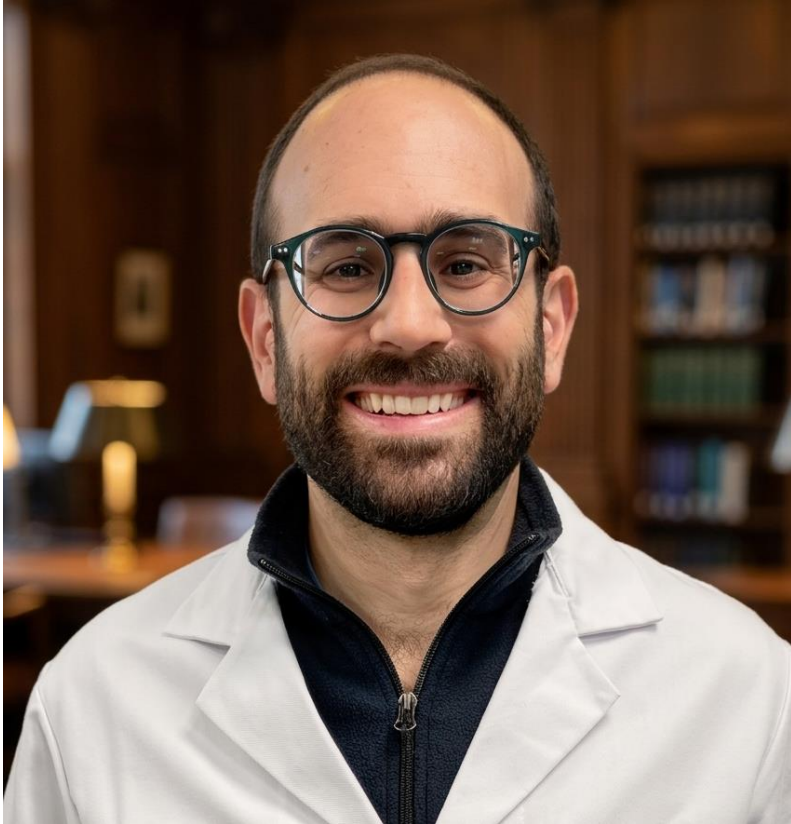


Overt, Obscure and Persistent: When the Bleeding Won't Stop

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- Boston University School of Medicine and Public Health
- Medicine Residency at University of Virginia
- Gastroenterology Fellowship at Beth Israel Deaconess in Boston
- Assistant Professor of Medicine at HMS
- Clinical focus: Inpatient GI, deep small bowel enteroscopy, GI bleeding, enteral access
- Academic focus: Impact of dedicated GI faculty on management of inpatients



DISCLOSURES

Consultant, Fujifilm endoscopy (ongoing)



OBJECTIVES



Review the decisions of obscure GI bleeding



Discuss approaches to evaluation and management



Categorize endoscopic approaches to persistent obscure GI bleeding



Understand the range of supportive measure and follow up for GI bleeding



Outline: Obscure GI bleeding

Definitions and epidemiology

Causes and history

Endoscopic and radiology evaluation

Management options

Pharmacologic therapies

Provocation: foolish or brave?

Conclusions



Case presentation

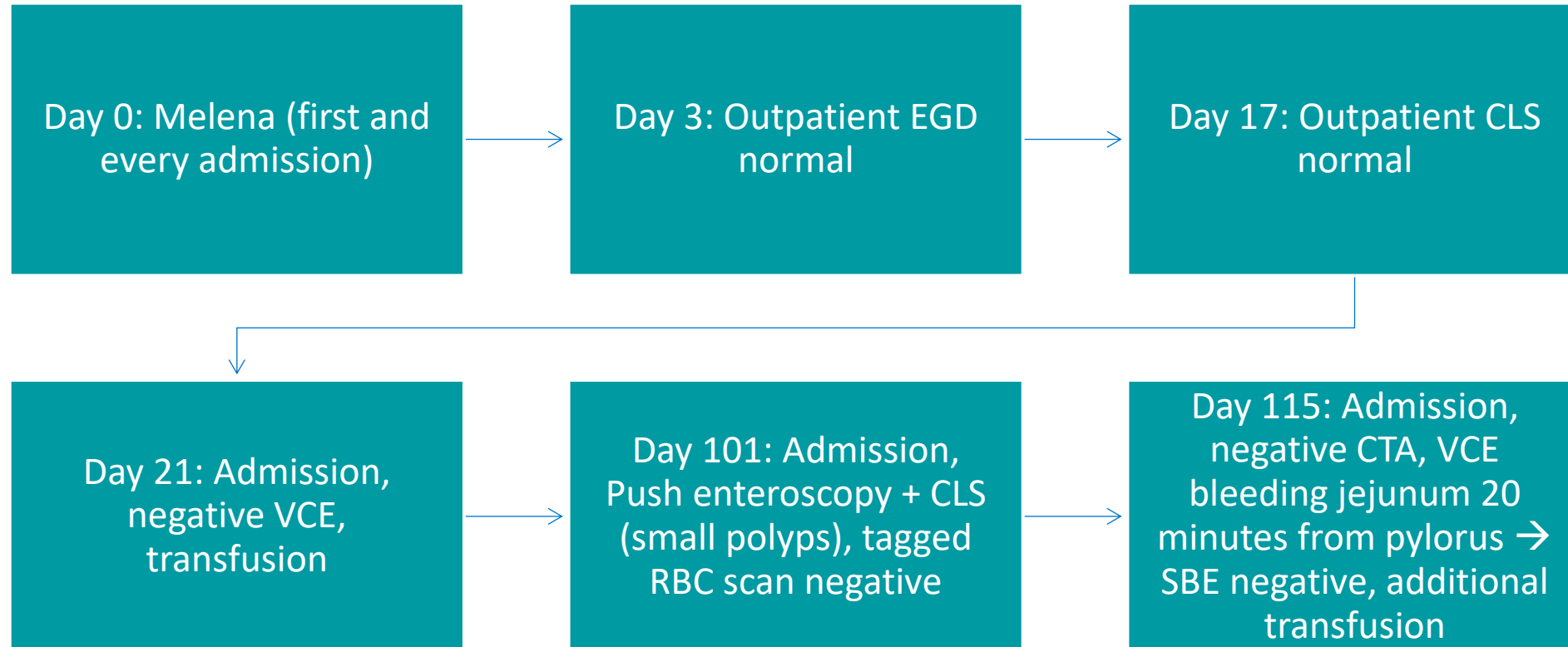
64M with a history of CAD (ASA monotherapy), stroke minimal deficit, mild CKD presenting with melena to the ED

This is his 6th admission in the last 4 months for the same problem

Previously active, working, independent, but now unable to work due to recurrent hospitalizations and transfusions



Timeline



Definitions

Obscure GI bleeding (OGIB): No identifiable source after upper/lower endoscopy and small bowel evaluation (pan-enteroscopy)

- **Overt-obscure:** Visible bleeding (melena, hematochezia) but **negative endoscopy**.
- **Occult-obscure:** No visible blood, presents as iron deficiency anemia (IDA) or positive fecal occult blood test (FOBT) with consistent clinical history

Overall 5-10% of bleeding, but 75% is small bowel



Causes of obscure GI bleeding (60-70% identified)

Category	Specific Causes	Key Features & Risk Factors
Vascular Lesions (~30-40%)	Angiodysplasia (AVMs)	Most common cause; associated with CKD, Heyde syndrome, von Willebrand disease.
	Dieulafoy's Lesions	Intermittent arterial bleeding, commonly in stomach/proximal small intestine.
	Gastric Antral Vascular Ectasia (GAVE, "Watermelon Stomach")	Found in portal hypertension, chronic liver disease, systemic sclerosis.
Small Bowel Tumors (~5-10%)	Gastrointestinal stromal tumors (GISTs), Carcinoid tumors, Adenocarcinomas, Lymphomas	Can cause occult or overt bleeding; consider in patients with IDA + weight loss.
	Metastatic Tumors (Melanoma, Lung, Breast, Renal Cancer)	Often found in the small bowel; suspect in unexplained bleeding with known malignancy.



