

# ACG CLINICAL GUIDELINE: DIAGNOSIS AND MANAGEMENT OF SMALL BOWEL BLEEDING

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CME

# ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding

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- ▣ Bleeding from the small intestine remains a relatively uncommon event, accounting for ~5–10% of all patients presenting with gastrointestinal (GI) bleeding
- ▣ Known previously as obscure GI hemorrhage (OGIB), we propose in this guideline that the former term referred to as OGIB be reclassified as small bowel bleeding.

# Definition of overt or occult small bowel bleeding:

## 1) Traditional definitions:

- ▣ The traditional definition of “OGIB” before the introduction of VCE and deep enteroscopy included patients with overt or occult GI bleeding who underwent normal upper and lower endoscopic examinations in addition to a small bowel series that did not reveal a source of bleeding.

Patients with overt obscure bleeding were defined as patients presenting with either hematochezia or melena, whereas patients with occult obscure bleeding were classified based on the presence of a positive fecal occult blood test with or without iron-deficiency anemia.

## 2) New definition:

- With the introduction of VCE in the United States in 2001 and deep enteroscopy in 2004, the majority (~75%) of patients previously classified as having obscure bleeding were found to have sources of bleeding identified in the small intestine
- The diagnostic yield included any causes of bleeding detected distal to the ampulla of Vater or proximal to the ileocecal valve by any testing modality including push enteroscopy, ileoscopy, deep enteroscopy, VCE, angiography, or an enterography examination.

- ▣ A source of small bowel bleeding should be considered in patients with overt or occult GI hemorrhage after performance of a normal upper and lower endoscopic examination.
- ▣ Patients should be classified as having small bowel bleeding if a source of bleeding is identified distal to the ampulla of Vater and/or proximal to the ileocecal valve.
- ▣ After normal upper and lower endoscopic examinations and before performance of capsule endoscopy, patients should be classified as having “potential small bowel bleeding.”

- ▣ “Overt small bowel bleeding” refers to patients presenting with either melena or hematochezia with a source of bleeding identified in the small intestine. The term “occult small bowel bleeding” can be reserved for patients presenting with iron-deficiency anemia with or without guaiac-positive stools who are found to have a small bowel source of bleeding.



- ▣ The term “obscure GI bleeding” should be reserved for patients not found to have a source of bleeding after performance of standard upper and lower endoscopic examinations , small bowel evaluation with VCE and/or enteroscopy, and radiographic testing.

- ▣ *Prevalence and etiology of small bowel bleeding:*
  - The prevalence of small bowel lesions has been estimated to be ~5–10% in patients presenting with GI bleeding.
  
  - A history of a bleeding diathesis as with vonWillebrand disease and medication usage including aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants, and/or other antiplatelet agents also can lend clues to the diagnosis.

- ▣ Knowledge of comorbidities such as valvular heart disease and prior procedures/surgeries such as liver biopsy, liver transplantation, abdominal aortic aneurysm repair, or bowel resection again can be very helpful.
  
- ▣ Common causes of small bowel bleeding are listed in **Table below** and are found in ~75% of patients with suspected small bowel bleeding.

**Table 2. Causes of small bowel bleeding**

Common causes		Rare causes
<b>Under age 40 years</b>	<b>Over age 40 years</b>	<b>Henoch–Schoenlein purpura</b>
Inflammatory bowel disease	Angioectasia	Small bowel varices and/or portal hypertensive enteropathy
Dieulafoy’s lesions	Dieulafoy’s lesions	Amyloidosis
Neoplasia	Neoplasia	Blue rubber bleb nevus syndrome
Meckel’s diverticulum	NSAID ulcers	Pseudoxanthoma elasticum
Polyposis syndromes		Osler–Weber–Rendu syndrome
		Kaposi’s sarcoma with AIDS
		Plummer–Vinson syndrome
		Ehlers–Danlos syndrome
		Inherited polyposis syndromes (FAP, Peutz–Jeghers)
		Malignant atrophic papulosis
		Hemato-bilia
		Aorto-enteric fistula
		Hemosuccus entericus

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

- ▣ An analysis comparing diagnostic yields from Western compared to Asian countries demonstrated that patients undergoing DBE in Asian countries were more likely to have neoplastic findings, whereas angioectasia were more common in Western countries.

- Age has been known to be a determinant for the type of small bowel pathology detected. Patients under the age of 40 years are more likely to have inflammatory bowel disease or Meckel's diverticulum.
- Small bowel neoplasms (e.g., GI stromal cell tumor, lymphoma, carcinoid, adenocarcinoma, or other polypoid lesions) and Dieulafoy's lesions can occur in both younger and older patient cohorts.
- Angioectasia, other vascular lesions, and ulcers secondary to anti-inflammatory agents are more likely in patients over the age of 40 years.
- Data regarding ethnicity and small bowel findings has not been extensively published to date.

