Small Bowel -- Obscure Overt and Occult GI Bleeding: Guideline Based Review
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Case Study

• 65-year-old male transferred with recurrent melena. Medical history notable for atrial fibrillation and anticoagulation with warfarin.
  • EGD, Push Enteroscopy and Colonoscopy negative on two occasions
  • Capsule endoscopy showed active bleeding
  • Deep enteroscopy negative after reversal of anticoagulation for bleeding source

• Next step: urgent deep enteroscopy on anticoagulation
Deep Enteroscopy

Principles of Endoscopy in Obscure GI Bleeding

- Be prepared to take longer than usual
- Try to do exam while patient bleeding
- Don’t fully correct INR if on anticoagulation
- Clean bowel of blood as you go in
- Use water immersion to identify exact bleeding source
Obscure Gastrointestinal Bleeding (OGIB)

**Definition**

- Obscure bleeding – bleeding of unknown origin that persists or recurs
  - Obscure overt (visible blood)
  - Obscure occult (positive FOBT or IDA)
- Normal upper and lower endoscopy

**Etiology**

**Vascular**
- Angioectasia
- Hemangiom	
- Dieulafoy lesion
- Portal hypertensive enteropathy
- Varices
- Radiation enteritis

**Inflammatory**
- Inflammatory bowel disease
- NSAID enteropathy
- Celiac disease
- Autoimmune enteropathy

**Neoplastic**
- Carcinoid
- GIST
- Adenocarcinoma
- Lymphoma
- Metastases

**True obscure causes** – hemobilia, hemosuccus pancreaticus, vasculitis
Historical Challenges Related to the Evaluation of “Obscure GI Bleeding”

- High miss rate for lesions on initial upper and lower endoscopy
- The need for invasive intra-operative enteroscopy and exploratory laparotomy to adequately examine the small bowel
- Finding a lesion in the small bowel doesn’t always mean that is the source of the problem
- Limited capacity of older diagnostic modalities to adequately examine the small bowel

The Challenge – The Small Bowel (SB)

Small intestine
- Duodenum
- Jejunum
- Ileum

Length: 600 cm or 20 feet

Capsule Endoscopy and Deep Enteroscopy have revolutionized our approach to this challenging problem.
Disruptive Technology Changed Our Approach
Middle GI Tract Bleeding

Today

Upper GI

Middle GI

Lower GI

Ell et al: Endoscopy 2006;38:73; Raju et al: Gastroenterology 2007;133:1697

New Definition (Guideline)

• Consider a small bowel bleeding source in patients after normal upper and lower endoscopic evaluation

• Patients should be classified as having potential “small bowel bleeding” prior to capsule endoscopy and other imaging techniques

• The term “obscure gastrointestinal bleeding” should be reserved for patients not found to have a source after new small bowel imaging techniques
Epidemiology and Natural History (Guideline)

- Type of lesion correlates with age but not gender or ethnicity
- Angioectasia are most common lesions
- Risk factors for angioectasia include advancing age, aortic stenosis, chronic renal failure, LVADs
- Recurrent bleeding from angioectasia correlates with number of lesions, advanced age, presence of co-morbid conditions and anticoagulant therapy

Etiology Based on Age (Guideline)

**Younger than 40 years**
- Crohn's disease
- Dieulafoy's lesion
- Neoplasia
- Meckel's diverticulum
- Polyposis syndromes

**Older than 40 years**
- Angioectasia
- Dieulafoy lesion
- Neoplasia
- NSAID enteropathy

Is It Possible to Predict Intestinal Angioectasias

- Retrospective study of 284 CE procedures for SB Bleeding:
  - 47 cases with angioectasia
  - 53 controls without vascular lesions
- Risk factors:
  - Overt bleeding
  - Older age
  - Elevated cholesterol
  - Hypertension