Causes continued

Category	Specific Causes	Key Features & Risk Factors
Inflammatory & Ulcerative (~10-15%)	Crohn's Disease	Small bowel ulcers, strictures, chronic inflammation; suspect in younger patients with diarrhea.
	NSAID-Induced Ulcers & Enteropathy	Erosions/strictures in small bowel due to chronic NSAID use.
	Radiation Enteritis	Telangiectasias and ulceration following pelvic or abdominal radiation.
Meckel's Diverticulum (~5%)	Ectopic gastric/pancreatic tissue	Suspect in younger patients; bleeding from acid secretion; diagnosed via Meckel's scan.
Rare & Miscellaneous Causes	Hereditary Polyposis Syndromes (Peutz-Jeghers, FAP)	Multiple small bowel polyps; increased malignancy risk.
	Hemobilia (Biliary Bleeding)	Due to hepatic trauma, tumors, vascular fistulas; presents with GI bleeding and jaundice.
	Aortoenteric Fistula (Life-Threatening)	Post-aortic graft surgery; herald bleed followed by massive hemorrhage.



Clinical History & Risk Factors

What kind of blood?

History helps,
melena is hard

Medications:

NSAIDs,
anticoagulants,
bisphosphonates

Surgical history:

Prior gastric bypass
or anastomotic
ulcers

Systemic diseases:

Cirrhosis, chronic
kidney disease,
coagulopathies.

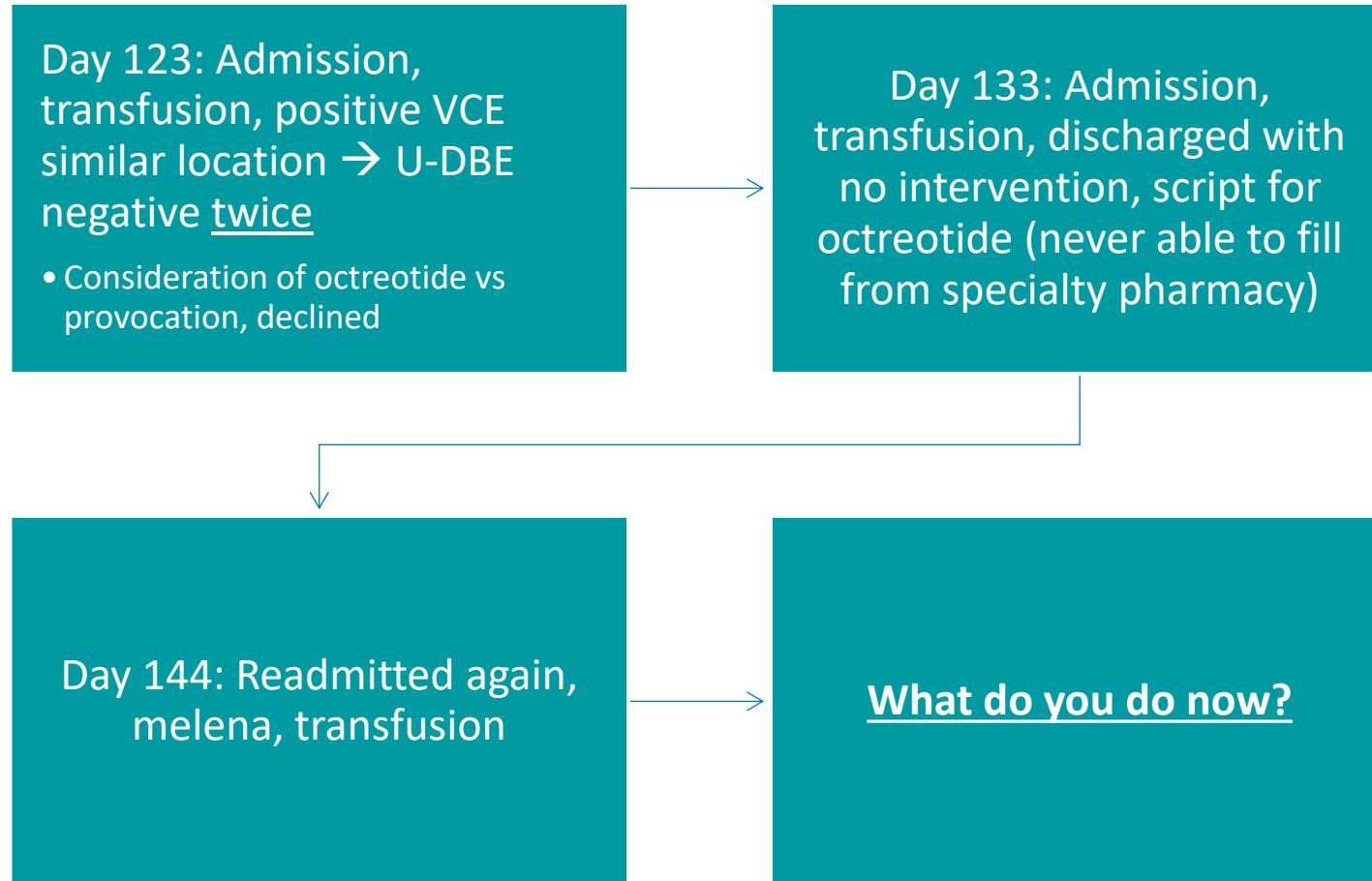
Hereditary

syndromes:

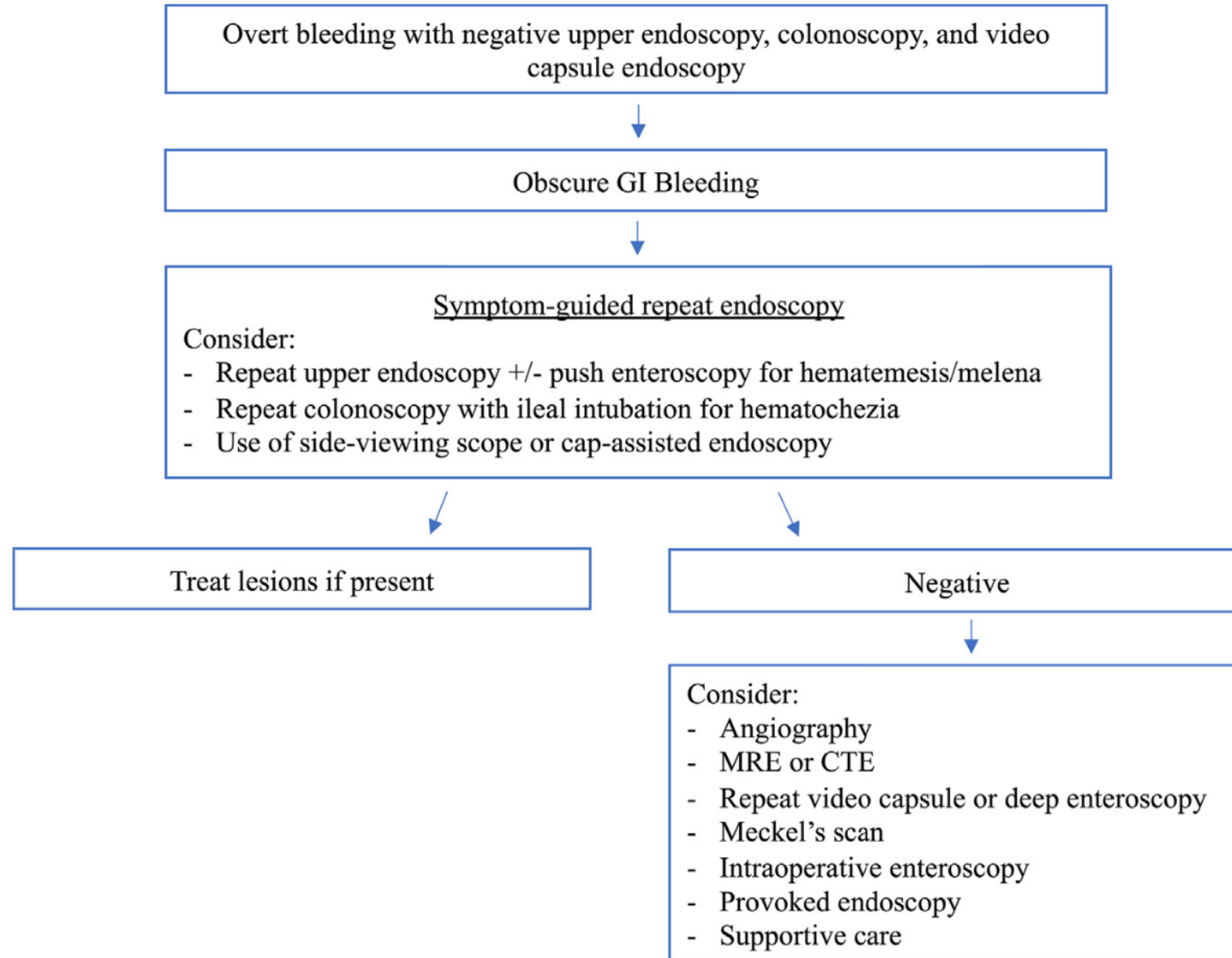
Polyposis syndromes
(Peutz-Jeghers, FAP)



Timeline continued



Next steps?