▣ *Differences in findings between patients with overt or occult small bowel bleeding :*

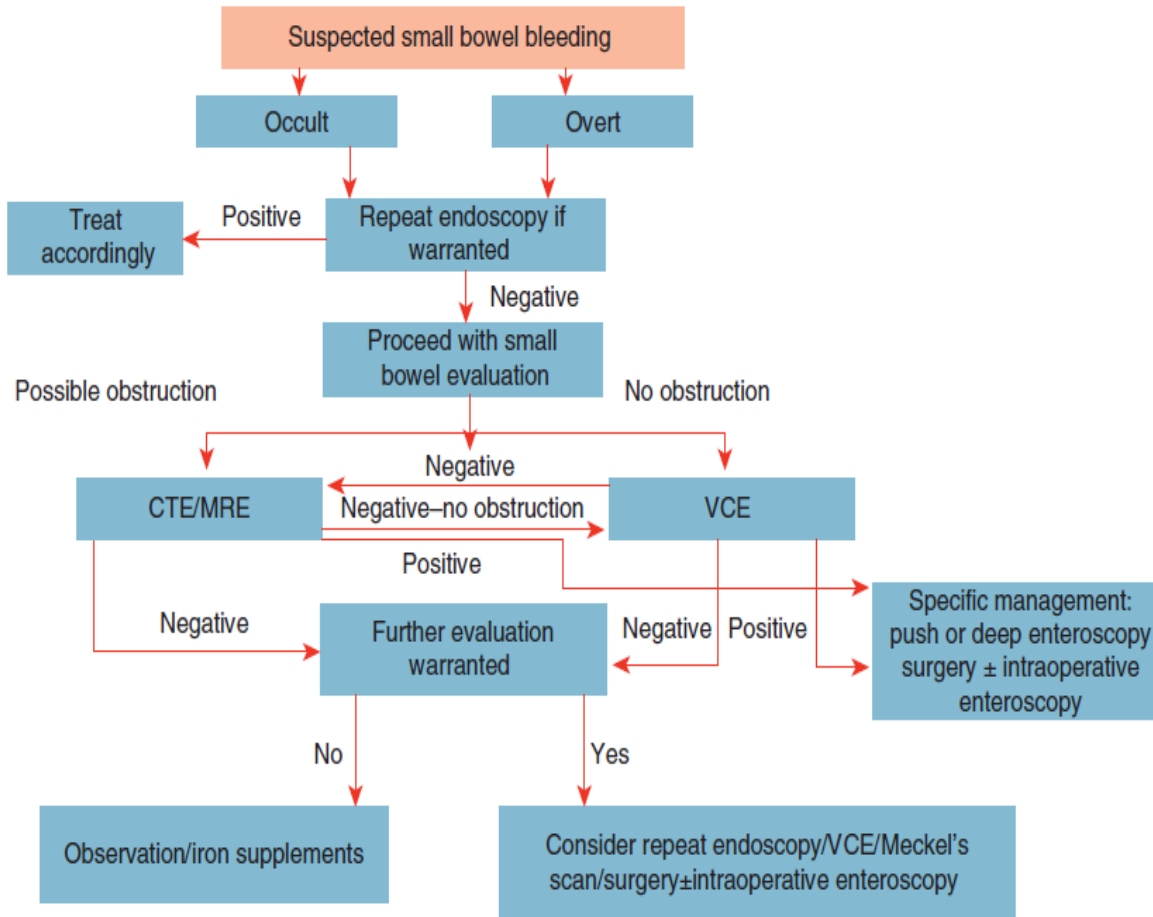
- ▣ Studies using VCE and deep enteroscopy have demonstrated higher diagnostic yields for patients with overt bleeding compared with patients with occult bleeding.
- ▣ For patients with prior overt bleeding, the diagnostic yield was less than that for current overt bleeders, and decreased substantially with time.

- ▣ In a 2004 study by Pennazio *et al.* ( 12 ) of 100 patients undergoing VCE, the diagnostic yield was 92% for patients with overt bleeding, 44% for occult bleeders, 67% for patients with prior overt bleeding who were studied within 10–14 days, and 33% at 3–4 weeks post bleeding episode.
- ▣ In addition to higher diagnostic yields for patients with overt bleeding, recurrence rates may be higher in patients presenting with overt bleeding.



- ▣ Prior clinical guidelines have listed celiac disease as a cause of small bowel bleeding , but there is emerging evidence that celiac disease leads to iron-deficiency anemia because of malabsorption and not because of the presence of occult GI bleeding.
- ▣ Although complications associated with celiac disease such as ulcerative jejunitis, lymphoma, and/or adenocarcinoma can cause bleeding from the small intestine, the entity of celiac disease is no longer listed as a cause of small bowel bleeding.

# Approach to suspected small bleeding



**Figure 1.** Algorithm for suspected small bowel bleeding. CTE, computed tomographic enterography; MRE, magnetic resonance enterography; VCE, video capsule endoscopy.

## ▣ Diagnosis of small bowel bleeding

### *Recommendations*

- 1 . Second-look upper endoscopy should be considered in cases of recurrent hematemesis, melena, or a previously incomplete exam (strong recommendation, low level of evidence)
- 2 . Second-look colonoscopy should be considered in the setting of recurrent hematochezia or if a lower source is suspected (conditional recommendation, very low level of evidence).
- 3 . If the second-look examinations are normal, the next step should be a small bowel evaluation (strong recommendation , moderate level of evidence).

- ▣ 4 . Push enteroscopy can be performed as a second-look examination in the evaluation of suspected small bowel bleeding(conditional recommendation, moderate level of evidence).
- ▣ 5 . VCE should be considered a first-line procedure for small bowel (SB) evaluation after upper and lower GI sources have been excluded, including second-look endoscopy when indicated (strong recommendation, moderate level of evidence).
- ▣ 6 . Owing to the lower detection rate of lesions in the duodenum and proximal jejunum with VCE, push enteroscopy should be performed if proximal lesions are suspected (strong recommendation, very low level of evidence).
- ▣ 7 . Total deep enteroscopy should be attempted if there is a strong suspicion of a small bowel lesion based on clinical presentation or abnormal VCE study (strong recommendation, moderate level of evidence).

