0.00	[0.00; 4.80]	2.6%
Holleran, 2013	0	64		0.00	[0.00; 5.60]	2.2%
Laine, 2010	0	40		0.00	[0.00; 8.81]	1.4%
Kim, 2009	0	25		0.00	[0.00; 13.72]	0.9%
Koulaouzidis, 2012	2	221		0.90	[0.11; 3.23]	7.6%
Sidhu, 2015	16	971		1.65	[0.94; 2.66]	33.4%
Kunihara, 2018	8	357		2.24	[0.97; 4.37]	12.3%
Van Tuyl, 2006	4	150		2.67	[0.73; 6.69]	5.2%
Olano, 2018	4	118		3.39	[0.93; 8.45]	4.1%
Yung, 2017	8	220		3.64	[1.58; 7.04]	7.6%
Apostolopoulos, 2006	2	51		3.92	[0.48; 13.46]	1.8%
Riccioni, 2010	8	138		5.80	[2.54; 11.10]	4.8%
Milano, 2011	4	45		8.89	[2.48; 21.22]	1.6%
Fixed effect model	56	2899		1.25	[0.81; 1.76]	100.0%

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.0027$, $P < .01$

0 5 10 15 20

Percentage of Patients with IDA/Occult Obscure GI Bleeding found to have Small Bowel Neoplasia

Figure 8.
Frequency of small bowel neoplastic lesions in patients with IDA. Shown is a *forest plot* depicting the frequency with which small bowel neoplasia was detected in different studies of patients with IDA. GI, gastrointestinal.

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Table 1.

PICO Questions

Question no.	Diagnosis or intervention related question	PICO question			
		Population	Intervention(s)	Comparator	Outcome
1	Establishing an accurate diagnosis of IDA?	Adults with anemia defined as hemoglobin <13 g/dL in men and <12 g/dL in nonpregnant women	Ferritin	Bone marrow biopsy (gold standard)	Diagnosis of IDA
2	What is the utility of bidirectional endoscopy in patients with suspected endoscopic gastrointestinal lesion as a source of IDA?	Women aged ≥45 y and men. Premenopausal women aged <45 y	Bidirectional endoscopy	Do nothing (observation only)	All-cause mortality, morbidity related to anemia (eg, cardiac events), mortality related to gastrointestinal lesions, morbidity related to gastrointestinal lesions, endoscopy-related or periprocedural morbidity, endoscopy-related or periprocedural mortality
3a	Should we obtain routine gastric biopsies for *H pylori* in patients with IDA?	Adults with IDA undergoing endoscopic workup without endoscopic gastric pathology	Routine gastric biopsies for *H pylori*	Do nothing, noninvasive testing	Resolution of anemia
3b	Should we obtain routine gastric biopsies for chronic autoimmune atrophic gastritis in patients with IDA?		Routine gastric biopsies	Do nothing	
4	Should we obtain routine small bowel biopsies for celiac disease in patients with IDA?	Adults with IDA undergoing endoscopic workup without endoscopic small bowel pathology	Routine small bowel biopsies for celiac testing	Do nothing, noninvasive testing	
5	In asymptomatic IDA patients with negative bidirectional endoscopy, should small bowel investigations be pursued?	Adults with IDA without warning signs.	Any small bowel investigation (endoscopy or imaging)	Do nothing	All-cause mortality, morbidity related to anemia (eg, cardiac events), mortality related to gastrointestinal lesions, morbidity related to gastrointestinal lesions, endoscopy-related or periprocedural morbidity, endoscopy-related or periprocedural mortality.

PICO, population, intervention, comparator, outcome.

Table 2.

Sensitivity and Specificity of Different Ferritin Cutoffs for Diagnosis of Iron Deficiency Anemia

Test result	No. of results per 1000 patients tested (95% CI)				No. of participants (studies)	Certainty of the Evidence (GRADE)	Comments
	Prevalence 20%, typically seen in men and postmenopausal women		Prevalence 60%, typically seen in premenopausal women				
	Ferritin <45 ng/mL Fer	ritin <15 ng/mL	Ferritin <45 ng/mL Feri	Ferritin <15 ng/mL			
TP	170 (164–174) 52 more TP in ferritin <45 ng/mL	118 (110–124)	510 (492–522) 156 more TP in ferritin < 45 ng/mL	354 (330–372)	809 (52)	⊕⊕⊕⊕ HIGH	Detection of TP will lead to starting iron replacement therapy and likely additional investigations to assess for blood loss as the source of IDA.
FN	30 (26–36) 52 fewer FN in ferritin <45 ng/mL	82 (76–90)	90(78–108) 156 fewer FN in ferritin <45 ng/mL	246 (228–270)			FN will likely have worsening of anemia with possible morbidity, or mortality, due to anemia and/or cardiopulmonary complications. They may or may not undergo anemia workup, and may or may not undergo endoscopy to evaluate for blood loss as the source of IDA.
TN	736 (728–752) 56 fewer TN in ferritin <45 ng/mL	792 (712–792)	368 (364–376) 28 fewer TN in ferritin <45 ng/mL	396 (356–396)	1860 (52)	⊕⊕⊕⊕ HIGH	TN will require different investigations to assess the etiology/mechanism of anemia. They may not need workup for blood loss.
FP	64 (48–72) 56 more FP in ferritin < 45 ng/mL	8 (8–88)	32 (24–36) 28 more FP in ferritin <45 ng/mL	4 (4–44)			FP will likely undergo unnecessary investigations to assess for blood loss as the source of IDA with possible delay in diagnosis of the actual etiology of the anemia.