Restart from the top? Repeating the EGD/colonoscopy

Repeat if:

- Poor prep in initial endoscopy.
- High suspicion of missed source
- Overall ~25% yield

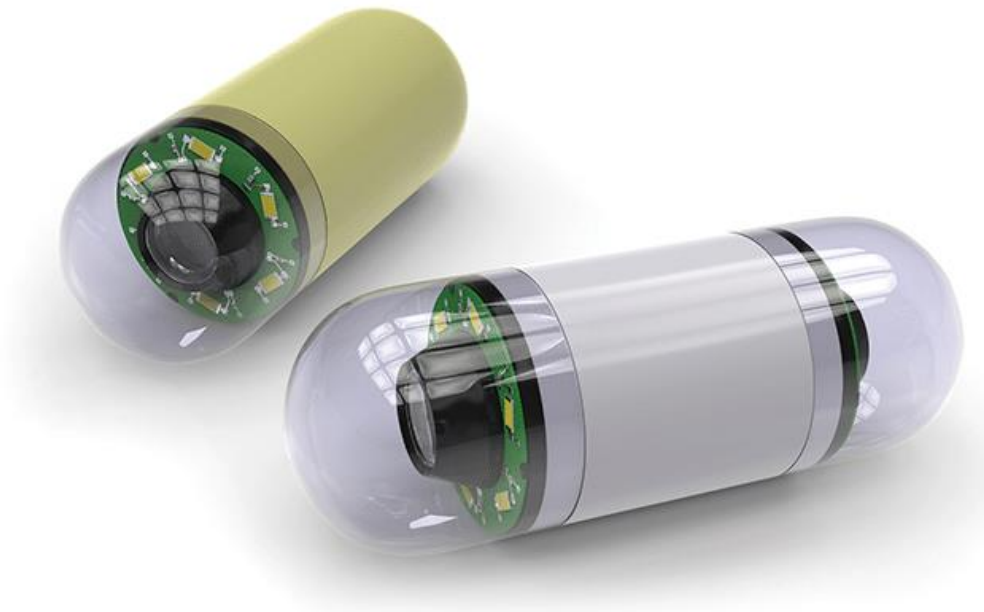
Commonly missed lesions:

- **Cameron's erosions** in hiatal hernias.
- **AVMs** in the stomach/duodenum



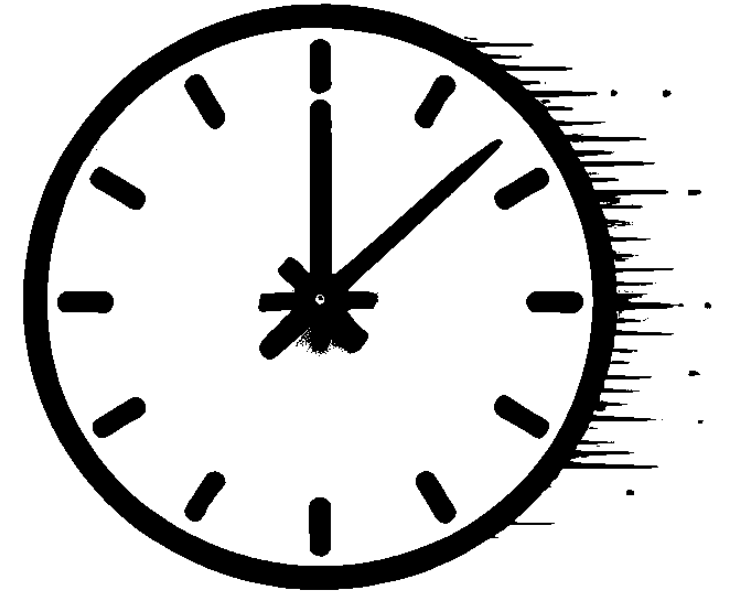
Video capsule endoscopy

- First-line for small bowel evaluation after negative endoscopy. Can help localize bleeding if source not apparent
- **Best for:** angioectasia, tumors, Crohn's, NSAID enteropathy
- **Limitations:**
 - **Obstruction risk**
 - **Cannot perform therapeutic intervention**
- Use VCE early, often and repeatedly for best yield (overall ~65% in OGIB)
- Yield drops ~35-50% as second look



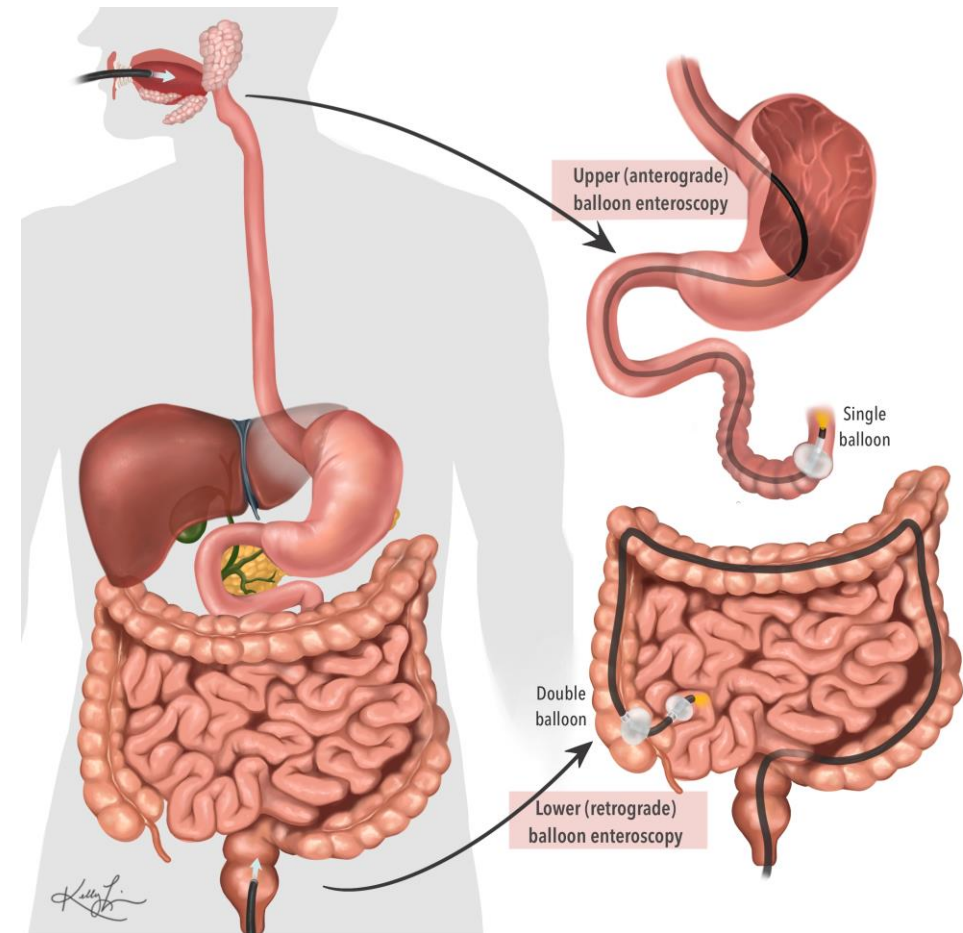
Time is of the essence

- VCE yield is highly dependent on timing
- Yield is highest when done within 24-48 hours
- **CONTINUE** anticoagulation whenever possible since lesions may otherwise stop
- Outpatient follow up VCE often misses the bleeding/underlying lesion if healed; should be done inpatient if patient admitted and still bleeding
- Extended (e.g. 12 hr) VCE can help provide a location if used quickly – anywhere from the esophagus to the right colon



