A DISCUSSION OF PEPTIC ULCER DISEASE, AND HELICOBACTER PYLORI UPDATE

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ECHO PROJECT
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Defect in GI mucosa, extending through the muscularis mucosa

Cost estimate: 5.65 billion dollars per year in the USA

Two major factors = H pylori and NSAIDS

Incidence: about 0.1% to 0.3% per patient year
  - 1% per year in those with active H pylori

Incidence increases with age, males = females
PEPTIC ULCER ETIOLOGY

- Infection: H pylori, HSV, CMV, H heilmanii, TB, syphilis
- Drugs: NSAIDS, aspirin, steroids, bisphosphonate, clopidogrel, sirolimus, mychophenolate, chemotherapeutics
- Hormonal: gastrinoma (ZE Syndrome), systemic mastocytosis
- Post surgical: antral exclusion, post gastric bypass
- Infiltrating disease: Crohn’s disease, sarcoidosis
PUD CLINICAL MANIFESTATIONS AND DIAGNOSIS

- Dyspepsia: present in 80% of endoscopically diagnosed ulcers
  - Asymptomatic: up to 70% without dyspepsia
  - Up to 85% of those presenting with a bleed deny dyspepsia
- Bleeding: Hematemesis, melena, hematochezia
- Perforation/Penetration
- Obstruction
PUD CLINICAL MANIFESTATIONS AND DIAGNOSIS

- Lab: most have normal CBC
  - Iron deficiency anemia
- Contrast imaging: may demonstrate an ulcer
  - If duodenal, benign appearing, and no alarm features => no need for endoscopy
  - Gastric => endoscopy to rule out malignancy
MANAGEMENT OF ANY GI BLEED

1) ASSESSMENT OF HEMODYNAMIC STABILITY

2) RESUSCITATION

3) DIAGNOSTIC STUDIES
INITIAL EVALUATION

- History and physical examination
- Laboratory analysis
- NG lavage?

Goal: assess severity, identify potential source, determine if other conditions are present that may affect management, start formulating a differential
Patient reported history of melena (LR 5.1-5.9)

Melenic stool on exam (LR 25)

Blood or coffee grounds via NG lavage (LR 9.6)

BUN/creatinine greater than 30 (LR 7.5)

Predictors of severe bleeding
  - Red blood via NG (LR 3.1)
  - Tachycardia (LR 4.9)
  - Hg < 8.0 gm/dL (LR 4.5-6.2)

Srygley FD, et al. Does this patient have a severe upper GI bleed? JAMA 2012;307:1072
PMH

- Prior GI bleed?
  - Liver disease or cirrhosis
    - varices, PHG
  - Renal dz, AS, HHT
    - angiodysplasia
  - NSAIDS use, tobacco, Hx H pylori
    - PUD
  - Tobacco, alcohol, Hx H pylori
    - cancer
  - Gastroenteric anastamosis
    - marginal ulcer
MEDICATION HISTORY

- Aspirin, NSAIDS
- Medications associated with pill esophagitis
- Antiplatelet agents
- Bismuth, iron
HYPOVOLEMIA

- Mild to moderate: Resting tachycardia
- Blood volume loss of at least 15%: Orthostatic hypotension
- Blood volume loss of at least 40%: Supine hypotension
ABDOMINAL PAIN AND TENDERNESS ON EXAM

- Signs of acute abdomen → imaging to rule out perforation urgently
  - Perforated PUD, ischemic gut, etc.
NASOGASTRIC LAVAGE

- Controversial
- Study: retrospective, 632 pts, admit with GIBL, those who had NG lavage were matched with controls
- Results: NGT lavage associated with shorter time to endoscopy, but no difference in mortality, length of hospital stay, surgery, transfusion requirement

NASOGASTRIC LAVAGE
POTENTIAL USES

- When unclear if patient has ongoing bleeding
- To remove particulate matter, fresh blood, clots to facilitate endoscopy
- Red blood, or coffee grounds→ confirms upper GI source and predicts whether bleeding is caused by a lesion at increased risk for ongoing bleeding
- Problem: lavage may be negative if bleeding ceased or arises from source distal to pylorus
- I suggest lavage only be performed if particulate matter, fresh blood, or clots need to be removed to facilitate endoscopy
DID I MENTION? DO A RECTAL EXAM!
LABS

- CBC, CMP, coagulation studies
- Cardiac enzymes and EKG for older patients, history of CAD, chest pain or dyspnea
- If initial labs show microcytosis, order iron studies prior to transfusing!
- Elevated BUN/creatinine common with upper source
- Initial hemoglobin may be normal
TRIAGE

- ICU: patients with hemodynamic instability (shock, orthostasis), obvious active bleeding
- General ward
- Out-patient management
ROCKALL CRITERIA

- **Age**
  - < 60 (0 points)
  - 60-79 (1 point)
  - > 80 (2 points)