- ▣ 8 . Any method of deep enteroscopy can be used when endoscopic evaluation and therapy is required based on similar diagnostic yields (strong recommendation, high level of evidence).
- ▣ 9 . Intraoperative enteroscopy (IOE) is a highly sensitive but invasive diagnostic and effective therapeutic procedure. Its usage should be limited to scenarios where enteroscopy cannot be performed, such as patients with prior surgeries and intestinal adhesions (strong recommendation, low level of evidence).
- ▣ 10 . VCE should be performed before deep enteroscopy to increase diagnostic yield. Initial deep enteroscopy can be considered in cases of massive hemorrhage or when VCE is contraindicated (strong recommendation, high level of evidence).

## ▣ Second-look endoscopy:

Most small intestinal bleeding is undramatic in presentation and either presents as stable overt or occult bleeding.

The prior literature demonstrated that a high percentage of patients designated as having “potential small bowel bleeding” were found to have missed bleeding sources within reach of conventional upper and lower endoscopy including diagnostic yields ranging from 2 to 25% in patients undergoing repeat esophagogastroduodenoscopy and 6 to 23% on repeat colonoscopy. More recent studies using DBE and capsule endoscopy have also confirmed these findings .

## ▣ Push enteroscopy

Push enteroscopy is an extended upper endoscopy performed with a long endoscope such as a pediatric colonoscope or with a commercially available push enteroscope, which is typically 250 cm in length.

▣ Push enteroscopy allows only limited evaluation of the proximal SB, ~70 cm distal to the ligament of Treitz. Push enteroscopy using a colonoscope typically can be passed 45–60 cm beyond the ligament of Treitz. When push enteroscopy is carried out with the variable stiffness design, it reaches a deeper distance of nearly 90 cm .



- ▣ The diagnostic yield of push enteroscopy is reported to range from 3 to 70%, with the majority of SB findings being vascular lesions .
- ▣ Interestingly, most of the lesions diagnosed on push enteroscopy have been found in locations accessible to standard esophagogastroduodenoscopy, emphasizing the importance of second-look endoscopy.
- ▣ The main disadvantages of this exam include looping of the enteroscope and patient discomfort. Its role is currently limited to endoscopic therapeutics in those patients who have only proximal SB lesions detected on VCE.

- ▣ Although it has only a limited range, push enteroscopy is an ideal second-look procedure because of the ability to examine the distal duodenum and proximal jejunum, a SB segment that is not always well seen with VCE.

## ▣ Comparison of endoscopic modalities in suspected small bowel bleeding:

✓ *Capsule endoscopy compared with push enteroscopy and small bowel follow-through :*

- ▣ Multiple retrospective and prospective studies have found VCE to be superior to both push enteroscopy and small bowel series in the evaluation of patients with suspected small bowel bleeding.
- ▣ A meta-analysis of studies that compared VCE and push enteroscopy showed that VCE had an incremental yield of 30% (yield 56% vs. 26%) for clinically significant findings in patients with small bowel bleeding sources.
- ▣ Similarly, VCE had an incremental yield of 36% over small bowel series (yield 42% vs. 6%) ( 132 ).

- ▣ Based on sub analysis of the data, VCE had a higher yield for both vascular and inflammatory lesions.
- ▣ VCE has hence largely replaced push enteroscopy and small bowel series in the evaluation of the SB, and is currently recommended as the third test of choice in patients with suspected small bowel bleeding, who have had a negative esophagogastroduodenoscopy and colonoscopy.

✓ *DBE compared with push enteroscopy and VCE:*

- ▣ A study by May *et al.* ( 85 ), which compared DBE to push enteroscopy in 52 patients with suspected small bowel bleeding, found that DBE not only allowed a greater depth of intubation (230 vs. 80 cm) but also had a higher yield for small bowel findings (73% vs. 44%). Furthermore , DBE facilitated detection of additional lesions in the distal small bowel in patients who had positive findings on push enteroscopy.

- ▣ Several studies have compared the yield of VCE with DBE, but have shown inconsistent results because of their small sample size
- ▣ A meta-analysis of 11 studies that compared these modalities in patients with SB disease (majority with suspected small bowel bleeding) showed a comparable diagnostic yield (60% vs. 57%; incremental yield of 3%) for all SB findings. The yield with the tests was also similar for vascular, inflammatory, and neoplastic lesions.

- ▣ Another meta-analysis of eight studies also found no difference in diagnostic yield between the two tests for the evaluation of SB disease (odds ratio 1.21, 95% confidence interval (CI): 0.64–2.29).
- ▣ In patients with small bowel bleeding, VCE had a higher yield as compared with DBE using a single approach (odds ratio 1.61, 95% CI: 1.07–2.43), but a significantly lower yield as compared with DBE using a combined antegrade and retrograde approach (odds ratio 0.12, 95% CI: 0.03–0.52).
- ▣ This finding reinforces the importance of total enteroscopy with DBE in patients with high clinical suspicion for an SB lesion.

- ▣ VCE has been reported to be useful as a screening tool before DBE in patients with suspected small bowel bleeding. This approach of a 'targeted DBE' has been reported to increase both the diagnostic (73–93%) and therapeutic yield (57–73%) of the test



- ▣ Furthermore, VCE transit times have been found useful in guiding the optimal route of DBE. Owing to deeper intubation of the small bowel and a higher success rate with the oral approach, this is the preferred route for lesions suspected to lie within the proximal 75% of the small bowel, whereas the rectal route is used for more distal lesions.
- ▣ Because of the high negative predictive value of VCE, the approach of VCE-guided DBE allows avoidance of DBE in patients with a low pretest probability for SB findings.