Device-assisted enteroscopy

- **Techniques:**
 - Double-balloon enteroscopy (DBE)
 - Single-balloon enteroscopy (SBE)
 - Motorized spiral enteroscopy (removed from market); manual still available
- **Diagnostic Yield:** 44-100%
- If high suspicion for missed small bowel bleed, consider empiric antegrade (or even bilateral for rapid bleeding/VCE contraindicated)
- Used as first line when lesion seen on VCE



CT and MRI enterography

- **Identifies:**
 - Tumors, Crohn's disease, strictures, vascular lesions
 - Sensitivity: CTE 34% vs. VCE 53%
- **MRE preferred in:**
 - **Young patients** (no radiation)
 - **Pregnant patients (after 25 weeks)**
- Consider if VCE contraindicated
- Yield overall dependent on history
 - May be particularly helpful in younger patients (IBD) or high suspicion for a tumor/malignant lesion



<https://radiopaedia.org/articles/ct-enterography-protocol>



Imaging options: Angiography

- **CTA:** Detects active bleeding at **0.3-0.5 mL/min** or 1-2 units + per day
- **Conventional Angiography:**
 - Used for **localization and embolization**
 - **Detects bleeding rate >0.5-1 mL/min**
- All forms of angiography require active bleeding
- Can be helpful to target your endoscopy → does not require angiographic management (if CTA)
 - Difficult to embolize small bowel, rectum
 - Good for recurrent rapid bleed (e.g. diverticulum)



Tagged RBC/Meckel Scan

Tagged RBC Scan

- Detects slow, intermittent bleeding as low as 0.05 mL/min
- Efficacy:
 - Sensitivity: ~85%, but poor specificity.
- Limitations:
 - Bleeding can **shift location due to peristalsis**, leading to misinterpretation.
 - CTA has largely replaced it

Meckel's Scan

- Detects ectopic gastric mucosa in Meckel's diverticulum
- Best for: <40 years with unexplained GI bleeding
- Efficacy:
 - 85-100% sensitivity in children, ~62% in adults
 - False negatives: If Meckel's **lacks ectopic gastric mucosa**.
 - False positives: Duplication cysts, vascular malformations



Management Options



Primary management challenge is usually finding the lesion, not fixing it



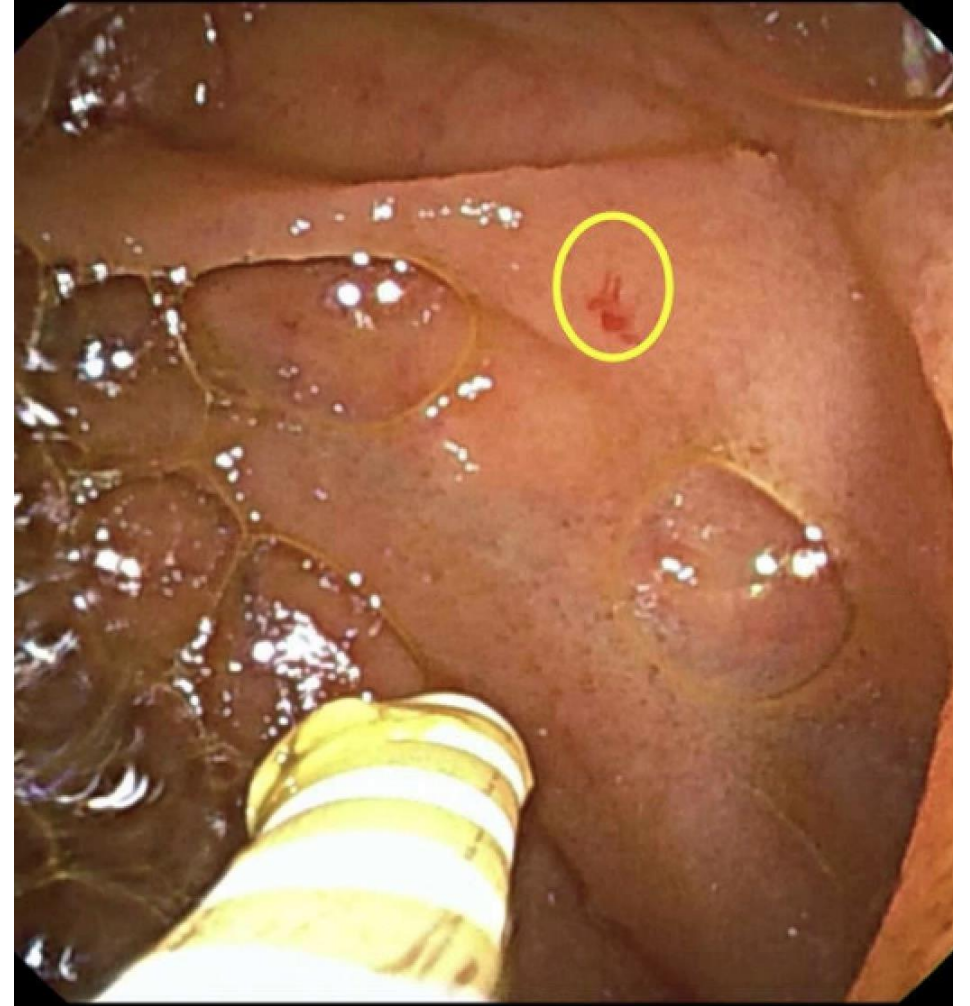
Endoscopic intervention ideal for small bowel, consider IR for colon/stomach



Tattoo anything that needs surgery

Management: Endoscopy

- Continue blood thinners in stable bleeding
- APC usually preferred for small bowel given thin wall, less depth of burn, but bipolar works fine
- Resection of polyps/tumors
- Treatment of complex vascular lesions by surgery/IR may be needed