Small Bowel Angioectasia: Frequency and Risk Factors for Rebleeding

- 68 patients diagnosed with CE and treated with APC
- Results:
  - Overall rebleeding rate over 30.5 months was 33.8% (23/68 cases)
  - Cumulative risk lower in patients who had endoscopic treatment but not significant (p=0.14)
  - Rebleeding controlled in 18/23 (78.3%)
  - Risk factor for rebleeding: multiple lesions (≥ 3) (OR 3.82; 95% CE 1.30-11.3, P=0.02)
Long-Term Follow-up: Vascular Lesions After Capsule and DBE

- Prospective, multicenter trial of 183 patients with SB Bleeding diagnosed with CE and treated with DBE

- Results:
  - 64 (35%) had rebleeding during 1 year follow-up.
  - Risk factors: cardiac disease, overt bleeding

Diagnostic Approach in Patients With Suspected SB Bleeding

- Document objective evidence of gastrointestinal bleeding especially in those presenting with iron deficiency anemia
  - Exclude hematologic causes for anemia
  - Exclude malabsorption

- Sufficiently rule out an upper and lower gastrointestinal tract bleeding source with second-look endoscopy as indicated

- Then proceed with a SB evaluation
Second Look Endoscopy (Guideline)

• Upper endoscopy
  • Consider in cases of recurrent hematemesis, melena, or previously incomplete exam
  • Consider push enteroscopy

• Colonoscopy
  • Consider for recurrent hematochezia or previously incomplete exam.

• If second look endoscopy is normal, then proceed with small bowel evaluation

Robinson CA et al. GIE 2011;74:1061-6

Techniques to Evaluate the SB

• Capsule Endoscopy

• Deep Enteroscopy

• Cross Sectional Imaging
Capsule Endoscopy

Capsule Endoscopy for Overt SB Bleeding
- 685 patients with acute overt SB bleeding
  - 37 had negative EGD and colonoscopy
  - Capsule endoscopy performed
    - Diagnostic yield was 91.9%
    - Changed management plan in 21 patients

Capsule Endoscopy Systematic Review
- 227 studies and 22,840 capsule endoscopes
- Suspected SB Bleeding most common indication (66%)
- Most common underlying lesion: angiodysplasia (50%)
Factors Associated With Diagnosis of SB Bleeding by CE

- 911 consecutive patients with suspected SB bleeding
  - Upper and lower endoscopy negative
  - Logistic regression utilized

Results
- 509 (565) had a confirmed lesion on CE
- Factors independently associated with a diagnosis by CE
  - Age >60 y/o [OR, 1.2]
  - Male sex [OR, 3.8]
  - Overt bleeding [OR, 3.8]
  - Current hospitalization [OR, 1.4]

Diagnostic Yield of CE and DBE in Overt vs. Occult SB bleed

Pennazio et al. Gastroenterol 2004;126:643-53
Shinozaki S et al. Clin Gastro Hepatol 2010;8:151-8
Diagnostic Yield of CE Deteriorates over time

Diagnostic Yield of CE for IDA
A Systematic Review

24 studies enrolling 1,960 patients

Results

• Pooled diagnostic yield was 47% (95% CE, 42-52%) but there was statistically significant heterogeneity (inconsistency index=78.8%; P<0.0001)

• Pooled diagnostic yield in studies focused on IDA (4 studies) was 66.6% (95% CE, 61.0-72.3%)
Diagnostic Yield of CE in IDA Without GI Bleeding

- Retrospective review of 934 patients
  - Negative endoscopic evaluations
- Results – 101 capsules in 97 patients
  - Group A – 25 patients with positive CE
  - Group B – 69 patients with negative CE
  - Group C – 3 patients with incomplete CE
- Overall diagnostic yield of 25.7%
- CE did not alter management in most patients
- Many lesions were in reach of standard endoscopes


“Deep Enteroscopy”
Tube or Balloon Assisted Enteroscopy

- Double-Balloon Enteroscopy (DBE)
- Single-Balloon Enteroscopy (SBE)
- Spiral Overtube Enteroscopy