- ▣ However, the concept of CE-guided DBE may not be applicable in all patients. VCE has a false-negative rate of 11% for all SB findings, and more importantly, up to 19% for neoplasms.
- ▣ Additional findings on repeat VCE have been detected in up to 75% of patients with suspected small bowel bleeding, thereby leading to a change in management in 62%.
- ▣ There have also been reports of neoplasms missed on VCE and subsequently diagnosed at DBE. Hence, in patients with a negative VCE, in whom there is a high clinical suspicion for an SB lesion, DBE should still be pursued, including consideration for total enteroscopy.

- ▣ The indications for DBE in patients with suspected small bowel bleeding is broad, and include:
  - ✓ patients who have a positive VCE, both for tissue diagnosis and therapeutics
  - ✓ patients in whom VCE is contraindicated
  - ✓ patients with a negative VCE, but high clinical suspicion for SB lesion
  - ✓ in patients with active bleeding

- ▣ *Spiral enteroscopy compared with DBE* . In a small prospective, cross-over, single-center trial comparing oral DBE to spiral enteroscopy in patients with suspected small bowel vascular malformations, the mean insertion time was significantly quicker for spiral enteroscopy (43 vs. 65 min;  $P = 0.007$ ).
- ▣ However, more importantly, the depth of insertion was significantly greater for DBE (310 vs. 250 cm;  $P = 0.004$ ).
- ▣ A more recent prospective study found them to be similar in terms of insertion time and distance, as well as of diagnostic and therapeutic yield .

Diagnosis using radiographic techniques

## Diagnosis using radiographic techniques

### *Recommendations*

1. Barium studies should not be performed in the evaluation of small bowel bleeding (strong recommendation, high level evidence).
2. CTE should be performed in patients with suspected small bowel bleeding and negative capsule endoscopy because of higher sensitivity for the detection of mural-based small bowel masses, superior capability to locate small bowel masses, and ability to guide subsequent deep enteroscopy. (strong recommendation, low level of evidence).
3. CT is preferred over MR imaging for the evaluation of suspected small bowel bleeding. MR can be considered in patients with contraindications for CT or to avoid radiation exposure in younger patients (conditional recommendation, very low level of evidence).
4. CTE could be considered before VCE in the setting of established inflammatory bowel disease, prior radiation therapy, previous small bowel surgery, and/or suspected small bowel stenosis (strong recommendation, very low level of evidence).
5. In patients with suspected small bowel bleeding and negative VCE examination, CTE should be performed if there is high clinical suspicion for a small bowel source despite the performance of a prior standard CT of the abdomen (conditional recommendation, very low level of evidence).

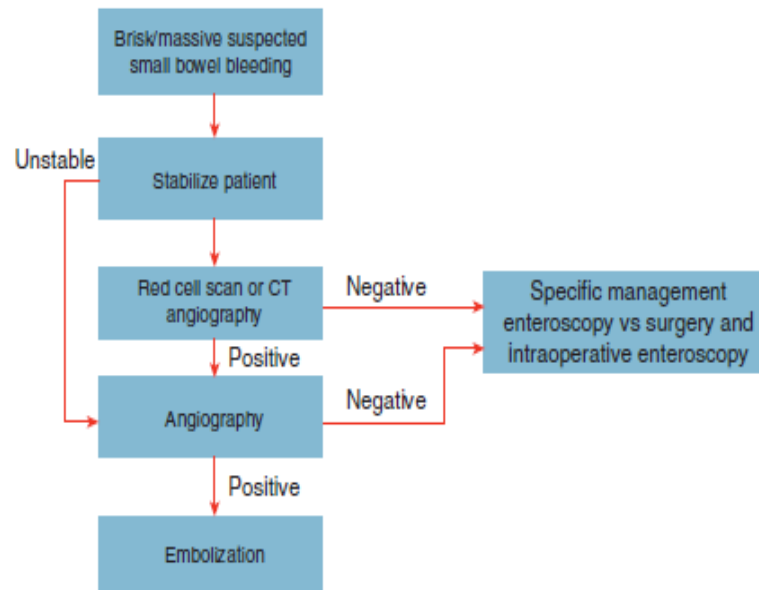
## ▣ *CT enterography* :

- ✓ Several studies have shown that VCE has higher yields for detecting vascular and inflammatory lesion compared with CTE
- ✓ However, some studies have shown that CTE can detect vascular and inflammatory abnormalities, which may be missed on VCE . The detection of subtle vascular abnormalities at CTE may be influenced by technique and experience.
- ✓ An advantage of CTE over VCE is the improved detection of small bowel masses, especially those that are mural-based. In a study by Huprich *et al*, CTE detected 9/9 small bowel tumors, whereas VCE only detected 3/9 of the lesions.

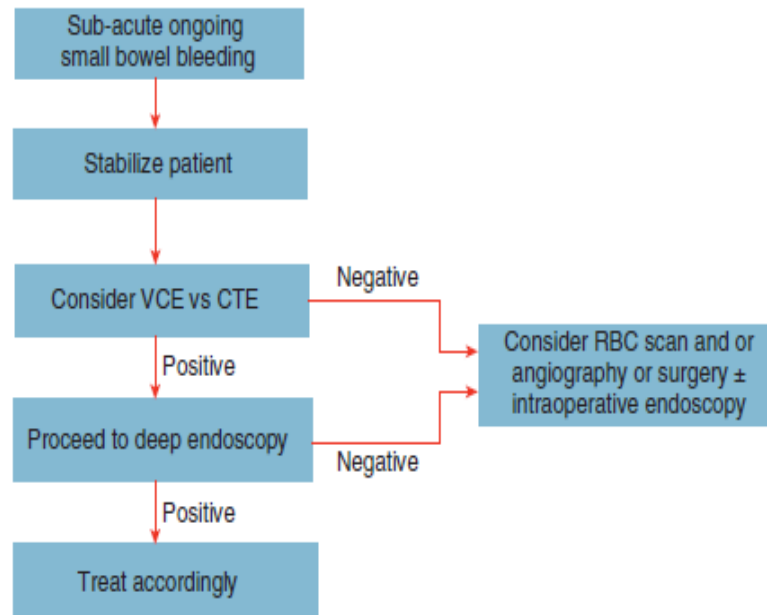
- ▣ Therefore, CTE and VCE are complementary examinations. In a study of 30 patients with negative CTE, subsequent VCE was positive in 57% . In another study of 52 patients with non diagnostic VCE, subsequent CTE had a 50% positive yield in those patients with overt small bowel bleeding
- ▣ Compared with cross-sectional imaging studies, VCE is uniformly superior for demonstration of vascular abnormalities whereas cross-sectional imaging can identify masses and some inflammatory changes missed at VCE.
- ▣ Another advantage of cross-sectional small bowel imaging techniques is the ability to screen for contraindications to capsule endoscopy. In one study, 11% of patients being evaluated for suspected small bowel bleeding were excluded from VCE secondary to high-grade strictures identified on MR enterography