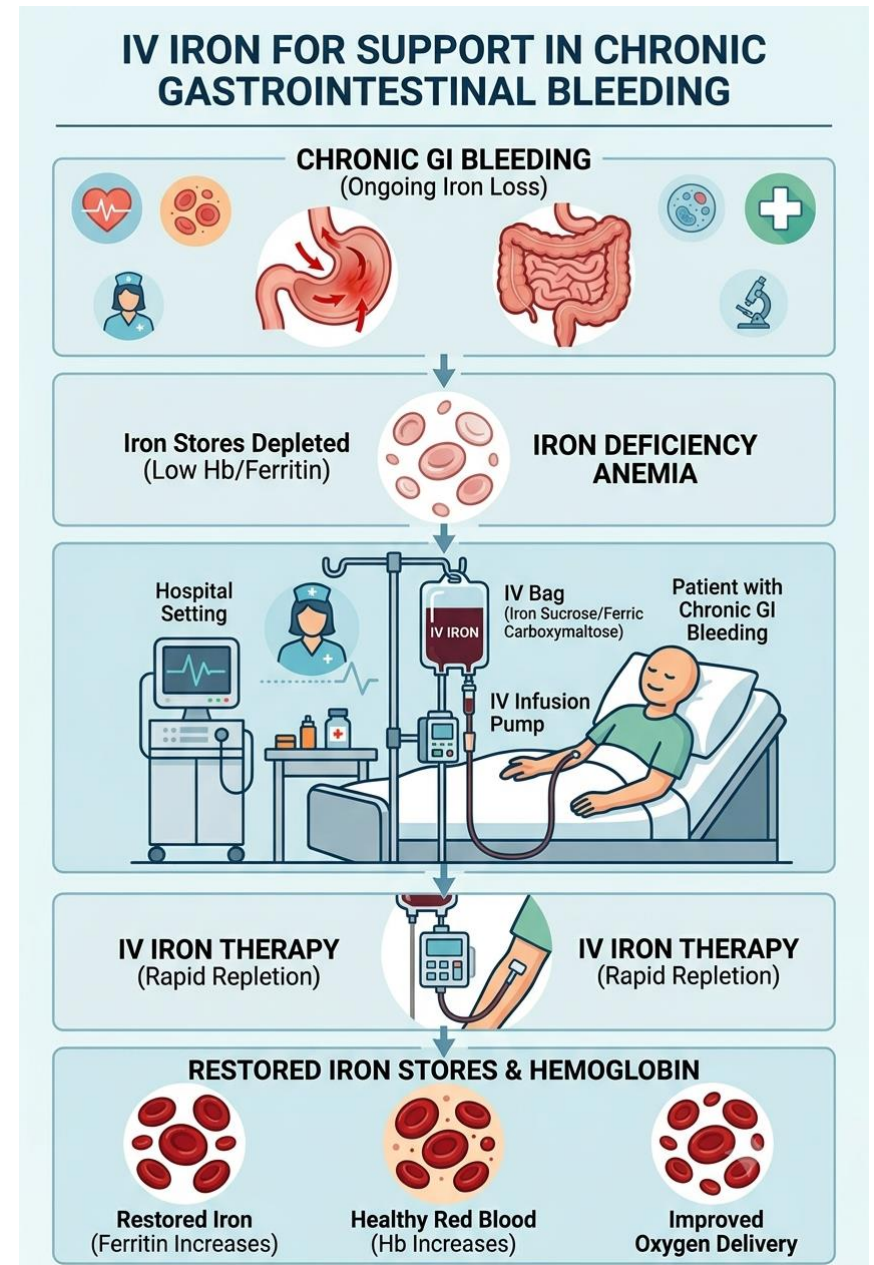
Management: Surgery

- **Segmental Resection:**
 - **Indication:** Localized bleeding source identified.
 - **Outcome:** High success rate in controlling bleeding IF SOURCE identified; rebleed if wrong location
- **Intraoperative Enteroscopy:**
 - Complete evaluation of the small bowel in 57-100%
 - Identification of a bleeding source in up to 80% of cases
 - 13% to 52% of patients experience recurrent bleeding,
 - Mortality is 5% and morbidity is 17%
 - Watch out for adhesions



Supportive Therapy

- Pharmacologic therapy is used when endoscopic or surgical interventions are not feasible or have failed
- Iron supplementation
 - Oral dosing: Every-other-day dosing preferred due to improved absorption and reduced GI side effects
 - IV iron: For patients with malabsorption or intolerant to oral iron (e.g., iron sucrose or ferric carboxymaltose)
 - Monitoring: Hemoglobin increase of 2 g/dL within 4 weeks is considered an adequate response.
- Patients may require an outpatient transfusion plan



Octreotide

Mechanism:

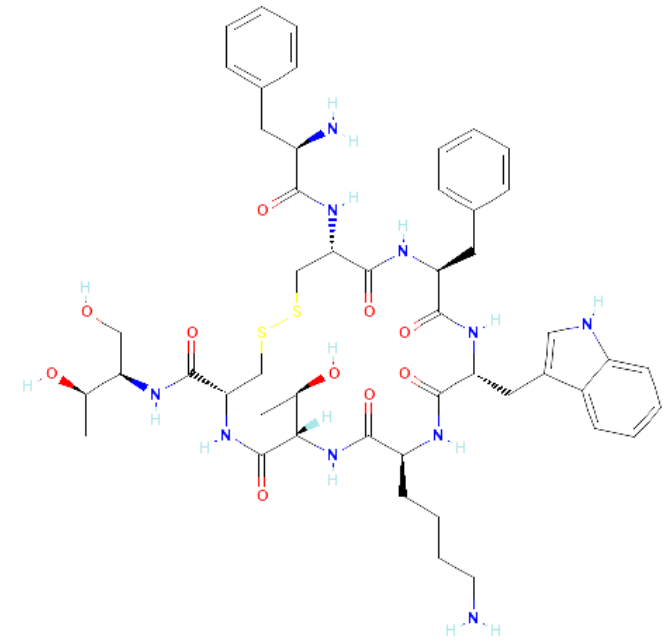
- **Inhibits angiogenesis** and reduces splanchnic blood flow, decreasing GI mucosal perfusion (and motility)

Efficacy:

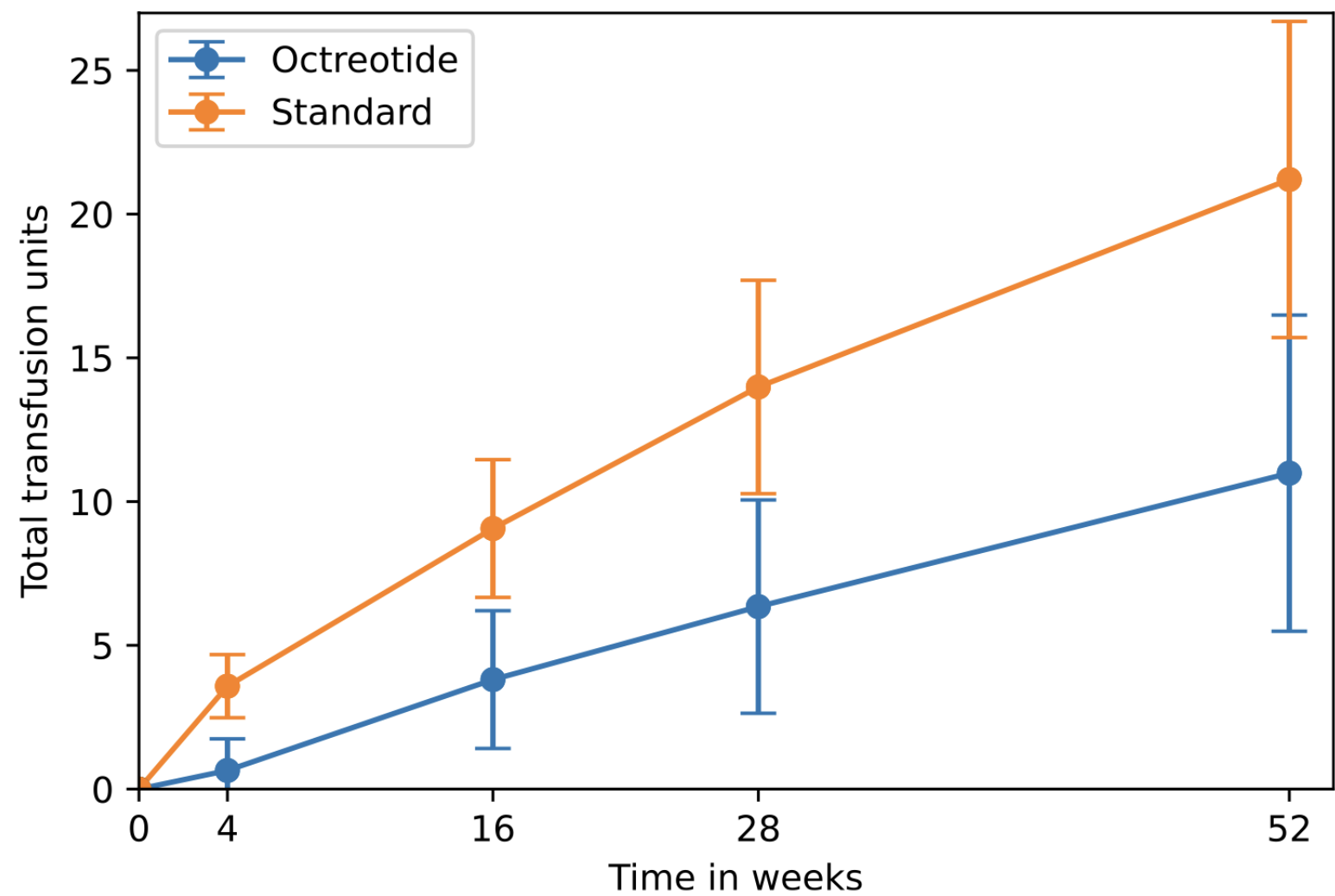
- Reduces bleeding episodes in patients with angiodysplasia (small studies suggest ~60-70%)
- OCEAN study 40mg LAR q28 days 50% reduction in transfusions (11.0 vs 21.2, $p=0.12$)
- Probably reasonable for most causes of bleeding