Forcep channel allows biopsy and therapy!
CE vs Deep Enteroscopy – Meta Analysis

- Pooled diagnostic yield
  - CE vs DBE (62% vs 56%, p=0.16)
  - However, diagnostic yield of DBE significantly increased to 75% if performed after a positive CE
  - DBE yield only 27.5% if performed after negative CE

Teshima CW et al. J Gastro Hep 2011;26;796-801

Degree of Concordance Between DBE and CE in SB Bleeding

Multicenter prospective study involving 193 patients who underwent CE followed by DBE

Results
- CE (vascular 38%; blood 18%; tumor 10%)
- DBE (vascular 37%; neoplasia 15%; ulcers 6%)
- Overall Kappa was 0.46 (95% CI 0.38-0.54)
  - Maximum concordance for vascular (0.72) and inflammation (0.78)
  - Minimum concordance for polyps (0.46)
- Blood on CE in 34 cases, 12 neg DBE

Conclusions
- CE and DBE have good agreement for vascular and inflammatory lesions but not for polyps/neoplasia
- DBE complements CE particularly in patients with neoplasia or polyp on CE
- DBE clarified origin of bleeding in 2/3 of patients with CE showing only blood

Marmo R et al: Endoscopy 2009;41:587-592
Diagnostic Yield of DBE over time

<1 month: 84% (107/128) vs. >1 month: 57% (24/42); p=0.002

Diagnosis of SB Bleeding (Guideline)

• CE should be first line procedure after second look endoscopy to increase diagnostic yield.

• If proximal lesions are suspected, would also include push enteroscopy

• Deep enteroscopy can be considered initially for active bleeding

• Total deep enteroscopy should be attempted if strong suspicion even if CE normal.

• Any method of deep enteroscopy can be employed
Case Study

49-year-old woman

- Intermittent overt bleeding with melena for 2 yr
- 3 mo transfusion-dependent anemia
- Hg 4.7 g/dL, 5.7 g/dL, 7.6 g/dL
- Dark formed stool on iron
- EGD, push enteroscopy, colonoscopy, SBFT normal
- Now in hospital

What next?

Our Case – Suspected SB Bleeding

49-Year-Old Female With Transfusion Dependent Recurrent IDA

- Single bleeding nodule
- 30% of small bowel transit
Case Study

- 200cm beyond pylorus
- Mid to distal jejunum
- Bleeding nodule: hemangioma?
- APC hemostasis

Deep Enteroscopy (Guideline)

- Total deep enteroscopy should be attempted if there is a strong suspicion of a SB lesion, even if CE is normal
- Any method is appropriate because of similar diagnostic yields
- CE should be performed before deep enteroscopy to increase diagnostic yield
- Consider deep enteroscopy in cases of active bleeding or when CE is contraindicated
Sub-Acute Ongoing Bleeding

- Sub-acute ongoing small bowel bleeding
- Stabilize patient
- Consider CE v CTE
  - Positive
  - Proceed to deep enteroscopy
  - Negative
  - Consider RBC scan and or angiography or surgery / intra-operative enteroscopy
- Treat accordingly

Case Study
- 70-year-old male with ischemic cardiomyopathy and LVAD placement on warfarin and aspirin presents with melena and hgb from 11 to 7.5
- EGD, Push Enteroscopy, negative
- Colonoscopy showed dark clots in cecum but ileum normal
- Proceeded with CE
Capsule Endoscopy

Deep Enteroscopy
Newer Radiologic Procedures

Cross-sectional imaging (CTE, CTA, MRE)

• May identify small bowel AVMs or tumors
• Diagnostic yield 10-40% (vs 50-80% CE)
• May miss lesions detected by deep enteroscopy (AVM, tumors, Meckel’s)
• Consider before capsule if concern for obstruction
• Consider if ongoing bleeding despite negative capsule or deep enteroscopy