# ▣ Overt acute GI bleeding



**Figure 2.** Algorithm for brisk or massive suspected small bowel bleeding. CT, computed tomography.



## ▣ *Recommendations*

- ▣ 1 . In acute overt massive GI bleeding, conventional angiography should be performed emergently for hemodynamically unstable patients (strong recommendation, low level of evidence).
  
- ▣ 2 . In hemodynamically stable patients with evidence of active bleeding, multiphasic CT (CTA) can be performed to identify the site of bleeding and guide further management (strong recommendation, low level of evidence).
  
- ▣ 3 . In patients with acute overt GI bleeding and slower rates of bleeding (0.1–0.2 ml/min), or uncertainty if actively bleeding, tagged red blood cell (RBC) scintigraphy should be performed if deep enteroscopy or VCE are not performed to guide timing of angiography (strong recommendation, moderate level of evidence).

- ▣ 4 . In brisk active overt bleeding, CTA is preferred over CTE(conditional recommendation, very low level of evidence).
- ▣ 5 . Conventional angiography should not be performed as a diagnostic test in patients without overt bleeding (conditional recommendation, very low level of evidence).
- ▣ 6 . Provocative angiography can be considered in the setting of ongoing overt bleeding and negative VCE, deep enteroscopy, and/or CT examination (conditional recommendation, very low level of evidence).
- ▣ 7 . In younger patients with ongoing overt bleeding and normal testing with VCE and enterography examinations, a Meckel's scan should be performed (conditional recommendation,very low level of evidence).

# Radiographic diagnosis for overt GI bleeding

- ▣ CT angiography:
- ▣ Most studies using CT to evaluate GI bleeding are performed during multiple phases of contrast enhancement with one of the phases occurring during the arterial phase of enhancement.
- ▣ When performed with oral contrast, this is referred to as multiphasic CTE.
- ▣ When no oral contrast is administered, the technique has been termed multiphasic CT or CTA.
- ▣ Multiphasic CT or CTA is usually performed to detect the site of active bleeding in cases of acute overt bleeding, which can occur sporadically or in the setting of small bowel bleeding. CTA has been shown to be able to detect bleeding rates as slow as 0.3 ml/min compared with 0.5–1.0 ml/min for conventional angiography and 0.2 ml/min for <sup>99m</sup>Tc tagged RBC scintigraphy.

- ✓ A meta-analysis of 9 studies with 198 patients showed CTA had a pooled sensitivity of 89% and specificity of 85% in diagnosing acute GI bleeding throughout the GI tract .
- ✓ Several of these studies showed detection by CTA which were negative by other techniques.
- ✓ CT is widely available and can be performed rapidly during the time of bleeding, which may aid in detection compared with other techniques.
- ✓ CT has also been shown to localize accurately the site of bleeding . Other studies have shown sensitivities of 79–94% and specificity of 95–100% for detecting active bleeding throughout the GI tract

- ▣ CTA can also be used to help triage patients for further management. In one study, 64/86 CT angiograms were negative and 92% of these patients required no further intervention. There were no cases with a negative CTA that had a subsequent positive conventional angiogram within 24 h.
- ▣ Therefore, some have recommended watchful waiting in cases with a negative CTA as the bleeding rate may be low or intermittent and conventional angiography rarely shows an additional site of bleeding.
- ▣ Factors predictive for a positive conventional angiogram following a positive CTA include non-diverticular etiologies and lower hemoglobin levels and should be performed soon after the CTA to enhance detection.

## ▣ CTA limitations:

- ✓ CTA has some limitations however. To detect contrast extravasation, the patient must be actively bleeding at the time of the scan.
- ✓ The findings of blood within the lumen or sentinel clot may help to localize the source if the bleeding is subtle or absent.
- ✓ If no active bleeding or source is identified at the time of the CTA additional workup may be necessary.
- ✓ In elderly patients with decreased renal function, the administration of the intravenous contrast for CT may increase the risk of renal complications if subsequent conventional angiography is required.



## ▣ **Scintigraphy:**

- ✓ 99m Tc-labeled RBC scintigraphy has been used in the evaluation of overt acute GI bleeding for many years.
- ✓ Advantages of scintigraphy include the ability to detect lower rates of bleeding and the ability to perform delayed imaging that can improve detection of intermittent or delayed bleeding.
- ✓ Detection of bleeding at angiography may be enhanced by timing the angiogram to evidence of active bleeding at scintigraphy.
- ✓ Therefore, the examination must be closely monitored so that the patient can be taken quickly to angiography.
- ✓ Limitations of scintigraphy include the reported variability in localization of bleeding, which may be more difficult in the foregut and small bowel, and the inability to characterize the source of bleeding.

