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Wolters Kluwer

# Evaluation of occult gastrointestinal bleeding

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## INTRODUCTION

Occult gastrointestinal (GI) bleeding refers to the initial presentation of a positive fecal occult blood test result and/or iron deficiency anemia when there is no evidence of visible blood loss to the patient or physician [1]. By contrast, the term overt is used to describe blood loss that is visible to the patient or clinician. Overt bleeding may manifest as hematemesis, melena, or hematochezia.

The major cause of iron deficiency in developed countries is blood loss [2]. In male patients, the blood loss is most commonly from the GI tract; in premenopausal female patients, menstrual blood loss must also be considered [3]. (See "[Causes and diagnosis of iron deficiency and iron deficiency anemia in adults](#)".)

The initial evaluation of patients with occult GI bleeding will be reviewed here. The evaluation of patients with overt GI bleeding, the evaluation for occult GI blood loss as it relates to screening for colorectal cancer, and the evaluation of patients with suspected small bowel bleeding (previously referred to as obscure GI bleeding) are discussed separately. (See "[Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)](#)" and "[Approach to acute lower gastrointestinal bleeding in adults](#)" and "[Approach to acute upper gastrointestinal bleeding in adults](#)" and "[Tests for screening for colorectal cancer](#)".)

## CAUSES OF OCCULT GI BLEEDING

The differential diagnosis for occult GI bleeding is broad ( [table 1](#) and [table 2](#)). Some of the more common causes include colon cancer, esophagitis, peptic ulcers, gastritis, inflammatory bowel disease, vascular ectasias, portal hypertensive gastropathy, gastric antral vascular ectasias, and small bowel tumors (eg, GI stromal cell tumor, lymphoma, carcinoid, adenocarcinoma, or polyp). However, less common causes, such as gastroesophageal cancers, hemosuccus pancreaticus, hemobilia, endometriosis, and infections also need to be considered. In addition, hemorrhoids can rarely lead to a positive fecal occult blood test [4]. While overt bleeding from hemorrhoids can result in anemia, anemia in the setting of occult GI bleeding should not be attributed to hemorrhoids. Non-GI sources of blood loss, such as hemoptysis and epistaxis, can also cause a positive fecal occult blood test.

The medical history and physical examination can help focus the differential diagnosis. As examples, colon cancer is a likely cause in patients older than 50 years, small bowel tumors are often seen in patients under the age of 40 years, and angiodysplasias are seen in association with several conditions, including aortic stenosis, renal disease, and presence of a left ventricular assist device. The presence of oral telangiectasias may signal the presence of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), and mucocutaneous pigmentation may be due to Peutz-Jeghers syndrome in which hamartomatous polyps may ulcerate and cause occult GI bleeding. (See "[Causes of upper gastrointestinal bleeding in adults](#)" and "[Etiology of lower gastrointestinal bleeding in adults](#)".)

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## TESTING FOR OCCULT BLOOD

Testing for occult blood is stool-based and should be done with high sensitivity tests for fecal occult blood or immunochemical tests. Overall, fecal occult blood testing has a sensitivity of 58 percent and a specificity of 84 percent for detecting a source of iron deficiency anemia [5]. Of note, fecal immunohistochemical testing detects only human globin and therefore does not detect upper GI bleeding (since the globin is digested in transit). (See "[Tests for screening for colorectal cancer](#)", section on 'Stool-based tests'.)

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## EVALUATION OF A POSITIVE FECAL OCCULT BLOOD TEST

**General approach** — The evaluation of a patient with a positive fecal occult blood test depends upon whether iron deficiency anemia is present ( [algorithm 1](#)) [1,6]. Patients without iron deficiency anemia can be evaluated with colonoscopy, with or without upper endoscopy (depending on the patient's symptoms). Patients with iron deficiency anemia require a more extensive evaluation, including upper endoscopy and colonoscopy. If upper endoscopy and

colonoscopy do not reveal a source of the bleeding, the next step is evaluation of the small bowel, typically with wireless capsule endoscopy.

**Iron deficiency anemia absent** — A patient with a positive fecal occult blood test and no anemia should undergo a colonoscopy [1,6]. If the patient has upper GI symptoms, an upper endoscopy should also be performed. If initial testing is negative and there are no signs of ongoing blood loss, further evaluation is not recommended.

