

# Gastrointestinal Bleeding/Peptic Ulcer Disease

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### Educational Goals

1. Understand the pathogenesis of peptic ulcer disease as a cause of upper GI bleeding
2. Be familiar with the complications and management options for management of peptic ulcers
3. Be familiar with the clinical presentations of gastrointestinal bleeding
4. Learn the initial steps in assessing and resuscitating patients with gastrointestinal hemorrhage
5. Learn the differential diagnosis of causes of upper and lower causes of GI bleeding
6. Understand the options for diagnosis and therapy of patients with GI blood loss

### Key Words:

- o adenocarcinoma
- o angiodysplasia
- o angiography
- o aortoenteric fistula
- o argon plasma coagulation
- o band ligation
- o bismuth
- o capsule enteroscopy
- o clean ulcer base
- o coffee grounds
- o colitis
- o colonoscopy
- o Crohn's disease
- o Dieulafoy lesion
- o diverticulosis
- o electrothermal tissue ablation
- o embolization
- o endoscopy
- o endoscopic predictors of rebleeding
- o endoscopic therapy
- o erythromycin
- o gastrin
- o gastrinoma
- o gastrointestinal bleeding
- o h. pylori stool antigen testing
- o H-2 receptor antagonist
- o hematochezia
- o hematemesis
- o hemobilia
- o hemoccult test
- o hemosuccus pancreaticus
- o histamine
- o hyperchlorhydria
- o Mallory-Weiss tear
- o Meckel scan
- o melena
- o MEN-1
- o misoprostol
- o mucoid cap
- o mucosal defense mechanisms
- o mucus-bicarbonate barrier
- o nasogastric aspirate
- o nasogastric lavage
- o NSAIDs
- o octreotide
- o orthostasis
- o pigmented protuberance
- o portal gastropathy
- o proton pump inhibitors
- o red cell scintigraphy
- o somatostatin
- o sucralfate
- o surface phospholipids
- o tight junctions
- o tobacco
- o transjugular intrahepatic portosystemic shunt (TIPS)
- o urease
- o urease breath test
- o urease test (CLOtest)
- o varices
- o vascular ectasia
- o visible vessel

## Peptic Ulcer Disease

### Gastric Mucosal Defense Mechanisms

In order to preserve the integrity of the gastric mucosa and protect it from the hostile luminal environment, there are a series of defense mechanisms intrinsic to the stomach:

1. Pre-epithelial
  - a. Mucus-bicarbonate barrier
    - i. Produced by the mucous neck cells

- ii. Defends against H<sup>+</sup> diffusion to the mucosal cells resulting in a buffered gradient from lumen to epithelium
      - iii. Serves as a mechanical barrier
    - b. Surface phospholipids
      - i. Increase viscosity and hydrophobicity of mucous layer
    - c. Mucoid cap
      - i. Injury response with a second mucous layer at neutral pH
      - ii. Provides microenvironment suitable for mucosal repair
- 2. Epithelial
  - a. Tight junctions between cells
  - b. Rapid turnover of damaged cells
  - c. Reconstitution
    - i. Migration of cells from along the pit to repair small defects
  - d. Regeneration
    - i. Cellular proliferation to repair larger defects
  - e. Surface cells can independently maintain neutral intracellular pH even if exposed to gastric acid if the surface mucus layer is damaged via active transport mechanisms
- 3. Subepithelial
  - a. Mucosal blood flow
    - i. Provides nutrients to support cell turnover
    - ii. Supply of HCO<sub>3</sub> for the mucus bicarbonate barrier
    - iii. Local buffer of H<sup>+</sup> ions
- 4. Duodenum
  - a. The major mechanism is the gradient of bicarbonate from pancreatic secretions that exists from the proximal to distal duodenum.