- ✓ There is a wide range of reported sensitivities (33–93%), specificity (30–95%), diagnostic yields (26–87%), and localization accuracy (19–100%) for scintigraphy throughout the GI tract
- ✓ Because bleeding is intermittent, scintigraphy may be helpful in identifying the site of bleeding when other diagnostic tests have been negative.
- ✓ Negative scintigraphy may also be an indicator of better outcomes. In some studies, many of the patients with negative scans may stop bleeding spontaneously and need no further treatment, whereas those with positive scans may need intervention.

## ▣ Scintigraphy limitations:

- ✓ Because of the large variations in the reported diagnostic yield, sensitivity, accuracy in localization, and correlation of outcomes combined with the inability to characterize the source of bleeding, there is considerable controversy on the use of scintigraphy for acute overt GI bleeding.

- ✓ In younger patients with ongoing overt bleeding and negative evaluation with VCE, CTE, or other testing modalities, consideration should be made for testing with a  $^{99m}\text{Tc}$ -pertechnetate scan for detection of Meckel's diverticulum .
- ✓ There are several false positives that occur related to uptake in ulcers, inflammatory lesion, arteriovenous malformations, obstruction, intussusceptions, and ectopic gastric mucosa in other lesions such as duplication cysts.
- ✓ False negatives can occur with anatomic or physiologic cause or other inflammation such as ectopic pancreatic mucosa, which can be present in up to 74% of diverticula.

## ▣ Angiography:

- ✓ As with scintigraphy, conventional angiography has been used for many years in patients with active GI bleeding, especially in those who may be more hemodynamically unstable.
- ✓ An advantage of angiography is the ability to perform therapeutic intervention with transarterial embolization at the time of diagnosis and angiography is not hampered by impaired visualization of the source by intraluminal blood.

- ✓ Limitations of angiography include the need for higher rates of bleeding (0.5–1.0 ml/min) for detection and the risk of complications (including renal failure, thromboembolic events, and more commonly infections or bleeding at the catheter site) that can occur in up to 10%.
- ✓ Predictors of positive angiography include hemodynamic instability, particularly in those who require transfusion of  $\geq 5$  U to achieve hemodynamic stability.
- ✓ A positive yield was shown to increase to 87% with more massive GI bleeding. Angiographic yields are highest when the patient is actively bleeding with minimal delay from presentation.

- ✓ Patients with a negative tagged RBC scan implying a slow bleeding rate or a negative CT angiogram are unlikely to have a positive conventional angiogram.
- ✓ In patients with a positive CT angiogram, those with non-diverticular etiologies and lower hemoglobin were more likely to have a subsequent positive conventional angiogram.

## ▣ Treatment and outcomes

### ▣ *Recommendations:*

1 . If a source of bleeding is found by VCE and/or deep enteroscopy in the small intestine that is associated with significant ongoing anemia or active bleeding, then the patient should be managed with endoscopic therapy (strong recommendation ,low level of evidence).

2 . If after appropriate small bowel investigation no source of bleeding is found, the patient should be managed conservatively with oral iron or by intravenous infusion as is dictated by the severity and persistence of the associated iron deficiency anemia. In this context, a small vascular lesion found on capsule endoscopy does not always need treatment(strong recommendation, very low level evidence).

3 . If bleeding persists in either of the above situations with worsening anemia, a further diagnostic workup should include a repeated upper and lower endoscopy, VCE, deep enteroscopy, CT, or MRenterography as is appropriate for the clinical situation and availability of investigative devices (strong recommendation, low level evidence).



4 . If bleeding persists or recurs or a lesion cannot be localized consideration may be given to medical treatment with iron, somostatin analogs, or antiangiogenic therapy (strong recommendation, moderate level evidence).

5 . Anticoagulation and/or antiplatelet therapy should be discontinued if possible in patients with small bowel hemorrhage (conditional recommendation, very low level evidence).

6 . Surgical intervention in massive small bowel bleeding maybe useful, but is greatly aided with pre surgical localization of the bleeding site by marking the lesion with a tattoo (strong recommendation, low level evidence).

- ▣ 7. IOE should be available at the time of the surgical procedure to provide assistance to localize the source of bleeding and to perform endoscopic therapy (conditional recommendation, low level of evidence).
- ▣ 8 . Patients with Heyde's syndrome (aortic stenosis and angiodysplasia) and ongoing bleeding should undergo aortic valve replacement (conditional recommendation, moderate level of evidence).
- ▣ 9 . For patients with recurrence of small bowel bleeding , endoscopic management can be considered depending on the patient's clinical course and response to prior therapy (conditional recommendation, moderate level of evidence).

## ▣ Treatment of small bowel vascular lesions

- ✓ Evidence from randomized controlled clinical trials as to how best to treat small bowel bleeding has been very limited. Data from the precapsule era on angioectasias found in the stomach and colon demonstrated that non-bleeding lesions were not treated, whereas those actively bleeding were treated endoscopically .
- ✓ Angioectasias in the stomach and colon may be markers for small bowel angioectasia. Despite endoscopic therapy, the recurrence rate after treatment of vascular lesions has ranged from 20 to nearly 50%.

## ▣ Endoscopic therapy:

- ▣ Data regarding efficacy of endoscopic therapy for small bowel vascular lesions were limited to studies using push enteroscopy and surgical intervention before 2001. Despite ongoing usage of push enteroscopy with heater probe therapy and introduction of deep enteroscopy after 2004, rebleeding rates from vascular lesions have not declined significantly.
- ▣ In the era before deep enteroscopy, most angioectasia in the stomach and/or colon were treated with tools including monopolar and bipolar probes that provided electrocoagulation, or neodymium yttrium-aluminum-Garnet laser that provided tissue coagulation. Since 2001, argonplasma coagulation has been primarily used as the treatment of choice.