- **Hemodynamic shock**
  - None with SBP > 100 and HR < 100 (0 points)
  - Tachycardia with HR > 100 but SBP > 100 (1 point)
  - Hypotension with SBP < 100 (2 points)

- **Major Comorbidities**
  - None (0 points)
  - Cardiac failure, ischemic heart disease (2 points)
  - Renal failure, hepatic failure, disseminated cancer (3 points)

- **Diagnosis**
  - MWT but no stigmata of recent bleeding or major findings (0 points)
  - Other nonmalignant gastrointestinal disease (1 point)
  - Upper GI tract malignance (2 points)

- **Recent Hemorrhage**
  - None, or dark spot only (0 points)
  - Blood found in upper GI tract, active spurting, visible vessel, adherent clot (2 points)
GENERAL SUPPORT

- NPO status
- Two large caliber (16 gauge or larger) peripheral IV catheters or central line
- Elective endotracheal intubation for ongoing hematemesis or altered respiratory or mental status
- Fluid resuscitation
  - Active bleeding: NS or LR 500 cc IV bolus while being typed and crossed
* BLOOD TRANSFUSIONS

- Most patients: initiate transfusion if hemoglobin < 7 g/dL

- Unstable angina/CAD: goal of maintaining hemoglobin > 9 g/dL

- Avoid over-transfusion
  - Several studies show worse outcomes, particularly in suspected variceal bleeding
** BLOOD TRANSFUSIONS

- **Study:** retrospective, 1677 pts, non variceal UGIB
  - Results: no difference in mortality but blood transfusion within 24 hours independently associated with increased risk of re-bleeding (OR 1.8, CI 1.2-2.8)

- **Study:** randomized, 921 pts assigned to restrictive or liberal protocol (target Hb at 7 vs 9 g/dL)
  - Results: restrictive had less transfusions (51% vs 14% avoided transfusion), received less units (mean 1.5 vs 3.8), lower mortality (5% vs 9%, adjusted hazard ratio 0.55, CI 0.33-0.92)
TRANSFUSION STRATEGY

- Platelets: transfuse when active bleeding and low platelet count (<50,000/microL)
- FFP: may transfuse in patients with a coagulopathy (INR>1.5) not due to cirrhosis
- Endoscopy is safe in patients with mild to moderate coagulopathy
  - Okay to proceed simultaneously with transfusion as long as INR < 3
  - If high risk stigmata found, or endoscopic therapy applied, transfuse to INR < 1.5

MEDICATIONS
ACID SUPPRESSION

- PPI intravenous infusion: significantly lowers the rate of ulcer re-bleeding

- Oral and IV PPI also decreases length of stay, need for transfusions

- IV PPI only shown to decrease chance of high risk stigmata at time of endoscopy
  - NOT SHOWN TO IMPROVE IMPORTANT CLINICAL OUTCOMES
PEPTIC ULCER
STIGMATA OF RECENT HEMORRHAGE
AND RISK OF RE-BLEEDING

- Active spurting 55%
- Visible vessel 43%
- Adherent clot 22%
- Flat spot 10%
- Clean base 5%

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WHO SHOULD GET IV PPI THERAPY FOR 72 HOURS AFTER ENDOSCOPY?

- Active bleeding
- Visible vessel
- Adherent clot
ANTICOAGULANTS/ANTIPLATELET AGENTS

- On going bleeding risk – vs- thrombotic risk
- Coumadin: FFP faster onset than vitamin K
- Pradaxa (dabigatran), Xarelto (rivaroxaban), Eliquis (apixaban)
  - Idarucizumab (PraxBind) for Pradaxa reversal
  - FEIBA (factor eight inhibitor bypassing activity) in cases of imminent death
    - An activated prothrombin complex concentrate
- TEG?
  - Not studied in this instance
RESUMPTION OF ANTICOAGULATION

- Aspirin: resume immediately post hemostasis if secondary prophylaxis
- Coumadin: hold for 72 hours post hemostasis
- DOAC: less clear
- Bridging indicated: weight based heparin preferred initially due to ability to hold with quick reversal of effect
* NSAIDS AND ULCERS

- If h pylori positive, may resume NSAIDS after eradication documented
- If h pylori negative, try not to resume NSAIDS
- If patient must resume, COX-2 selective, or NSAID + PPI therapy
RISK OF GI BLEEDING FROM COMBINATIONS OF MEDICATIONS

- Link to individual drugs (risk) is known
- Patients are increasingly on combination of medications
- Particularly among the elderly
- Highest risk seen when nonselective NSAIDs combined with corticosteroids (RR=12.8)
  - Decreases to RR=6 when steroid combined with COX-2 inhibitor
  - Effect was mitigated when patient on low dose aspirin
- Slightly increased risk for PPI therapy!
  - High risk patients
- Pearl: use NSAIDS for shortest duration possible and at lowest dose
Infection linked to PUD, H pylori associated gastric cancer
Challenges exist in eradication of H pylori
Responsible for most cases of gastric cancer world-wide
Declared Class I carcinogen by WHO in 1994
  Via inflammation
Hence push to eradication (Japan)
We are seeing gastric cancer go away in USA
  But… it is being imported
  80% immigrating from Central and South America are infected, for instance
HELICOBACTER PYLORI THERAPY