**Iron deficiency anemia present** — A patient with a positive fecal occult blood test and iron deficiency anemia should undergo upper endoscopy and colonoscopy [1,6]. Since there is often uncertainty as to whether a positive finding on one endoscopic examination represents the true cause of bleeding, both examinations are recommended in the majority of cases. However, the risks of diagnostic testing must be weighed against those of missing important lesions.

Patients without a lesion identified on standard endoscopic evaluation (assuming the examinations were adequate) should have a small bowel examination. The small bowel examination of choice in the majority of patients is wireless capsule endoscopy. If the initial evaluation with upper endoscopy, colonoscopy, and capsule endoscopy is unrevealing, alternative non-GI sources for the patient's iron deficiency should be considered. If the suspicion for a GI source of blood loss remains high, additional testing is indicated. (See '[Small bowel evaluation](#)' below and "[Causes and diagnosis of iron deficiency and iron deficiency anemia in adults](#)" and "[Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)](#)".)

## Diagnostic tests

**Upper endoscopy** — Important lesions in the upper digestive tract are frequently detected in patients who test positive for fecal occult blood or have iron deficiency anemia ( [picture 1](#)). While the presence of symptoms referable to the upper GI tract has been associated with the detection of corresponding findings, even in patients without symptoms, the prevalence of lesions in the upper GI tract is greater than or equal to that of colonic lesions [7-10]. (See "[Overview of upper gastrointestinal endoscopy \(esophagogastroduodenoscopy\)](#)".)

A number of studies have evaluated the yield of performing upper endoscopy or small bowel examination in patients who have a positive test for occult blood, iron deficiency anemia, or both [11-15]. In a meta-analysis of 21 studies of patients with a positive fecal occult blood test, clinically significant upper GI lesions were detected in 31 percent of patients [16]. Upper GI cancers were found in 0.8 percent, whereas nonmalignant lesions were found in 30 percent. Nine of the studies compared patients with and without anemia, and patients with anemia were more likely than those without anemia to have clinically significant lesions (OR 4.3, 95% CI 2.2-

8.4,  $p = 0.0001$ ), including upper GI cancer (OR 6.3, 95% CI 1.3-32,  $p = 0.025$ ). GI symptoms, however, were not associated with upper GI lesions (OR 1.3, 95% CI 0.6-2.8,  $p = 0.51$ ). Clinically significant upper GI lesions were found in 33 percent of patients with positive findings during colonoscopy. In individual studies, the proportion of patients with both upper and lower GI lesions ranged from 5 to 17 percent [12,14,15].

If no visible lesions or gastritis are seen during the upper endoscopy, biopsies should be taken from the stomach to exclude *H. pylori* infection, which has been associated with iron deficiency anemia, and from the small bowel to exclude celiac disease [17].

**Colonoscopy** — Because of the high prevalence of colorectal cancer and adenomatous polyps in developed countries, most patients should undergo colonoscopy. Colonoscopy is the preferred modality for evaluating the colon because it can detect a wide range of lesions, including polyps, cancers, and angiodysplasias. Colonoscopy also permits therapeutic intervention.

Radiographic studies (including [barium](#) enemas and computed tomographic [CT] colonography, also called "virtual colonoscopy") do not offer the option of biopsy or polypectomy. However, they may have a role in selected patients. (See "[Overview of computed tomographic colonography](#)".)

**Small bowel evaluation** — If complete endoscopy and colonoscopy with adequate visualization do not reveal the source of the bleeding, additional evaluation is recommended ( [algorithm 2](#)). While an upper GI series with a small bowel follow-through and/or enteroclysis was traditionally the next test performed, wireless capsule endoscopy, CT enterography, and magnetic resonance (MR) enterography have replaced these modalities [18]. (See "[Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)](#)".)

Wireless capsule endoscopy is generally the test of choice for evaluating suspected small bowel bleeding in patients who have had an adequate upper endoscopy and colonoscopy. Its main advantages are that it is noninvasive and permits examination of the entire length of the small bowel most of the time. Its main disadvantages are that it does not permit tissue sampling or therapeutic intervention and that not all of the small bowel mucosa is visualized. Patients at risk for capsule retention due to possible small bowel strictures should undergo small bowel imaging (eg, CT or MR enterography) or a patency capsule study prior to capsule endoscopy. A more detailed discussion of capsule endoscopy can be found elsewhere. (See "[Wireless video capsule endoscopy](#)".)