### Mucosal Damage

Mucosal damage occurs when the balance between the “aggressive” factors and the “defense” mechanisms is altered:

1. Increase the direct insults
  - a. Gastrin overproduction
    - i. Gastrinoma (sporadic or MEN-1)
    - ii. G-cell hyperplasia (H *pylori*-associated)
    - iii. Retained gastric antrum syndrome
  - b. Histamine overproduction
    - i. Leukemia – basophils, eosinophils
    - ii. Systemic Mastocytosis
  - c. H *pylori* via direct parietal cell stimulation
  - d. Head trauma (Cushing Ulcer)
  - e. Burns (Curling Ulcer)
  - f. Idiopathic
  - g. Other chemical injury (medication, caustic)
2. Sabotage the defense
  - a. Compromise mucus/bicarbonate layer integrity
  - b. Damage surface phospholipids
  - c. Damage the epithelial cells
  - d. Decrease mucosal blood flow

The two most common causes of peptic ulcers are **H *pylori* infection and NSAID use:**

#### **Helicobacter *pylori*:**

- Most prevalent human infectious organism in the world affecting up to 80% of individuals in the 3<sup>rd</sup> world
- Infection generally occurs in childhood prior to 10 years of age
- Lives in the stomach and sites of ectopic gastric metaplasia

- 11% of infected individuals develop peptic ulcers over 10 years compared to 1% of those without infection
- Eradication of *H pylori* prevents recurrence of ulcers
- Stronger association with duodenal ulcers (up to 90%) than with gastric ulcers (up to 70%)

### Diagnosis of *H pylori*

1. Serum *H pylori* IgG Antibody (blood test)
  - a. Designates past infection, does not suggest active or current infection
  - b. Use for the patient with a documented ulcer that is treatment naïve
  - c. Do not use to confirm eradication
2. Urease breath test
  - a. Patients ingest labeled <sup>13</sup>C- or <sup>14</sup>C-labeled urea. *H pylori* will hydrolyze the urease yielding labeled bicarbonate which is secreted by the lungs as CO<sub>2</sub>
  - b. False negative for patients on proton pump inhibitors, Bismuth, or antibiotics
  - c. Positive test denotes active infection
3. Biopsy of gastric mucosa
  - a. H & E or dedicated stains (Giemsa Stain or Warthin-Starry Stain)
  - b. Urease test (CLOtest)
    - i. Detects urease activity in the biopsy specimen, as pH in the agar rises, color changes
    - ii. False negatives in patients in active bleeding, patients on PPI, bismuth, antibiotics
  - c. PCR of biopsy material
4. Stool Antigen testing
  - a. Detects active infection
  - b. Can be used to confirm eradication

### Nonsteroidal Anti-inflammatory Drugs

- 2-4% of NSAID users experience serious GI related adverse effects of bleeding and/or perforation
- Stopping NSAID use reduces development of ulcers

### Pathogenesis of NSAID induced Ulceration

1. Direct effects
  - a. High intracellular NSAID concentrations are toxic to epithelial cells. The acid environment maintains the hydrophobicity of NSAID medications facilitating diffusion across cell membranes. Within the more neutral intracellular pH, drug molecule loses a proton thereby becoming trapped within the epithelial cell This effect is mitigated by enteric coated preparations
2. Indirect/Systemic Effects
  - a. Systemic effects result from the physiologic activity of the medications to reduce prostaglandin synthesis
    1. Prostaglandin biology involved in all layers of mucosal defense
      - a. Mucus bicarbonate layer
        - i. Quantity and quality of mucous are reduced with prostaglandin inhibition
        - ii. Amount of bicarbonate secretion markedly reduced
      - b. Epithelial layer
        - i. NSAIDs reduce epithelial cell proliferation reducing ability for epithelial self-repair
      - c. Subepithelial Layer
        - i. Prostaglandins instrumental in maintenance of mucosal blood flow. NSAIDs reduce the flow weakening defenses and promoting ulceration

## Complications of PUD

1. Bleeding
  - a. Occurs in 15%
  - b. Risk factors:
    - i. Increasing age
    - ii. Comorbid diseases (i.e. coronary artery disease)
    - iii. Antiplatelet and anticoagulant medication
      1. NSAIDs not only cause ulcers and bleeding but inhibit platelet function affecting hemostasis
2. Perforation
3. Penetration
  - a. Ulcer bores into adjacent organs
    - i. GU left hepatic lobe, colon
    - ii. DU posteriorly to pancreas
      1. If gastroduodenal artery involved can lead to rapid exsanguination
4. Obstruction
  - a. 2% of cases
    - i. Functional – hypomotility of the stomach
    - ii. Mechanical – inflammation and scarring of pylorus results in narrowing and obstruction
  - b. Initial complaints are of reflux, progressing to early satiety, abdominal pain, weight loss and emesis