Gerson: GIE 2008;68:920

Case Study

• 64-year-old male with recurrent GI bleeding for four months characterized by melena and hemoglobin in the 4-7 range requiring transfusions. Negative endoscopy. At the time of evaluation he was bleeding

• STAT CT Angiogram performed
CT Angiogram

Long segment serpiginous intramural enhancing venous malformation in mid ileum

Surgery Results
**Diagnosis Using Radiographic Techniques (Guideline)**

- Barium studies should not be performed
- CTE should be performed if CE is negative
- CTE is preferred over MR imaging
- CTE should be considered before CE in the setting of Crohn’s disease, prior radiation therapy, and/or obstructive symptoms
- CTE should also be performed if there is a high clinical suspicion despite the performance of a prior standard abdominal CT

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**So, Which Test To Order and When?**

- Little evidence-based medicine to give specific recommendations
- CE, Deep Enteroscopy, and Radiology are often complimentary
- Deep enteroscopy most cost-effective approach for overt SB bleeding
- At this time, must use your clinical suspicion
Suspected small bowel bleeding

- Occult:
  - Positive: Repeat endoscopy if warranted
  - Negative: Proceed with small bowel evaluation

- Overt:
  - Positive: Specific management: Push or deep enteroscopy surgery +/- intra-operative enteroscopy
  - Negative: Observation/iron supplements

Further evaluation warranted:

- CTE/MRE
  - Negative: Consider repeat endoscopy/Meckel's scan/surgery/intra-operative enteroscopy
  - Positive: Capsule endoscopy

- Capsule endoscopy
  - Negative: No obstruction
  - Positive: Specific management: Push or deep enteroscopy surgery +/- intra-operative enteroscopy

CE as a Screening Tool Prior to Deep Enteroscopy

- CE transit times are useful
  - Antegrade approach for lesions within the proximal 75% based on transit time
  - Retrograde for more distal lesions

- Increases both the diagnostic (73-93%) and therapeutic (57-73%) yield

- A negative CE allows for the avoidance of Deep Enteroscopy in patients with a low pre-test probability for SB findings
If Surgery Not Planned, Review of Capsule Endoscopy
Estimate Location to Plan Deep Enteroscopy Approach

0% small bowel transit
0-75%
start with oral approach
75-100%
start with anal approach

Case Study

- 89-year-old referred for anemia and occult blood in stool
- Multiple comorbidities including CAD, CHF, Afib on warfarin
- Underwent EGD and Colonoscopy which were negative
- CE and Deep enteroscopy performed
Capsule Endoscopy

Lesion within 75% SB transit

Antegrade Deep Enteroscopy
CE vs Deep Enteroscopy vs CTE/CTA for OGIB
A Reasonable Approach

- For most SB bleeding patients, CE should be performed before Deep Enteroscopy
- For obstructive symptoms or suspicion of IBD, would recommend CTE/MRE
- If no source identified with CE or Deep Enteroscopy, consider CTA
- For active bleeding, would recommend Deep Enteroscopy

Case Study

- 73-year-old female with end stage liver disease presents with hematochezia. History of esophageal varices without stigmata of bleeding
- Two EGDs, two colonoscopies, nuclear RBC scan negative
- At Mayo, push enteroscopy negative and bleeding continued
- Retrograde deep enteroscopy performed….
Retrograde Deep Enteroscopy 150cm Proximal to IC Valve

Jejunal Varix

In the Setting of Recurrent Bleeding

- Next steps are not completely evidence-based
- Don’t forget second-look endoscopy
- In setting of recurrent bleeding
  - Repeat capsule
  - Deep Enteroscopy from opposite route for total enteroscopy
  - CTE or CTA
  - Medical therapy, i.e., oral iron, iron infusions, somatostatin, thalidomide, stop anticoagulants if possible
- Limited data, and clinical experience, suggests benefit for intervention
Acute Overt Small Bowel Bleeding (Guideline)