CT enterography involves ingestion of a neutral contrast agent to distend the small bowel, followed by CT imaging of the abdomen. Using neutral contrast allows for better evaluation of

the wall of the small bowel, which is difficult to see when standard [barium](#) solutions are used.

MR enterography is an alternative to CT enterography. It has the advantage of not using ionizing radiation, which allows for sequential imaging of the small bowel. Like CT enterography, a neutral contrast agent (often polyethylene glycol) is used to distend the small bowel.

Other methods available for evaluating the small bowel include push enteroscopy, deep small bowel enteroscopy, and intraoperative enteroscopy. (See "[Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)](#)".)

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## EVALUATION OF ISOLATED IRON DEFICIENCY ANEMIA

Patients with unexplained iron deficiency anemia but a negative fecal occult blood test should be evaluated for a GI source of blood loss ( [algorithm 1](#)). This is particularly important in male patients and postmenopausal female patients. Patients with isolated iron deficiency anemia should be evaluated for celiac disease if an alternative source of blood loss is not identified. (See "[Diagnosis of celiac disease in adults](#)".)

If patients have symptoms suggesting either an upper or lower GI source, it is reasonable to start the evaluation with an upper endoscopy or colonoscopy, respectively [[19](#)]. For patients who are asymptomatic, a colonoscopy is often the first test obtained, but in patients with anemia, we typically start the evaluation with both an upper endoscopy and a colonoscopy. (See '[Diagnostic tests](#)' above and "[Causes and diagnosis of iron deficiency and iron deficiency anemia in adults](#)" and "[Diagnosis of celiac disease in adults](#)".)

If patients do not undergo both an upper endoscopy and colonoscopy initially and no lesion is identified during the initial examination that explains the anemia, the other test (either an upper endoscopy or colonoscopy) should be performed. If both upper endoscopy and colonoscopy are negative, additional testing such as wireless capsule endoscopy should be pursued ( [algorithm 2](#)). (See "[Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)](#)".)

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## SPECIAL SITUATIONS

**Patients with a known risk factor for gastrointestinal blood loss** — A positive fecal occult blood test should not be attributed to GI lesions that are infrequently associated with occult bleeding (eg, esophageal varices and colonic diverticula). It is rare for esophagogastric varices

to cause occult GI bleeding, with the possible exception of varices that have been treated with endoscopic sclerosis or banding (which is transient and should resolve after the associated ulcers have healed). Similarly, most patients with bleeding colonic diverticular disease present with overt, rather than occult, bleeding. (See "[Clinical manifestations and diagnosis of acute colonic diverticulitis in adults](#)" and "[Colonic diverticular bleeding](#)".)

Thus, in a patient with known esophagogastric varices or colonic diverticula, a positive test for occult blood or otherwise unexplained iron deficiency anemia should not preclude a diagnostic evaluation. Colonic diverticula commonly occur in the age bracket with the highest incidence of colon cancer, and colon cancer is far more likely to bleed in an occult manner.

**Aspirin, antiplatelet agents, and anticoagulants** — Data are conflicting regarding the effect of antiplatelet agents and anticoagulants on fecal occult blood testing [20-23]. It should **not** be assumed that a positive test in a patient on one of these agents is a false-positive.

- In one study, the use of [aspirin](#), nonsteroidal antiinflammatory agents, [clopidogrel](#), or [warfarin](#) was associated with lower positive predictive values of fecal occult blood testing for advanced colorectal neoplasia compared with patients not taking these agents (21, 19, 7, and 20 percent, respectively, versus 31 percent) [20].
- In a second study, the use of low-dose [aspirin](#) was associated with an increased sensitivity for detecting advanced colorectal neoplasms with only a slight decrease in specificity [22].

**Alcohol abuse** — The presence of fecal occult blood should not be attributed to alcohol ingestion alone unless coexistent pathology has been excluded. In a study of 1000 patients hospitalized for alcohol detoxification, 22 patients (2.2 percent) without overt GI bleeding tested positive for occult blood [24]. The subsequent endoscopic evaluation found that 24 percent of these individuals had peptic ulcer disease, 32 percent had premalignant colonic neoplasia, and all had upper GI mucosal inflammation.