## Therapy: Medical Management

1. Acid suppression
  - a. H<sub>2</sub> receptor antagonists
  - b. Proton pump inhibitors
    - i. Used in acute bleeding
    - ii. Maintenance for patients at high risk for NSAID induced ulcer (increased age, comorbid medical illness, coagulopathy)
2. Sucralfate
  - a. Sucrose based compound that becomes a viscous paste in the stomach and duodenum
  - b. Mechanical barrier to caustic acid, pepsin, bile salts
  - c. Promotes the mucus/bicarbonate layer and the mucoid cap promoting epithelial regeneration
3. Bismuth
  - a. Mechanism felt to be related to formation of a glycoprotein-bismuth complex over ulcer crater preventing further ulceration and promoting healing
4. Prostaglandin Analogs
  - a. Misoprostol – PGE<sub>1</sub> analog
    - i. Enhances the mucus/bicarbonate layer
    - ii. Improves mucosal blood flow
    - iii. Side effects limit use
      1. Diarrhea
      2. Uterine muscle contraction
5. *H Pylori* treatment
  - a. Two general therapeutic regimens:
    - i. PPI with 2 antibiotics
      1. PPI with amoxicillin and clarithromycin (PPI-AC)
    - ii. Acid suppressing agent with 3 antibiotics
      1. PPI or H<sub>2</sub>RA, Bismuth, Metronidazole, Tetracycline (BMT)
  - b. Eradication rates generally 85-90%
  - c. Metronidazole resistance is common, as is clarithromycin resistance. There is significant regional variation. Amoxicillin resistance much less prevalent.

### **Therapy: Endoscopic**

Endoscopic methods may be used to manage ulcer bleeding as will be described later this lecture

Endoscopic dilation may be used for gastric outlet obstruction

### **Therapy: Surgery**

1. Indication
  - a. Persistent bleeding
  - b. Failure of endoscopic therapy to manage bleeding
  - c. Perforation
  - d. Obstruction
2. Procedure choice depends on complication requiring therapy (i.e. bleeding vs perforation vs penetration)
  - a. Anti-ulcer
    - i. Antrectomy + vagotomy – lowest recurrence rate
    - ii. Vagotomy + pyloroplasty
    - iii. Vagotomy – super selective – highest recurrence rate
  - b. Directed to pathology
    - i. Oversew ulcer
    - ii. Mesenteric patch of penetrating/perforated ulcer
    - iii. Partial gastrectomy and gastrojejunostomy to remove ulcer, fibrosis, and to manage obstruction

### **Ulcer Recurrence**

1. Failure to eradicate *H pylori*
2. Surreptitious NSAID use
3. Tobacco use
4. Malignancy
5. ZE syndrome – hypergastrinemia and hyperchlorhydria

### **Gastrointestinal Bleeding**

**Clinical Presentation** – depends upon the volume, speed, and location of blood loss

1. Overt Bleeding
  - a. Hematochezia – bright red blood per rectum
    - i. Suggest colonic bleeding
    - ii. May be seen with brisk bleeding from proximal sites
  - b. Melena
    - i. Black, tarry, malodorous stool
    - ii. Generally attributed to upper GI losses from the esophagus, stomach or duodenum
    - iii. Result of bacterial metabolism of red blood cells
  - c. Hematemesis – Emesis of red blood and/or coffee grounds
    - i. Upper GI source
  - d. Symptoms of anemia may be the initial presentation prior to gross blood loss.
    - i. Occurs with very rapid volume loss and is attributed to hemodynamic compromise more so than a lack of oxygen carrying capacity in the blood
    - ii. Syncope, chest pain, dyspnea
2. Occult Bleeding
  - a. Results from subclinical blood loss
  - b. Anemia identified on laboratory studies
  - c. Symptomatic anemia
    - i. Due to decreased oxygen carrying capacity
    - ii. Pallor, dyspnea on exertion, chest pain, fatigue, lightheadedness
  - d. Positive stool hemoccult test
3. Obscure Bleeding
  - a. Refers to overt (gross) bleeding that is from an unidentified source

- i. May be anywhere within the gastrointestinal tract, but more interesting sites include:
  1. Small bowel
  2. Biliary tree - hemobilia
  3. Pancreas - hemosuccus pancreaticus

**Initial Evaluation**

The initial patient assessment should be a global consideration of “how sick is the patient?” Consider both the volume of blood loss and the speed with which blood is lost. In a few minutes you can generate an accurate assessment of the severity of the bleed. A few basics:

**Assess the volume of blood loss**

1. Assess the rapidity of blood loss by assessing the clinical presentation of the patient. Bear in mind the information that can be obtained by combining information from the physical examination including an NG aspirate and rectal examination.
2. Orthostatic Vital Signs
  - a. Decrease in systolic blood pressure by 20mm Hg, or increase in diastolic blood pressure by 10mm Hg or increase in heart rate by 20 BPM (20/10/20 rule) with a change in position suggests significant volume depletion and hemodynamic embarrassment

<b>Estimated Fluid and Blood Losses in Shock</b>				
	<b>Class 1</b>	<b>Class 2</b>	<b>Class 3</b>	<b>Class 4</b>
<b>Blood Loss, mL</b>	Up to 750	750-1500	1500-2000	>2000
<b>Blood Loss,% blood volume</b>	Up to 15%	15-30%	30-40%	>40%
<b>Pulse Rate, bpm</b>	<100	>100	>120	>140
<b>Blood Pressure</b>	Normal	Normal	Decreased	Decreased
<b>CNS/Mental Status</b>	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

3. Consider what possible source of blood loss you are dealing with
  - a. Best clues are from the clinical presentation, history and results of the rectal examination and NG tube aspirate
  - b. Patients with liver disease are generally at the highest risk of death from an acute upper GI bleed, early recognition of stigmata of liver disease will aid in the management of the patient.
    - i. Look for, spider angiomas, jaundice, abdominal distention, palmar erythema, etc...

<b>Effect of the Color of the Nasogastric Aspirate and of the Stool on UGIB Mortality</b>		
<b>Nasogastric Aspirate Color</b>	<b>Stool Color</b>	<b>Mortality Rate (%)</b>
<b>Clear</b>	<b>Brown or Red</b>	6%
<b>Coffee-ground</b>	<b>Brown or black</b>	8.2%
	<b>Red</b>	19.1%
<b>Red blood</b>	<b>Black</b>	12.3%
	<b>Brown</b>	19.4%
	<b>Red</b>	28.7%

## Resuscitation

1. Obtain IV access
  - a. Antecubital or femoral
  - b. 14g or 16g catheter
2. Replete intravascular volume
  - a. Colloid – normal saline, lactated Ringers
  - b. Blood transfusion
    - i. Goal of Hb > 10mg/dl in patients with underlying cardiovascular disease
    - ii. Consider side effects of blood transfusion:
      1. Volume overload
      2. Respiratory compromise
      3. Massive transfusion
        - a. Coagulopathy
        - b. Hypocalcemia
3. Consider other sites of end-organ damage that may need to be addressed early:
  - a. Cardiovascular – obtain EKG
  - b. Neurologic – document physical examination, consider imaging in first hours to days

## Monitoring

1. ICU setting is appropriate for significant bleeding
2. Assess and reassess the patient
3. Foley catheter - monitor urine output as a measure of intravascular volume
4. Cardiac monitoring, serial EKGs
5. Central venous pressure monitoring for persistent hypotension

## Establish a Diagnosis – Consider the anatomic site of bleeding

### 1. Esophagus

- a. Esophagitis
  - i. Reflux
  - ii. Infectious
  - iii. Caustic
- b. Ulcer
  - i. Infectious
  - ii. Medication
- c. Mallory-Weiss tear
  - i. Tear at the GE junction with retching
- d. Varices
- e. Neoplasia
- f. Aorto-esophageal fistula

### 2. Stomach

- a. Gastritis
  - i. Alcohol
  - ii. Medications
  - iii. Stress/ICU
  - iv. Infectious
- b. Ulcer
  - i. Acid peptic
  - ii. H pylori.
  - iii. Medications
  - iv. Crohn's Disease
- c. Gastric varices
- d. Portal gastropathy
- e. Neoplasia
- f. Angiodysplasia
- g. Dieulafoy lesion

### 3. Duodenum

- a. Duodenitis
- b. Duodenal ulcer
- c. Duodenal varices
- d. Neoplasia
- e. Angiodysplasia
- f. Aortoenteric fistula
- g. Hemobilia
- h. Hemosuccus pancreaticus

### 4. Small Bowel (Jejunum/Ileum)

- a. Ulcer
  - i. Medication
  - ii. Crohn's Disease
- b. Angiodysplasia
- c. Neoplasia
- d. Meckel's diverticulum