Side effects:

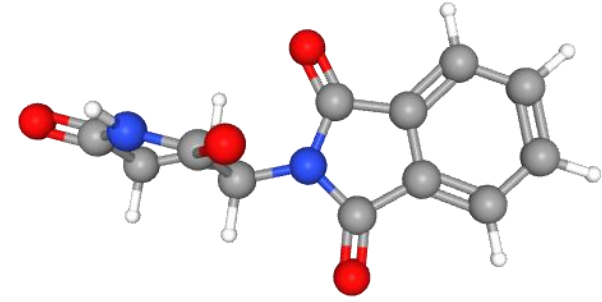
- GI distress/abd pain in around 50%, gallstones



OCEAN study



Thalidomide



Mechanism:

- Inhibits VEGF (vascular endothelial growth factor), reducing abnormal vessel formation in angiodysplasias

Efficacy:

- **Clinical trials report a 71-85% reduction in bleeding episodes** in patients with angiodysplasias
- **Reduces transfusion dependence** in refractory cases
- Largest RCT (2023) with over 68.6% of patients w/50% reduction in episodes of bleeding (vs 16.0% placebo)

Limitations:

- **Adverse effects:** Teratogenicity, neuropathy, fatigue, constipation, thrombosis/DVT
- **Requires close monitoring** in long-term use, needs REMS



Provoked Endoscopy?

- No widely-accepted protocols; heparin is most common, other vary
- Personal experience: prefer ultrashort agents (no-bolus cangrelor, bivalirudin) but are expensive
- MUST BE PREPARED with blood available, rapid endoscopy (w/DAE) available, CTA/IR as backup
- Consider using intra-procedure
- Success variable (reported 27-71%)



ORIGINAL ARTICLE: Clinical Endoscopy

Pharmacologic provocation combined with endoscopy in refractory cases of GI bleeding

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New Orleans, Louisiana; Salt Lake City, Utah, USA

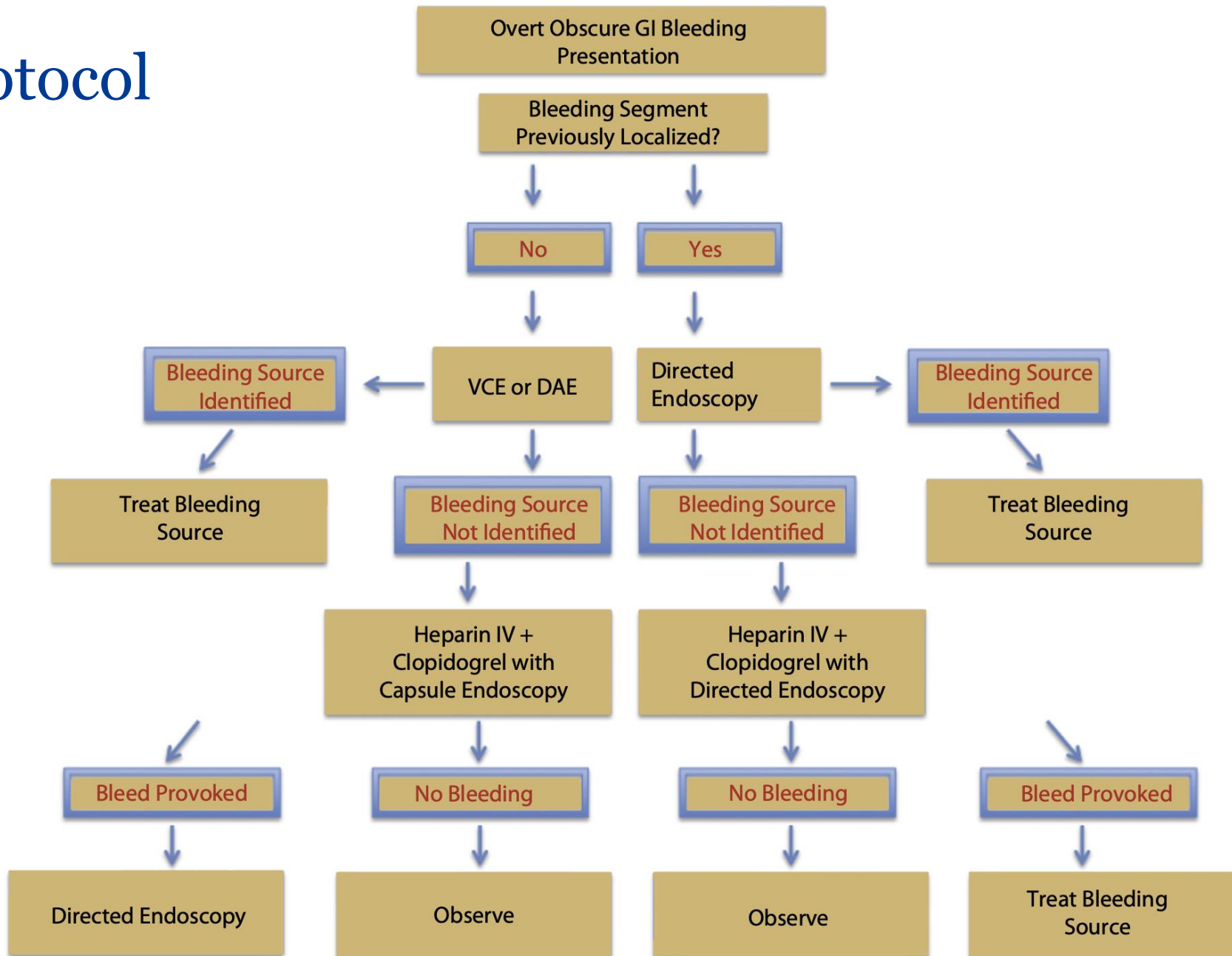


Background and Aims: The source of GI bleeding may elude us despite exhaustive testing in some cases. Bleeding in these cases is often related to a vascular lesion that is discernible only when actively bleeding. The objective of this study was to determine the efficacy and safety of endoscopy combined with the administration of antiplatelet and/or anticoagulant agents to stimulate bleeding in order to define a source.