**Premenopausal female patients** — The optimal approach to iron deficiency anemia in female patients who continue to menstruate is uncertain. In one series, a clinically important lesion was detected in 23 of 186 premenopausal female patients (12 percent) who underwent endoscopy [25]. The most common source of bleeding was in the upper GI tract, including peptic ulcer disease (3 percent) and gastric cancer (3 percent). On multivariable analysis, independent predictors of a significant finding on endoscopy included a positive fecal occult blood test, hemoglobin <10 g/dL, and abdominal symptoms. Another study of 187 premenopausal female patients found an exclusive and possible GI cause for iron deficiency anemia in 27 and 35 percent of patients, respectively [26].

While the high prevalence of positive findings in these studies may have reflected referral bias, endoscopic evaluation should be obtained if a fecal occult blood test is positive, if the iron deficiency anemia is out of proportion to menstrual blood loss, if the patient has abdominal symptoms, or if the patient has a family history of GI malignancy in a first-degree relative, particularly if the patient is older than 40 years of age.

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## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Gastrointestinal bleeding in adults](#)".)

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## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "[Patient education: Upper endoscopy \(The Basics\)](#)" and "[Patient education: Colonoscopy \(The Basics\)](#)" and "[Patient education: Angiodysplasia of the GI tract \(The Basics\)](#)")
- Beyond the Basics topics (see "[Patient education: Upper endoscopy \(Beyond the Basics\)](#)" and "[Patient education: Colonoscopy \(Beyond the Basics\)](#)")

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## SUMMARY AND RECOMMENDATIONS

- **Clinical manifestations and detection** – Occult bleeding refers to the initial presentation of a positive fecal occult blood test and/or iron deficiency anemia when there is no evidence of visible blood loss to the patient or clinician. By contrast, the term overt is used to describe blood loss that is visible to the patient or clinician. Overt bleeding may manifest as hematemesis, melena, or hematochezia. (See ['Introduction'](#) above.)

Testing for occult bleeding should be done with high sensitivity tests for fecal occult blood or immunochemical tests. (See ["Screening for colorectal cancer: Strategies in patients at average risk"](#), section on ['Choosing a screening test'](#).)

- **Evaluation** – The initial evaluation depends on whether the patient has iron deficiency:
  - Patients without iron deficiency – Patients with a positive fecal occult blood test but without iron deficiency anemia should be evaluated by colonoscopy. If upper gastrointestinal (GI) tract symptoms are present, an upper endoscopy should also be performed. If the endoscopic evaluation is negative and there are no signs of ongoing blood loss, additional testing usually is not recommended ( [algorithm 1](#)). (See ['General approach'](#) above and ['Diagnostic tests'](#) above.)
  - Patients with iron deficiency – Patients with a positive fecal occult blood test and iron deficiency anemia should be evaluated with upper endoscopy and colonoscopy ( [algorithm 1](#)). If these studies are unrevealing, we recommend evaluation for a small bowel source of bleeding, preferably with wireless capsule endoscopy. (See ['General approach'](#) above and ['Diagnostic tests'](#) above and ["Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)"](#).)

Most patients with iron deficiency anemia but a negative fecal occult blood test should also undergo an upper endoscopy and colonoscopy. Possible exceptions are patients with a clear alternative explanation for their iron deficiency anemia (eg, celiac disease or significant hematuria) and asymptomatic, young female patients who continue to menstruate and have mild iron deficiency, provided there is no family history of GI malignancy in a first-degree relative. (See ['Evaluation of isolated iron deficiency anemia'](#) above and ['Premenopausal female patients'](#) above.)

If the initial evaluation with upper endoscopy, colonoscopy, and capsule endoscopy is unrevealing, alternative non-GI sources for the patient's iron deficiency should be considered. If the suspicion for a GI source of blood loss remains high, additional testing is indicated. (See ["Causes and diagnosis of iron deficiency and iron deficiency anemia in adults"](#) and ['General approach'](#) above and ["Evaluation of suspected small bowel bleeding \(formerly obscure gastrointestinal bleeding\)"](#).)