- If massive and hemodynamically unstable, proceed with conventional angiography
- Do not perform conventional angiography without overt bleeding
- If active bleeding but stable, proceed with multiphasic CTA over CTE
- If slower rates of bleeding or uncertain of active bleeding, proceed with tagged RBC scintigraphy if CE or deep enteroscopy not performed
- Consider provocative angiography if all imaging studies negative
- In younger patients, don’t forget Meckle’s scan

Brisk/Massive Bleeding

If Unstable

- Stabilize patient
- Red cell scan or CT angiography
  - Positive: Specific management
    - Enteroscopy vs surgery
    - and intra-operative enteroscopy
  - Negative: Embolization
- Angiography
  - Positive: Specific management
  - Negative: Embolization
Treatment and Outcomes (Guideline)

• If non-neoplastic source identified, the patient should be managed with endoscopic therapy
• If no source identified, manage patient conservatively with oral or IV iron
• If bleeding persists, then a further diagnostic workup should be repeated as is appropriate
• If bleeding persists, and workup is again non-diagnostic, then consider stopping anticoagulation/antiplatelet therapy where appropriate and/or institute IV iron, somatostatin analogs or antiangiogenic therapy

Management of Angioectasia:
A Systematic Review and Meta-Analysis

• 22 studies, 623 patients over a mean of 22 months
• Results:
  • Endoscopic therapy recurrence rate for entire GI tract (14 studies): 36% (95%CI, 28-44%)
    • small bowel only: 45% (95%CE, 37-52%), n=341
  • Somatostatin analogues (4 studies) for bleeding cessation: pooled OR was 14.5 (95%CE, 5.9-36)
  • Hormonal therapy not effective (2 studies)
Is Endoscopic Therapy Effective for Angioectasia in SB Bleeding? A Systematic Review

- 24 articles (n=490) and 6 natural history cohorts receiving no therapy (n=130)
  - 121 had push enteroscopy
  - 427 had deep enteroscopy

Results:
- Therapy group: 209/490 rebled (42.7%; 95% CI, 38%-47%)
- Control group: 64/130 rebled (49.2%; 95% CI, 40%-58%)
- NNT: 15

IDA and Iron Supplements

- 38 patients with occult SB Bleeding and IDA
  - Treated empirically with iron
  - Anemia resolved in 30/38 at 20 months

Poor Response to Oral Iron

- Consider parenteral supplementation with iron sucrose (iron dextran)
  - Maximum recommended dose is 100 mg (2 mL)
  - Start with test dose of 25 mg (0.5 mL) over 5-10 minutes

Rockey DC et al: NEJM 329:1691-1695, 1993
**Pharmacologic Therapy**

- **Hormonal therapy:** current evidence does not support a role
- **Thalidomide:** benefit for angiodysplasia with a decrease in blood transfusions and an increase in hemoglobin
- **Octreotide:** benefit in various case series and a meta-analysis but no published randomized controlled trials

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**Heyde’s Syndrome (Guideline)**

- Aortic stenosis and angioectasia
- In the setting of ongoing bleeding, consider aortic valve replacement
Surgical Intervention (Guideline)

- Try to limit to scenarios where deep enteroscopy cannot be performed
- Consider in ongoing active bleeding and no source identified with imaging studies
- Intraoperative enteroscopy should be available at the time of the surgical procedure
- When possible, presurgical localization of the bleeding site using a tattoo is always recommended

Summary

- The majority of cases of previously termed “occult GI bleeding” can now be classified as having small bowel bleeding
- Endoscopic techniques such as CE, push enteroscopy, and deep enteroscopy, as well as cross-sectional techniques can help localize small bowel bleeding sources
- Medical therapies are an alternative in cases of refractory or recurrent bleeding
- Surgery should be reserved for patients who fail other modalities
Thank You