- ▣ As a general statement, the outcomes associated with treatment of small bowel sources of bleeding have been disappointing and there has been a paucity of data regarding outcomes after treatment of small bowel angioectasia.
- ▣ To date, there have not been any published trials comparing endoscopic therapy of angioectasia compared with sham therapy or trials where only actively bleeding lesions or lesions of a certain size are treated compared with therapy for all visualized lesions.

- ▣ Given these limitations, recurrence of bleeding has been used as a surrogate as to the effectiveness of treatment. Even this strategy is limited because we know little of whether there are subsets of vascular lesions in the small intestine that do benefit from therapy.
- ▣ Two randomized controlled studies demonstrated lack of benefit of either intervention, VCE vs. radiology, or by hormonal therapy compared with placebo.
- ▣ In the radiology study vs. VCE, the rebleeding rate was 30% in those studied by capsule vs. 24% investigated by radiology, a nonsignificant difference.
- ▣ Similarly, the rebleeding rate in the study using hormonal therapy vs. placebo showed a nonsignificant 7% difference after a mean of 412 days of follow-up.

- ▣ There have been several studies looking at the recurrence of bleeding after endoscopic treatment of vascular lesions in the small intestine as a measure of its effectiveness.
- ▣ The most recent was of a retrospective cohort study carried out at a French tertiary-referral center between January 2004 and December 2007. Of 261 patient who presented with suspected small bowel bleeding, 129 of 133 (97%) patients with small bowel vascular lesions were successfully treated with argon plasma coagulation (using DBE).
- ▣ At 36 months, rebleeding occurred in 45/98 (46%) patients.

- ▣ A second study involved 274 patients who had undergone DBE at two different centers between 2004 and 2006. At 12 months, 43% of 101 patients reported no further overt bleeding, 23% reported recurrent overt bleeding, and 35% reported ongoing iron and/or transfusion requirements.



- ▣ Risk factors for recurrent bleeding from small bowel angioectasia have included:
  - ✓ the number of vascular lesions
  - ✓ age over 65 years
  - ✓ presence of lesions in the jejunum
  - ✓ presence of cardiac valvular disease,
  - ✓ chronic renal disease
  - ✓ usage of anticoagulant medication
  - ✓ need for transfusion.

- ▣ Heyde's syndrome is a controversial association between the presence of aortic stenosis and angiodysplasia, thought to be secondary to an acquired type 2 von Willebrand deficiency.
- ▣ In support of this relationship is the fact that some patients with aortic stenosis have demonstrated resolution of GIB after aortic valve replacement.
- ▣ Patients with left ventricular assist devices have also been demonstrated to be at risk for angiodysplasia and recurrent bleeding, again secondary to an acquired von-Willebrand deficiency syndrome. Pilot studies have demonstrated that decreased levels of von Willebrand factor are predictive of recurrent bleeding from small bowel angiodysplasia in patients with left ventricular assist device

- ▣ **Medical treatment of small bowel bleeding**
- ▣ Supportive care with iron given orally or intravenously is a mainstay of treatment for mild small intestinal bleeding. This not only helps maintain an adequate level of hemoglobin, but in more severe cases help reduce the frequency of transfusion. In more severe bleeding, transfusion of packed RBCs is an essential element of treatment, particularly when mechanistic and medical methods fail.
- ▣ Although anticoagulation has been associated with an increased risk of recurrent bleeding, there is no prospective data showing that withdrawal of anticoagulation therapy is beneficial.

- ▣ In a 2009 assessing 162 patients with small bowel bleeding, risk factors for recurrent bleeding after DBE included the presence of small bowel vascular disorders and comorbid conditions, but not the usage of anticoagulants or antiplatelet therapy.
- ▣ Another follow-up study in 2010 demonstrated that transfusional requirements , number, and type of vascular lesions were predictors for recurrent bleeding, but not anticoagulant usage. There is no data that cessation of antiplatelet therapy reduces the risk for recurrent bleeding.
- ▣ Specific medical treatment for small bowel bleeding is poorly developed. Hormonal therapy has not been shown to be helpful. Thalidomide and octreotide have been shown to have some benefit.

## ▣ Somatostatin analogs:

- ▣ The proposed mechanism of action for these agents has included reduction of bleeding by the inhibition of angiogenesis, decrease in splanchnic flow, increase in vascular resistance, and improved platelet aggregation.
- ▣ Those with refractory bleeding, defined as patients requiring >5 U of blood within 3 months after conventional treatment, were given depot octreotide LAR intramuscularly monthly or Lanreotide 90 mg monthly for a mean of 12 months (range 6–36 months).
- ▣ Transfusion requirements during treatment decreased to 2 (range 0–14) vs. 10 (6–24) in the period before treatment ( $P < 0.001$ ).
- ▣ The number of patients experiencing a bleeding episode also decreased to 20% in the treatment group compared with 73% in the pretreatment phase ( $p = 0.001$ ).

- ▣ Most recently, Nardone *et al.* performed a retrospective analysis of the use of octreotide in 98 patients. The investigators demonstrated a reduction of transfusion requirements over a mean follow-up period of 78 months.
- ▣ Forty percent were categorized as complete responders, 32% were partial responders, and 26% were non-responders.
- ▣ The protocol used octreotide 100  $\mu$ g (three times a day) subcutaneously for 1 month; at 2 weeks, patients received an injection of depot preparation of 20 mg monthly for 6 months.
- ▣ Multivariate analysis showed age over 65 years, male gender, use of antiplatelet therapy, and the presence of chronic obstructive pulmonary disease or chronic renal failure were independent predictors of poor outcome.
- ▣ In summary, a recent meta-analysis confirms the value of octreotide and its analogs but provides no support for hormonal treatment.