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## Topic 2544 Version 23.0

**GRAPHICS****Causes of occult gastrointestinal bleeding**

<b>Inflammatory/mechanical trauma</b>
Reflux esophagitis
Cameron lesions
Erosive gastritis
Gastric ulcer
Duodenal ulcer
Celiac sprue
Whipple disease
Meckel diverticulum with ulceration
Idiopathic cecal ulcer
Crohn disease
Ulcerative colitis
<b>Mass lesions</b>
Carcinoma (any site)
Large polyps (any site)
<b>Vascular</b>
Vascular ectasia(s)
Portal hypertensive gastropathy
Portal hypertensive enteropathy and colopathy
Gastric antral vascular ectasia
Hemangiomas
Blue rubber bleb nevus syndrome
<b>Infectious</b>
Hookworm
Strongyloidiasis
Ascariasis
Tuberculous enterocolitis
Amebiasis

<b>Miscellaneous</b>
Long-distance running
Factitious
Hemoptysis
Epistaxis
Oropharyngeal

Graphic 69451 Version 3.0

## Causes of small bowel bleeding

Common causes		Rare causes
Under age 40 years	Over age 40 years	
<ul style="list-style-type: none"> <li>▪ Inflammatory bowel disease</li> <li>▪ Meckel's diverticulum</li> <li>▪ Dieulafoy lesions</li> <li>▪ Neoplasia</li> <li>▪ Polyposis syndromes</li> </ul>	<ul style="list-style-type: none"> <li>▪ NSAID ulcers</li> <li>▪ Angioectasia</li> <li>▪ Dieulafoy lesions</li> <li>▪ Neoplasia</li> </ul>	<ul style="list-style-type: none"> <li>▪ Immunoglobulin A vasculitis (Henoch-Schönlein purpura)</li> <li>▪ Small bowel varices and/or portal hypertensive enteropathy</li> <li>▪ Amyloidosis</li> <li>▪ Blue rubber bleb nevus syndrome</li> <li>▪ Pseudoxanthoma elasticum</li> <li>▪ Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)</li> <li>▪ Kaposi sarcoma with AIDS</li> <li>▪ Plummer-Vinson syndrome</li> <li>▪ Ehlers-Danlos syndrome</li> <li>▪ Inherited polyposis syndromes (FAP, Peutz-Jeghers)</li> <li>▪ Malignant atrophic papulosis</li> <li>▪ Hematobilia</li> <li>▪ Aortoenteric fistula</li> <li>▪ Hemosuccus entericus</li> </ul>

FAP: familial adenomatous polyposis; NSAID: nonsteroidal anti-inflammatory drug.

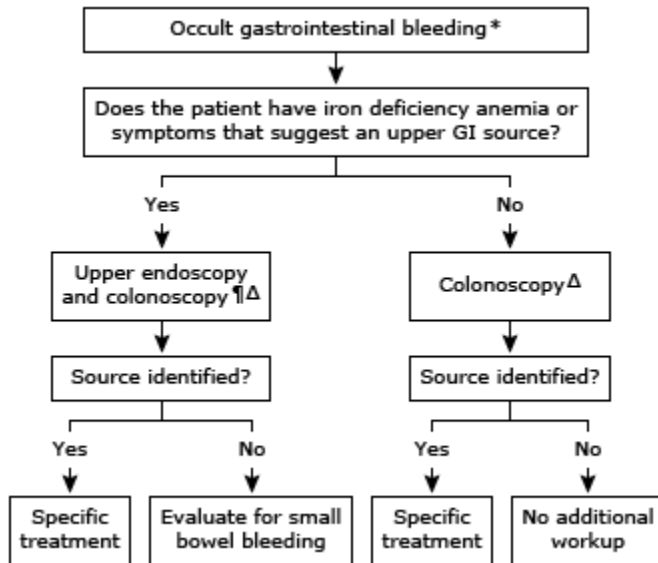
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*Adapted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding. Am J Gastroenterol 2015; 110:1265. Copyright © 2015. [www.nature.com/ajg](http://www.nature.com/ajg).*

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Graphic 104990 Version 3.0

## Evaluation of occult gastrointestinal bleeding



GI: gastrointestinal.

\* Occult bleeding refers to hemocult-positive stool and/or iron deficiency anemia without visible evidence of bleeding (eg, melena or hematochezia).

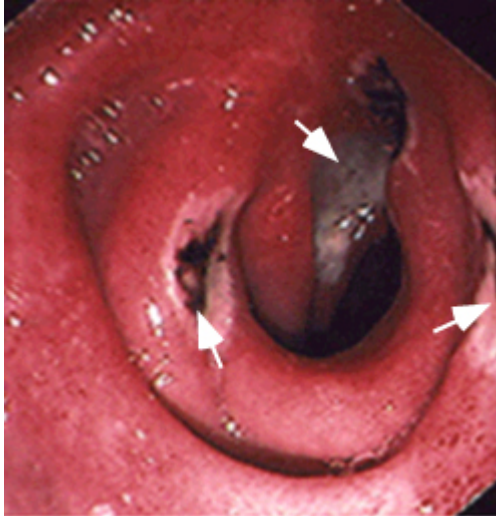
¶ Consider evaluation with a side-viewing duodenoscope if there are risk factors for hemobilia or hemosuccus pancreaticus, or a push enteroscopy in patients at risk for an aortoenteric fistula (though if the suspicion for an aortoenteric fistula is high, the evaluation should also include computed tomographic angiography).