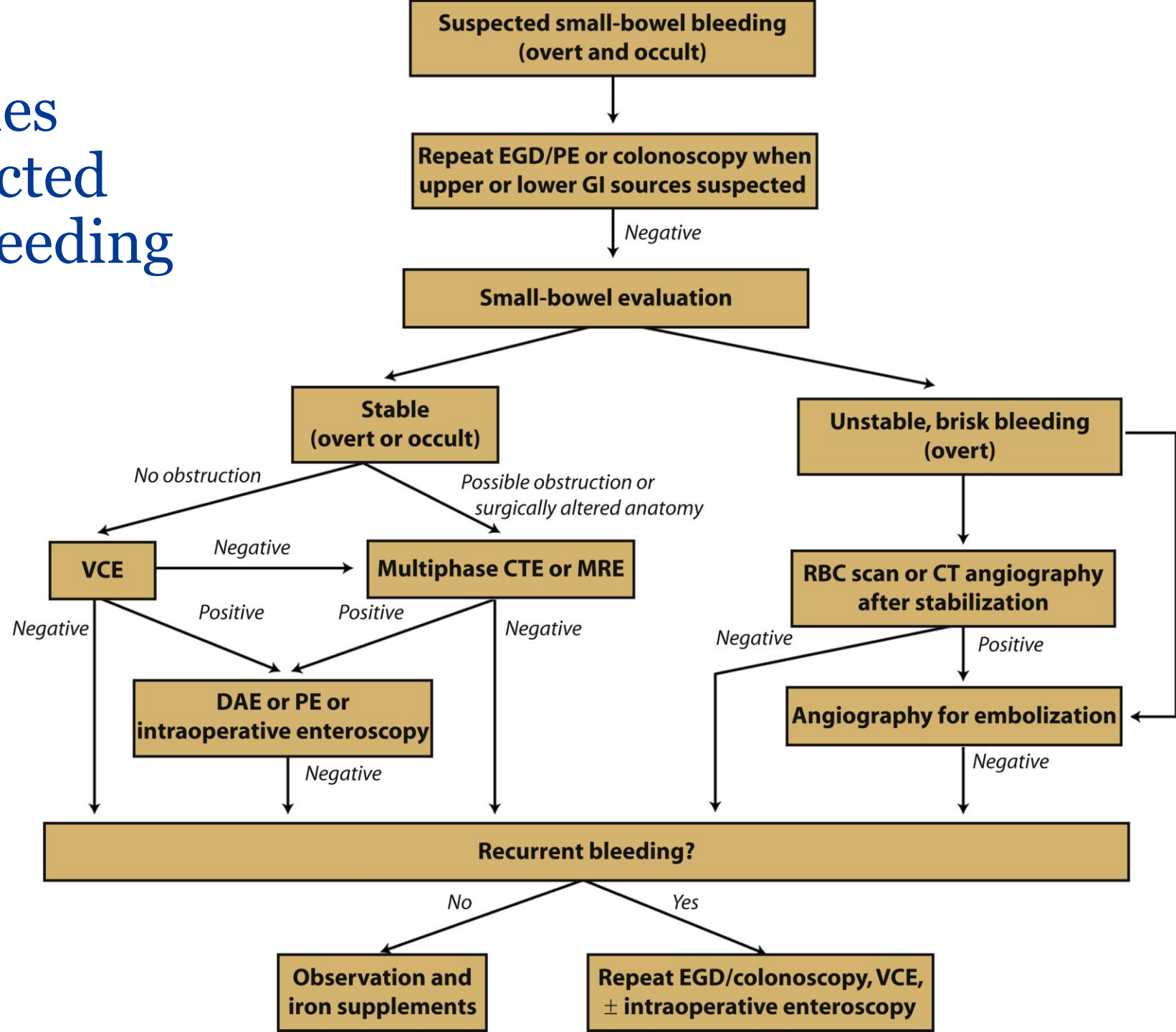
Methods: A retrospective review of a database of device-assisted enteroscopy (DAE) procedures was completed to identify cases in which provocation with antiplatelet or anticoagulant agents was used as part of a GI bleeding evaluation. Procedures were divided into 3 groups based on the method of provocation: patients with a history of bleeding associated with an antiplatelet/anticoagulant (*provocation-experienced*); patients naïve to these medications (*provocation-naïve*); and cases of recurrent, overt GI bleeding in which a combination of clopidogrel and intravenous heparin was administered for provocation (*Louisiana State University [LSU] protocol*).

Results: A review of 824 DAE procedures was completed to identify a total of 38 instances in which provocation was attempted in 27 patients. These cases were subdivided into 13 provocation-experienced procedures, 18 provocation-naïve procedures, and 7 LSU protocol procedures. The diagnostic yield of provocative testing per procedure was 53% in the provocation-experienced group, 27% in the provocation-naïve group, and 71% in the full protocol group. Provocative testing was revealing in 15 of 27 patients; angioectasias and Dieulafoy lesions were the most common pathologies. Provocative testing was not beneficial in 4 patients who were eventually diagnosed with bleeding caused by intestinal angioectasias (3) and an aorto-enteric fistula (1). There were no adverse events.

LSU protocol



ASGE guidelines (2018) –suspected small bowel bleeding



WWAID (What Would AI do?)

Provoked (provocative) endoscopy using antiplatelet/anticoagulant agents is a **rarely used, last-resort technique** for refractory obscure GI bleeding, supported only by small retrospective case series with **no randomized controlled trials**. The largest endoscopic provocation study reported a diagnostic yield of 27–71% depending on the protocol used, with **no adverse events** in 38 procedures. Gastrointestinal... However, major society guidelines characterize this approach with caution, noting **safety concerns and limited benefit**. Gastrointestinal...

Available Evidence on Provocative Endoscopy

The seminal study by Raines et al. (2017) is the first and largest reported case series of pharmacologic provocation combined with device-assisted enteroscopy (DAE). Gastrointestinal... From a database of 824 DAE procedures, 38 instances of provocation were identified in 27 patients, divided into three groups:

- **Provocation-experienced** (patients already on antiplatelets/anticoagulants whose bleeding was associated with these agents): diagnostic yield **53%** per procedure
- **Provocation-naïve** (patients not previously on these medications): diagnostic yield **27%**
- **LSU protocol** (combination of clopidogrel and IV heparin administered specifically to provoke bleeding): diagnostic yield **71%**

Overall, provocative testing identified a source in **15 of 27 patients** (56%). The most commonly identified lesions were **angioectasias and Dieulafoy lesions**. Notably, there were **no adverse events** across all 38 procedures. Gastrointestinal...



Course completed

Patient elected to undergo full provocation protocol, Brigham-modified

- Heparin with full therapeutic target (80-120 PTT)
- Cangrelor 0.75mcg/kg/min (can increase dose if no response)
- Initiation 12 hours prior to planned procedure time

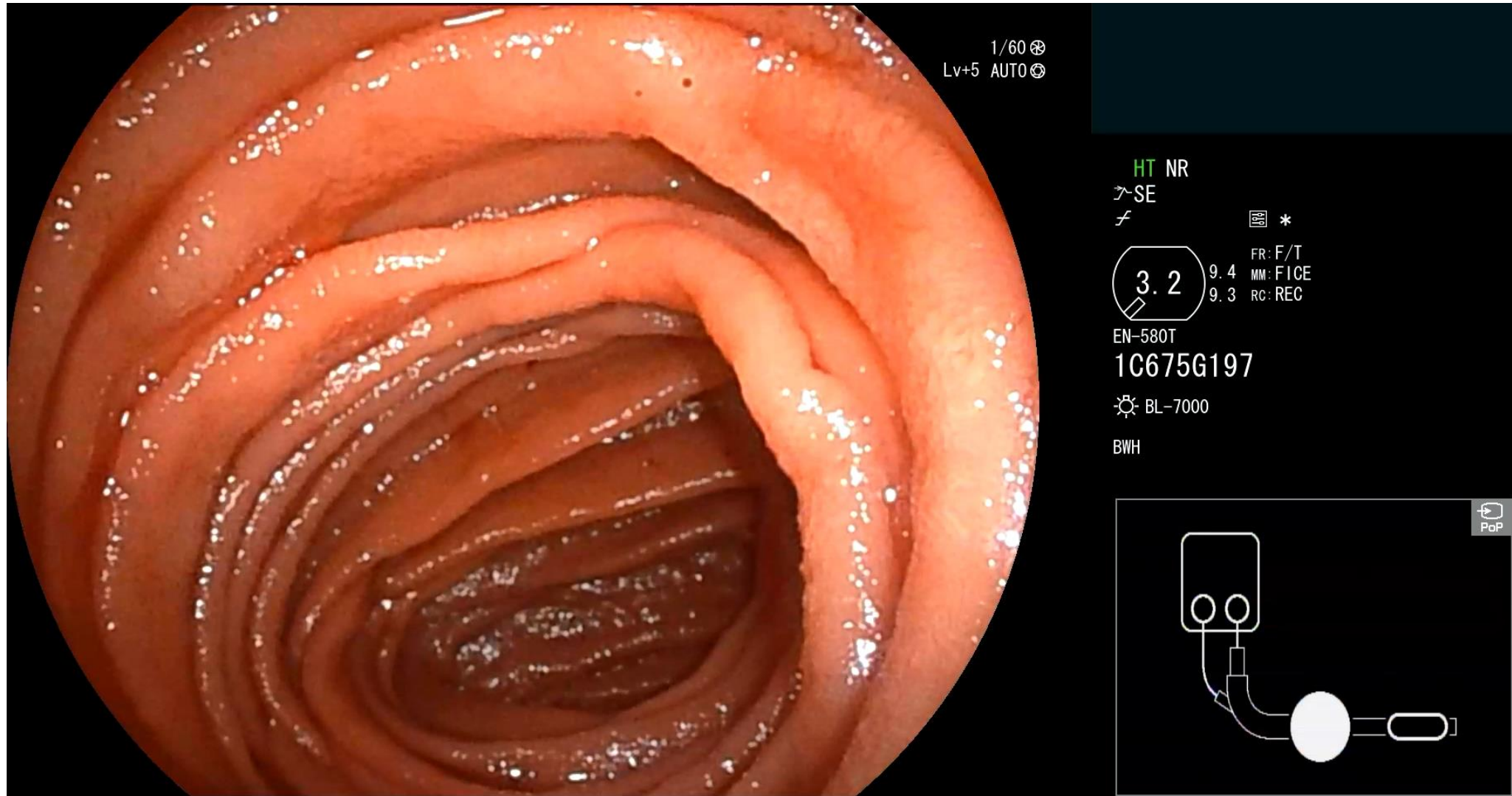
Hgb drop, feeling unwell in AM

DBE with jejunal dieulafoy with bleeding, cauterized and clipped x1

Discharged with no recurrence, hgb normalized



Antegrade double balloon enteroscopy



MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)