NOTE. Summary of findings: PICO (population, intervention, comparator, outcome) 1: Should ferritin <45 ng/mL vs ferritin <15 ng/mL be used to diagnose iron deficiency in patients with anemia?

Patient or population: Patients with anemia.

Setting: Outpatient.

New test: Ferritin cutoff value: 45 ng/mL and 15 ng/mL.

Reference test: Bone marrow biopsy.

Pooled sensitivity ferritin <45 ng/mL: 0.85 (95% CI, 0.82–0.87). Pooled specificity ferritin <45 ng/mL: 0.92 (95% CI, 0.91–0.94).

Pooled sensitivity ferritin <15 ng/mL: 0.59 (95% CI, 0.55–0.62). Pooled specificity ferritin <15 ng/mL: 0.99 (95% CI, 0.89–0.99).

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Table 3.

Outcomes Associated With Different Ferritin Cutoffs in IDA

	Population	Premenopausal women		Men and postmenopausal women	
1	Prevalence of colon cancer	0.06%		0.67%	
1	Prevalence of gastroesophageal (GE) cancer	0.01%		0.07%	
2	Theoretical population count	1,000,000		1,000,000	
3	Estimated prevalence count of colon cancer in the theoretical population	592		6,667	
3	Estimated prevalence count of GE cancer in the theoretical population	62		728	
4	Estimated prevalence count of anemia in the theoretical population	56,500		43,500	
5	Estimated prevalence count of iron-deficiency anemia (IDA) in the theoretical population	32,900		8,187	
6	Estimated prevalence of colon cancer in patients with IDA	0.95%		8.88%	
6	Estimated prevalence of GE cancer in patients with IDA	0.24%		1.96%	
7	Estimated prevalence count of colon cancer in IDA patient from the theoretical population	313		727	
7	Estimated prevalence count of GE cancer in IDA patient from the theoretical population	79		160	
8	Ferritin Threshold	15	45	15	45
9	Sensitivity	0.59	0.85	0.59	0.85
10	Specificity	0.99	0.92	0.99	0.92
11	Estimated number of missed colon cancers due to false negatives (patients with IDA being considered to be iron-sufficiency)	128	47	298	109
11	Estimated number of missed GE cancers due to false negatives	32	12	66	24
12	Estimated number of unnecessary endoscopic procedures due to false positives (iron-sufficient patients mislabeled as iron-deficient)	329	2632	82	655
13	Estimated number of endoscopic perforations due to false positive	0.31	2.48	0.08	0.62

NOTE.

1. Calculated by dividing the estimated prevalence counts of colon or GE cancer in the population (from the SEER Cancer Statistics Review) by the counts of the population (from the US Census Database).[73]

2. A theoretical number of people from the age/gender group.

3. Calculated by multiplying the prevalence from 1 by the theoretical population count.

4. Calculated by multiplying the estimated prevalence percentage of anemia from Ioannou GN et al. (2002) by the theoretical population count.[42]

5. Calculated by multiplying the estimated prevalence percentage of iron-deficiency anemia from Ioannou GN et al. (2002) by the count in line 4.[42]

6. Estimated from pooling the prevalence studies as detailed in PICO 2.

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7. Calculated by multiplying the estimated prevalence percentage in line 6 by the estimated prevalence count in line 5.

8–10. From Guyatt GH et al. (1992).[41]

11. Calculated by multiplying the estimated prevalence of colon or GE cancer (line 6) by the false negatives rate (1-sensitivity from line 9).

12. Calculated by multiplying by the false positives rate (1-specificity from line 10) by the estimated count of patients with IDA (line 5).

13. Calculated by multiplying the estimated number unnecessary procedures by estimated prevalence of perforation (0.08%).

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Table 4.