Δ If the initial colonoscopy was inadequate, a repeat colonoscopy should be performed.

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Graphic 94181 Version 3.0

## Multiple duodenal ulcers



Upper gastrointestinal endoscopy shows multiple duodenal ulcers (arrows) in an elderly patient who was chronically treated with a nonsteroidal antiinflammatory drug. The patient was asymptomatic, and presented only with anemia.

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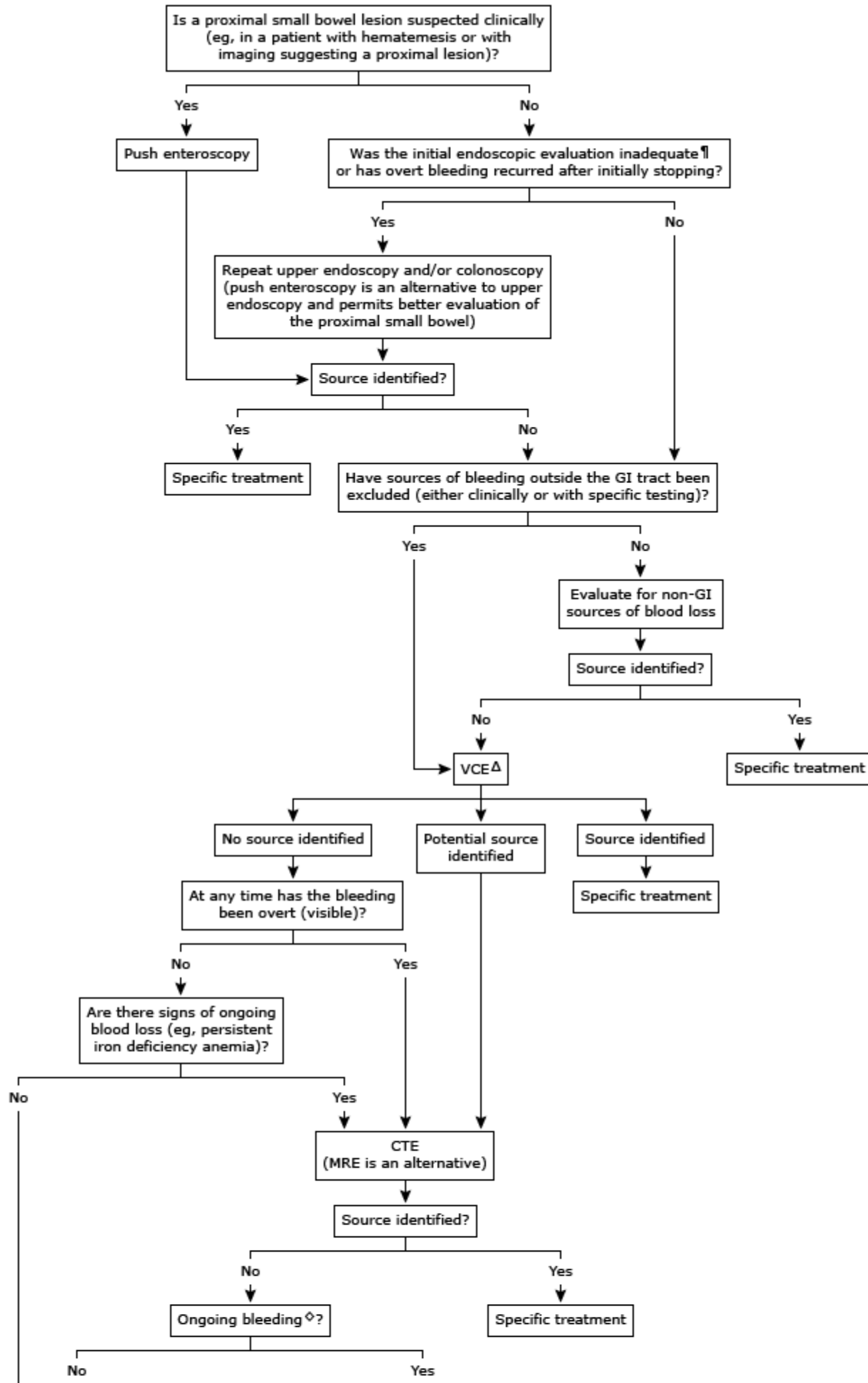
*Courtesy of James B McGee, MD.*