## ▣ **Thalidomide**

- ▣ Thalidomide, a drug with a tragic past, has made a resurgence owing to its properties as an antiangiogenic agent, possibly by its inhibition of vascular endothelial growth factor. It is also an antitumor necrosis factor agent and an immune modulator.
- ▣ Patients enrolled in a randomized open-label controlled trial were required to have at least six or more bleeding episodes (measured by positive immunoassay fecal occult blood test) and received either 25 mg (four times a day) of thalidomide or 100 mg of iron daily for 4 months, with at least a 12-month follow-up. The primary end point, defined as the proportion of patients showing a reduction of bleeding episodes by  $\geq 50\%$ , was met in 20/28 (71%) of patients on thalidomide compared with 1/27 (4%) of those on iron supplementation ( $p < 0.001$ ).

- ▣ Adverse events including fatigue, constipation, and somnolence were reported by 73% of the thalidomide group and 34% of the iron cohort.
- ▣ Levels of vascular endothelial growth factor were consistently and significantly lower in the thalidomide group.
- ▣ The benefit of thalidomide for patients with small bowel angioectasia failing endoscopic therapy was demonstrated in 9/12 (75%) patients in a study published in 2012 where patients received daily doses of 200 mg for 4 months.
- ▣ The mean hemoglobin concentration before treatment was 6.5 g/dl and at the end of treatment was 12.1 g/dl. Three patients were withdrawn from the study because of adverse side effects.



## ▣ Treatment with angiography

- ▣ Throughout the years, catheter-based intervention has shown significant advances with transition from vasopressin infusion to superselective transarterial embolization, resulting in improved results and decreased complications.
- ▣ In 15 studies from 1992 to 2006, consisting of 309 patients and using superselective transarterial embolization, there was an 82% success rate, 95% overall clinical success rate, 76% 30-day success rate, and rebleed rate of 12%. However, the majority of these cases were performed for bleeding sources outside of the small bowel.

- ▣ In a recent retrospective study of 70 patients, Hongsakulet *al* had a 99% technical success rate, 71% primary clinical success rate, and 79% secondary clinical success rate after repeat embolization.
- ▣ Bowel infarction was seen in 4%, with the majority of the cases involving bleeding sources outside of the small bowel.
- ▣ Predictors of failure to achieve 30-day hemostasis include hemoglobin <8 g/dl, coagulopathy and upper GIB, contrast extravasation, and more than one vessel embolized .

## ▣ **Surgical treatment**

- ▣ Surgical treatment for small intestinal bleeding is generally regarded as a last resort or for patients requiring lysis of adhesions in order to perform successful deep enteroscopy. In the pre-enteroscopic era, a right hemicolectomy was performed as the treatment of choice for recurrent GI bleeding, presumed to originate from right-sided diverticulosis as the source of bleeding.
- ▣ Subsequently, surgical treatment of small intestinal bleeding has been guided by IOE where possible or by a combination of VCE deep enteroscopy and/or angiographic techniques .

- ▣ In a report by Hartmann *et al*, 47 consecutive patients with suspected small bowel bleeding had a negative conventional workup followed by VCE studies. These patients then underwent IOE via an enterotomy; the endoscopist was blind to the results of the prior VCE study. A bleeding source was identified on IOE in 73% of all cases. Diagnostic yields were 100% for patients with ongoing overt bleeding, 70% in overt previous bleeding, and 50% in occult bleeding with an overall mortality rate of 2%.

- ▣ An interesting combined radiological and surgical option has been recently re-reported involving angiographic localization of small bowel vascular lesions. The angiographic catheter is left in place and the patient is transferred to the operating room. At laparotomy, methylene blue is injected via the angiographic catheter. The dye highlights the vasculature and mesentery related to the intestinal lesion, making it easy for the surgeon to resect the relevant segment of small intestine.

- ▣ Surgery displays excellent results with discrete lesions such as tumors or localized arteriovascular malformations.
- ▣ More diffuse lesions, such as multiple angioectasias, are usually treated endoscopically at the time of operation. As the treatment is the same as that delivered at deep or push enteroscopy, rebleeding rates can be anticipated to be similar, but there is no long-term follow-up data.
- ▣ For patients with Heyde's syndrome (aortic stenosis and angioectasia), a recent meta-analysis suggested a reduced bleeding risk after aortic valve replacement based on data from two studies

# CONCLUSION

- ▣ The occurrence of small bowel bleeding remains a relatively uncommon event. A significant percentage of patients with suspected small bowel bleeding will have sources of bleeding detected upon repeat upper and lower endoscopic examinations.
- ▣ The remainder of the patients will likely demonstrate sources of bleeding in the small bowel on VCE, deep enteroscopy or CTE studies. Given the efficacy of these new imaging modalities, the prior classification of “obscure GI bleeding” should be reserved for patients in whom a bleeding source cannot be demonstrated after an extensive evaluation.

- ▣ Small bowel angiodysplastic lesions remain the most common cause of small bowel bleeding, and despite endoscopic therapy, demonstrate high recurrence rates.
- ▣ Medical therapy with somatostatin analogs or antiangiogenic agents may be an option for refractory patients.
- ▣ Surgical therapy should be reserved for patients requiring lysis of adhesions for successful deep enteroscopy, and aortic valve replacement should be considered for patients with Heyde's syndrome.