Bidirectional Endoscopy in Asymptomatic Men And Postmenopausal Women With Iron Deficiency Anemia

Certainty assessment		Summary of findings
Outcome No. of participants (studies)	Overall certainty of evidence	Impact
Detection of malignancy 12,040 (18 studies)	⊕⊕⊕◯ MODERATE[a]	Although we could not identify any direct evidence from comparative studies using bidirectional endoscopy in men and postmenopausal with IDA, high-quality indirect evidence from screening trials (RCTs and nonrandomized studies) demonstrate substantial mortality reduction even in a setting with substantially lower baseline risk for colon cancer than found in IDA. This provides us with at least moderate certainty in the evidence of benefit in the endoscopic evaluation for IDA. We focused on the outcome of identifying malignancy as an outcome, which is critical for decision making in this setting. We were able to identify studies of the diagnostic yield of bidirectional endoscopy. Bidirectional endoscopy detected 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 asymptomatic men and postmenopausal women with IDA. Although this estimate is likely an overestimation due to the inclusion of symptomatic patients (high risk of bias), which makes the exact baseline risk for malignancy in IDA uncertain in this risk group, we have high certainty in the evidence that it is many fold higher (approximately 100-fold) than an average risk screening population of similar age.

[a]Certainty in the evidence rated down due to indirectness (for the intervention).

Table 5.

Bidirectional Endoscopy in Asymptomatic Premenopausal Women With Iron Deficiency Anemia

Certainty assessment		Summary of findings
Outcome No. of participants (studies)	Overall certainty of evidence	Impact
Detection of malignancy 1026 (10 studies)	⊕⊕⊕◯ MODERATE[a]	Although we could not identify any direct evidence from comparative studies using bidirectional endoscopy in asymptomatic premenopausal women with IDA, high-quality indirect evidence from screening trials (RCTs and nonrandomized studies) demonstrate substantial mortality reduction, provided the baseline risk for colon cancer does not substantially fall below established thresholds (ie, 0.6/1000 for 50-year-old woman at average risk without IDA). This provides us with at least moderate certainty in the evidence of benefit in the endoscopic evaluation for IDA. We focused on the outcome of identifying malignancy as an outcome, which is critical for decision making in this setting. We were able to identify studies of the diagnostic yield of bidirectional endoscopy. Bidirectional endoscopy detected lower gastrointestinal malignancy in 0.9% (95% CI, 0.3–1.9) and upper gastrointestinal malignancy in 0.2% (95% CI, 0.0–0.9) of asymptomatic premenopausal women with IDA. Although this estimate is likely an overestimation due to the inclusion of symptomatic patients (high risk of bias), which makes the exact baseline risk for malignancy in IDA uncertain in this risk group, we are confident that it is several fold higher than the 0.6/1000 (0.06%) rate, particularly in the mid to upper age range of premenopausal women. However, the high propensity of benefit of endoscopy in IDA quickly diminishes as age declines and therefore, the harms of endoscopy will eventually outweigh the benefits. No reliable data were found that further defined this age threshold.

[a] Certainty in the evidence rated down due to indirectness (for the intervention).

Table 6.

Testing/Treating for *Helicobacter pylori* + Iron Replacement Compared With Iron Replacement Alone for Patients With Iron Deficiency Anemia

No. of participants (studies), follow-up	Certainty assessment					Summary of findings			
						Number of participants		Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With iron replacement alone	With testing/treating for *H pylori* + iron replacement	Improvement with iron replacement alone	Mean difference with testing/treating for *H pylori* + iron replacement
Improvement of Hgb (follow-up: range 8–12 wk; assessed with: change in Hgb, *g/dL*)										
123 (3 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	61	62	The mean improvement of Hgb was 2.8 g/dL	MD 2.2 g/dL higher (1.3 higher to 3 higher)
Improvement of ferritin (follow-up: range 8–12 wk; assessed with: change in ferritin, *ng/mL*)										
123 (3 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW	61	62	The mean improvement of ferritin was 0 ng/mL	MD 23.2 ng/mL higher (12.2 higher to 34.3 higher)

Hgb, hemoglobin; MD, mean difference.

[a]Due to lack of allocation concealment.

[b]Due to the small sample size.

Table 7.