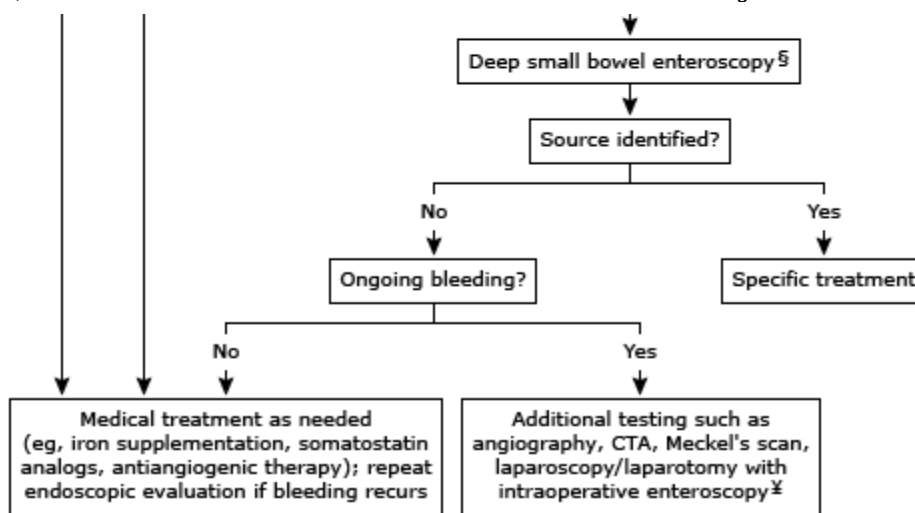
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Graphic 68358 Version 1.0



## **Evaluation of suspected small bowel bleeding in hemodynamically stable patients\***





GI: gastrointestinal; VCE: video capsule endoscopy; CTE: computed tomographic enterography; MRE: magnetic resonance enterography; CTA: computed tomographic angiography.

\* Small bowel bleeding should be suspected in patients with signs of GI bleeding who have had a negative initial endoscopic evaluation (typically upper endoscopy and colonoscopy). The evaluation of hemodynamically unstable patients is discussed in the context of the specific bleeding manifestations (eg, hematemesis). Refer to UpToDate topic reviews on the evaluation and management of GI bleeding for details.

¶ For patients with risk factors for hemobilia or hemosuccus pancreaticus, the upper endoscopy should have included evaluation with a side-viewing duodenoscope. Patients with risk factors for an aortoenteric fistula should also have undergone CTA. If the initial upper endoscopy and/or colonoscopy was inadequate (eg, fair or poor visualization, failure to reach the cecum), repeat examination should be considered before initiating an evaluation for small bowel bleeding.

Δ VCE should be done as close to the acute bleeding episode as possible to increase diagnostic yield. Patients at risk for capsule retention should undergo small bowel imaging (eg, CTE) or a patency capsule study prior to VCE.

◇ In patients with significant comorbid illnesses with slow rates of blood loss, it may be reasonable to stop the evaluation and treat with iron repletion and/or transfusions as needed.

§ Push enteroscopy is an alternative if not already done and if deep small bowel enteroscopy is not available. Intraoperative enteroscopy is an alternative if there are contraindications to deep small bowel enteroscopy, such as dense intra-abdominal adhesions.

‡ The choice of test will depend on the rate of bleeding, patient characteristics, and the degree of suspicion for a small bowel lesion. A Meckel's scan should be performed in younger patients with overt bleeding. Angiography or CTA can be obtained if there is active bleeding. Surgical exploration is appropriate if no other studies have revealed a source and significant bleeding continues or if there is high suspicion for a small bowel neoplasm. If the evaluation is still negative, non-GI sources of blood loss should be reconsidered.

## Contributor Disclosures

**Molly Perencevich, MD** No relevant financial relationship(s) with ineligible companies to disclose. **John R Saltzman, MD, FACP, FACG, FASGE, AGAF** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Anne C Travis, MD, MSc, FACG, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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