Obscure GI bleeding (OGIB) remains a diagnostic challenge



Repeat endoscopy is usually necessary, go with VCE early and often since majority of cases are small bowel



Deep enteroscopy, CT/MR enterography, and angiography provide additional diagnostic and therapeutic options



Pharmacologic therapy (octreotide, thalidomide) can be useful for refractory bleeding, but requires careful patient selection and are most effective for small bowel



Surgical intervention is reserved for refractory cases, since success depends on accurate localization and is morbid



Consider provocation studies, but must be prepared for bleeding

Board-style question

CLINICAL VIGNETTE

A 68-year-old man presents with recurrent melena. He has coronary artery disease on aspirin 81 mg daily and CKD stage III. Two weeks ago, he was hospitalized for similar symptoms; EGD and colonoscopy performed with excellent bowel prep were both normal. On exam, he is hemodynamically stable (BP 118/72 mmHg, HR 82 bpm) with mild pallor. Hemoglobin is 8.2 g/dL (down from his baseline of 10.5 g/dL). Normal BUN/Creatinine ratio. He is resuscitated with intravenous fluids.

What is the next best step in management?

- A** Repeat EGD and colonoscopy
- B** Computed Tomography Angiography (CTA)
- C** Video Capsule Endoscopy (VCE)
- D** Push Enteroscopy
- E** Conventional Angiography



Reasoning review

✓ Correct Answer: C (Video Capsule Endoscopy)

In a hemodynamically stable patient with overt obscure GI bleeding (visible blood but negative prior standard EGD/colonoscopy), **Video Capsule Endoscopy (VCE)** is the first-line diagnostic approach. VCE has a dynamic diagnostic yield of ~65% for small bowel evaluation, and its yield is optimized when performed early (within 24–48 hours of a bleeding episode).

Why the Other Options are Incorrect:

A is incorrect: Repeating upper/lower scopes is only indicated if the initial exams were incomplete, had poor prep, or there is a strong suspicion of a missed index lesion (e.g., gastric antral vascular ectasia).

B & E are incorrect: Radiographic (CTA) and conventional angiography require active, brisk bleeding (>0.3 mL/min and >0.5 mL/min respectively) to detect a contrast extravasation, which is highly unlikely in this stable patient.



VCE provides complete evaluation of the small bowel mucosa and can easily identify common etiologies like small bowel angiodysplasias or ulcers.

Board-style question

CLINICAL VIGNETTE

A 72-year-old female with severe calcific aortic stenosis and recurrent obscure GI bleeding from small bowel angiodysplasias presents with worsening dyspnea on exertion. Despite multiple rounds of endoscopic argon plasma coagulation (APC) of jejunal lesions, she remains transfusion-dependent, requiring 12 units of packed red blood cells over the past year. She is not a candidate for aortic valve replacement. A repeat capsule endoscopy reveals diffuse, scattered non-bleeding jejunal angiodysplasias.

Which of the following medical therapies is most supported by recent randomized controlled trial evidence to reduce her rate of recurrent bleeding episodes?

- A** Thalidomide
- B** Combined estrogen-progesterone
- C** Tranexamic acid
- D** Danazol
- E** Sildenafil



Reasoning review

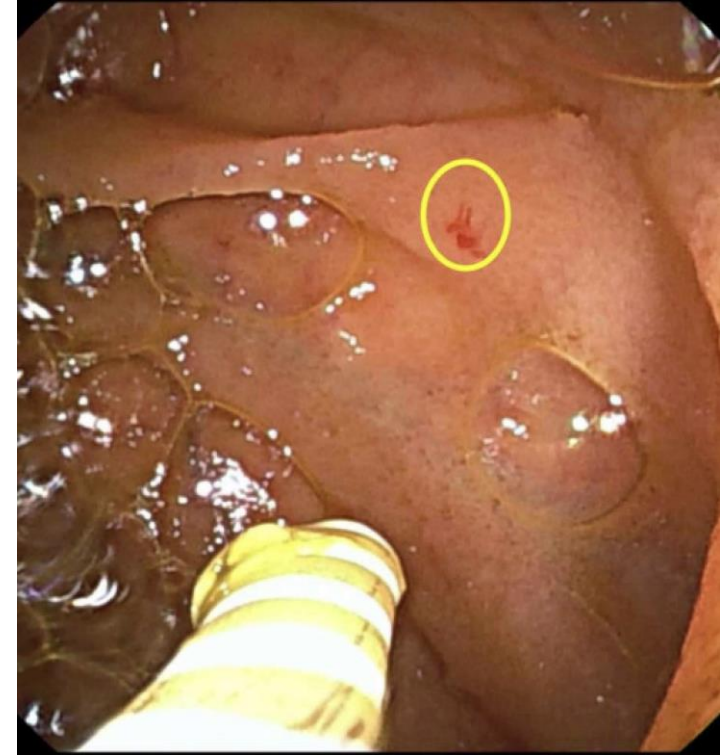
✓ Correct Answer: A (Thalidomide)

A landmark multicenter, double-blind RCT (Chen et al., NEJM 2023) demonstrated that **Thalidomide** (at doses of 50 mg or 100 mg daily for 4 months) resulted in a $\geq 50\%$ reduction in bleeding episodes in 51.0% and 68.6% of patients, respectively, compared to 16.0% in the placebo group. Thalidomide acts by inhibiting VEGF (Vascular Endothelial Growth Factor), directly addressing abnormal vascular proliferation.

Why Other Therapies are Inappropriate:

B is incorrect: Combined hormonal therapy (estrogen-progesterone) was shown to be ineffective for gastrointestinal angiodysplasia in a prospective RCT and increases thrombotic risks.

C, D, and E are incorrect: These agents do not have robust trial data supporting their use in small bowel angiodysplasias or vascular ectasias.



Vascular angiodysplasias (ectasias) represent aberrant mucosal vessel structures. They are the most common small bowel bleeding source in older adults.

REFERENCES

- Thakral D, Stein DJ, Saltzman JR. Diagnosis of Occult and Obscure Gastrointestinal Bleeding. *Gastrointest Endosc Clin N Am*. 2024;34(2):317-329.
- Chen H, Wu S, Tang M, et al. Thalidomide for Recurrent Bleeding Due to Small-Intestinal Angiodysplasia. *N Engl J Med*. 2023;389(18):1649-1659
- Goltstein LCMJ, Grooteman KV, Bernts LHP, et al. Standard of Care Versus Octreotide in Angiodysplasia-Related Bleeding (the OCEAN Study): A Multicenter Randomized Controlled Trial. *Gastroenterology*. 2024;166(4):690-703.
- Raines DL, Jex KT, Nicaud MJ, Adler DG. Pharmacologic provocation combined with endoscopy in refractory cases of GI bleeding. *Gastrointest Endosc*. 2017;85(1):112-120
- Singh S, Mohan BP, Adler DG. Management of Obscure Gastrointestinal Bleeding. *Am J Gastroenterol*. 2025;120(3):500-503
- ASGE Standards of Practice Committee, Gurudu SR, Bruining DH, et al. The role of endoscopy in the management of suspected small-bowel bleeding. *Gastrointest Endosc*. 2017;85(1):22-31.



Questions?

Thank you!