Routine Gastric Biopsies to Test for Atrophic Gastritis vs Not Testing for Atrophic Gastritis in Patients With Iron Deficiency Anemia

Certainty assessment		Summary of findings
Outcome No. of participants (studies)	Overall certainty of evidence	Impact
Benefits and harms of diagnosing autoimmune gastritis in the context of IDA		
567 (6 studies)	⊕○○○ VERY LOW[a,b]	Neither RCTs or observational studies have directly assessed the benefits of routine gastric biopsies during EGD to assess for atrophic body gastritis in patients with IDA. The pooled diagnostic yield of routine gastric biopsies to assess for non-*H pylori* atrophic body gastritis in patients with IDA was 10.0% (95% CI, 7.6–12.7).[a,b] The pooled estimate of 10% is unlikely to reflect the true incidence of non-*H pylori* atrophic body gastritis in patients with IDA due to very serious risk of bias related to the patient selection methods.
		We could not identify any study that evaluated the benefits of diagnosing non-*H pylori* atrophic body gastritis in patients with IDA. There were no studies that evaluated whether the use of IV iron replacement compared with oral has any additional benefits in this population, that is, by overcoming poor iron absorption. Observational studies of patients suspected to have autoimmune gastritis or pernicious anemia have shown a pooled gastric cancer incidence of 0.27% per person-year. However, there was insufficient comparative evidence to support the benefit of surveillance endoscopy.[c]

IV, intravenous.

[a] None of the studies was an inception cohort and they were all referred patients; many of them included only patients with negative bidirectional endoscopy (selection bias).

[b] The point estimates of individual studies ranged from 7.4% to 19.5%.

[c] The diagnosis in many of the included studies was based on low vitamin B-12 level only.

Testing Strategies in Celiac Disease

Table 8.

Certainty assessment		Summary of findings
Outcome No. of participants (studies)	**Overall certainty of evidence**	**Impact**

Benefits and harms of diagnosing celiac disease in the context of IDA

7993 (11 studies)	⊕◯◯◯ VERY LOW[a,b]	Neither RCTs or observational studies have directly compared routine small bowel biopsies during EGD in asymptomatic patients with IDA to clinically targeted workup (symptoms and signs followed by serologic testing). The pooled diagnostic yield of random duodenal biopsies to assess for celiac sprue-like histologic changes in patients with IDA in the United States was 1.15% (95% CI, 0.89–1.44). Serologic testing with TTG IgA antibodies has a pooled sensitivity of 0.93 (95% CI, 0.90–0.95) and pooled specificity of 0.98 (95% CI, 0.96–0.99). If patients with asymptomatic IDA are screened with TTG before EGD, 9 cases of 115 celiac disease cases in 10,000 patients with IDA will be missed and 208 additional patients will undergo duodenal biopsies due to false positives. As patients with IDA will be expected to undergo diagnostic EGD regardless of the serologic testing status, there are no expected additional harms from the procedural standpoint considering the comparable safety profiles of EGD with and without small bowel biopsies.

Cost of obtaining routine small bowel biopsies compared with obtaining biopsies based on the results of serologic testing

Not measured	—	Unless the pretest probability is high, that is, >10%, it is highly unlikely that routine small bowel biopsies in asymptomatic patients with IDA will be cost-effective. Routinely obtaining small bowel biopsies compared with determining TTG IgA status will cost $67,000 for every missed celiac disease case due to false-negative TTG IgA. If patients present for endoscopy with unknown TTG IgA status, obtaining routine small bowel biopsies will cost $48,000 to avoid missing the 1 in 1000 false-negative case of celiac disease case if diagnostic EGD is followed by serologic testing. Therefore, the balance between the expected benefits, potential harms, and cost is likely to favor serologic testing over routine small bowel biopsies unless the prevalence of celiac disease is >5% in the nontertiary referral setting.

[a] Some of the studies were not inception cohorts and/or did not clearly state enrolling consecutive patients (selection bias).

[b] The point estimates of individual studies ranged from 0% to 8%.

Table 9.

Video Capsule Endoscopy Compared With Nothing for Asymptomatic Patients With Iron Deficiency Anemia and Negative Bidirectional Endoscopy

Certainty assessment		Summary of findings
Outcome No. of participants (studies)	Overall certainty of evidence	Impact
Reduction of adverse outcomes 2899 (16 studies)	⊕◯◯◯ VERY LOW[a]	We could not identify any direct evidence from comparative studies that performing VCE would reduce the risk of having or developing any adverse outcomes such as death or cancers in asymptomatic patients with IDA and negative bidirectional endoscopy. We could not identify any direct evidence from diagnostic accuracy studies that informs the rate of falsely negative or falsely positive VCE. We were able to identify studies of the diagnostic yield of VCE that were limited by very serious risk of bias. Although arteriovenous malformations and other benign lesions are well known to be identified in the small bowel, we focused on the outcome of finding malignancy because it is the most serious finding. VCE detected malignancy in 1.3% (95% CI, 0.8–1.8) of patients with IDA and negative bidirectional endoscopy. This estimate is likely an overestimation due to the aforementioned risk of bias, which stems from the inclusion of symptomatic patients. The comparative efficacy of VCE in IDA remains undefined.

VCE, video capsule endoscopy.

[a] Most of the studies were not inception cohorts, included referred patients, and/or did not clearly state enrolling consecutive patients (selection bias).