## 5. Colon

- a. Diverticulosis
  - b. Angiodysplasia
  - c. Neoplasia
  - d. Colitis
  - e. Ischemia
  - f. Radiation
  - g. Infection
  - h. IBD – Crohn's or UC
6. Hemorrhoids and fissures
  7. Dieulafoy's
  8. Portal Colopathy
  9. Runners colopathy

### Diagnostic Testing

Initial testing is at the time of the physical exam with rectal exam and NG lavage

Other tests include:

1. Upper GI evaluation
  - a. Endoscopy
    - i. Esophagus, stomach, duodenum
    - ii. Proximal jejunum can be reached with an enteroscope (longer than a standard endoscope)
2. Small bowel evaluation
  - a. Capsule enteroscopy
    - i. Mostly used for identification of obscure causes of bleeding
    - ii. Perform after endoscopic examinations are negative
    - iii. Administer capsule at the time of active bleeding
  - b. Meckel scan
  - c. Small bowel barium x-ray
  - d. Enteroscopy
3. Colonic evaluation
  - a. Colonoscopy
    - i. Not generally helpful with active lower GI bleeding due to blood obscuring the visualization of the lumen
    - ii. Allows for differential diagnosis by identifying structural abnormalities (diverticulosis, cancer, etc...)
    - iii. Terminal ileal intubation may be helpful to distinguish colonic source from a small bowel source of bleeding
    - iv. Therapy may be applied to a bleeding source
  - b. Nuclear medicine
    - i. Red Cell Scintigraphy
      1. Detects bleeding at 0.5-1.0 mL/min
    - ii. Sulfur Colloid Scan
      1. Bleeding rates as low as 0.1mL/Min
  - c. Angiography
    - i. Highly accurate for diagnosis and provides options for therapy
    - ii. Generally proceed to angiography after a positive nuclear medicine study

### Therapy

1. Upper GI bleeding
  - a. Pharmacotherapy
    - i. Proton pump inhibitors
    - ii. Somatostatin analogue (octreotide) administered IV for bleeding due to esophageal varices
      1. Lower portal pressures by decreasing splanchnic flow
    - iii. IV erythromycin to enhance gastric motility and assist with subsequent endoscopy
    - iv. Vasopressin / terlipressin
      1. Decreases portal venous inflow via splanchnic vasoconstriction
      2. Treat along with nitrates to prevent end-organ ischemia
  - b. Endoscopic therapy

- i. To intervene with endoscopic therapy is determined by the findings on urgent upper endoscopy.

<b>Endoscopic Predictors of Rebleeding in Peptic Ulcers</b>		
<b>Endoscopic Finding</b>	<b>Risk of Rebleeding</b>	<b>Risk after endoscopic therapy</b>
Active bleeding	90%	45-50%
Non bleeding visible vessel	50%	20-30%
Adherent clot	30%	10-20%
Oozing without visible vessel	10-20%	5-8%
Flat spot	5-10%	4%
Clean base	3-5%	1-3%

- ii. Injection to provide local tamponade, vasoconstriction, and/or ablation of bleeding vessels.
  1. Dilute epinephrine (most often used)
  2. Saline
  3. Sclerosant
  4. Alcohol
- iii. Electrothermal applications in which bleeding vessels are directly ablated
- iv. Band ligation for portal hypertensive varices
- v. Argon plasma coagulation to ablate sites of blood loss. Better for diffuse mucosal diseases
- vi. Endoscopic clips to tamponade a bleeding vessel
- vii. Minnesota tube to provide direct compression to esophagogastric varices.

c. Interventional Radiology

- i. Embolization
- ii. Transjugular Intrahepatic Portosystemic Shunt (TIPS)
  1. Variceal bleeding
  2. Refractory esophageal varices
  3. Gastric varices

d. Surgery

- i. Failure of medical and endoscopic therapies
- ii. Surgery tailored to the disease process

2. Therapy - Lower GI Bleeding (LGIB)

a. Colonoscopy

- i. Mostly diagnostic and helps to direct other, more definitive therapies
- ii. Problem with visualization with active bleeding
- iii. Not likely to offer much therapeutic benefit

b. Angiography

- i. Patients are often stratified to angiography based on a positive nuclear medicine scan (RBC or sulfur colloid)
- ii. Detect bleeding at 0.5-1.0 mL/min
- iii. Embolization is primary therapy

c. Surgery

- i. Failure of other therapies
  1. Angiography
  2. Medical therapies
- ii. Massive bleeding
- iii. Recurrent bleeding - diverticulosis