- Prevalence: increased among minority groups and low socioeconomic groups.
  - AA, Latinos and immigrants have much higher prevalence
  - Demographics of US population are changing…

- ACG Guideline (2/2/17)
- Patient susceptibility and population susceptibility can help choose a therapy with 95% cure rate as the goal

- New interest in relationship of H pylori to other disorders
  - Iron def anemia, ITP

- Tried and true indications for testing, and if appropriate treating: PUD, MALT, gastric adenocarcinoma
H PYLORI AND ULCERS

- Verify eradication
  - DO NOT USE SEROLOGY
- If H pylori eradicated patient does not need long term PPI therapy
H PYLORI

- Test and treat strategy: Means to deal with patient with uninvestigated dyspepsia
  - Cost effective strategy
- Guideline also recommends:
  - gastric biopsy in patients undergoing EGD for investigation of dyspepsia
  - treating H pylori prior to instituting therapy with low dose aspirin
  - testing and treating prior to chronic NSAIDS therapy
- Iron deficiency anemia: adults with unexplained iron def anemia have higher incidence of H pylori
  - Eradication may make easier to replete with oral iron
- ITP: number of studies showing eradication in those with ITP leads to increase in platelet count. Oncology society recommends those with ITP be tested and if appropriate, treated
H Pylori

- Diagnosis: mucosal biopsy for histology, rapid urease testing, serology, urea breath test, fecal antigen test
- Active tests: UBT and fecal antigen test
  - Both highly sensitive and specific
- Role for serology: acute UGIB
  - Blood in the stomach reduces sensitivity of all other tests
  - Individual with PUD bleeding has higher pretest probability of infection
H PYLORI DIAGNOSTIC TESTS

- **RUT:**
  - Sensitivity: 90-95%
  - Specificity: 95-100%
  - PPI or GIBL decreases sensitivity substantially

- **Histology:**
  - Sensitivity: 83-84%
  - Specificity: 100%

- **Serology:**
  - Sensitivity: 90-100%
  - Specificity: 76-96%

- **Stool Antigen:**
  - Sensitivity: 94-96%
  - Specificity: 86-92%

- **UBT:**
  - Sensitivity: 88-95%
  - Specificity: 95-100%
H PYLORI TREATMENT

- 2007 guideline: first line clarithromycin containing
  - Now controversial

- Changes in current guideline: triple therapy (clarithro + PPI + amox) still recommended but with clarification.
  - Need to try to move away from clarithro
  - Inquire about macrolide antibiotics exposure
  - Eradication rate: 85-90% -vs- 20%

- Bismuth quadruple therapy (bismuth + tetracycline + metronidazole + PPI)
  - Good choice for patient with multiple macrolide exposures
  - Could use the for everybody as first choice

- Concomitant therapy (quadruple + clarithromycin)
H PYLORI TREATMENT

- Failure...
  - Guideline recommends quadruple therapy or levofloxacin based therapy for patient who failed triple therapy (clarithro containing)
  - If failed a bismuth containing therapy, salvage with clarithromycin containing (concomitant recommended) or levofloxacin containing therapy

- When to confirm eradication?
  - 2007 guideline was more selective
  - 2017 guideline recommends proving eradication after antibiotics (Universal)
  - This aligns with European and Canadian Guidelines

- New terms: ‘concomitant therapy’, ‘sequential therapy’
  - ‘Concomitant’ eradication rate is higher (85-90%)

- Take away: we are moving away from a one size fits all approach to therapy
PEARLS

- Assess hemodynamic stability first and begin resuscitation
- Focus on resuscitation- IVF, two large bore IVs, correct coagulopathy
- Do a rectal examination
- Utilize BUN/creatinine ratio
- Pantoprazole drip not shown to affect clinical outcomes
- Know transfusion parameters- focus on hemoglobin of 7 g/dL
- Attention to H pylori and NSAIDS after a peptic ulcer
SUMMARY

- Peptic ulcers are commonly asymptomatic, and when symptomatic commonly present with epigastric pain, food provoked pain and fullness, early satiety, nausea
- Complications may be heralded by new ulcer symptoms or change in symptoms
- All patients diagnosed with PUD should undergo H pylori testing
- Tailor therapy for H pylori based on patient history of antibiotics
RECENT STUDY DATA
ADVERSE OUTCOMES WITH TRANSFUSION FOR UGIB

- Recent data suggests those with non-variceal UGIB receiving PRBC transfusions have elevated 30-day mortality
  - (NEJM JW Gastroenterol Feb 9 2016)
- Study: Australia, retrospective, 2228 pts, acute NVGIB
- Results: Transfusion > 4 U significantly associated with elevated rate of re-bleeding, no affect on mortality. Transfusion of > 5 U FFP led to increased mortality at 30 days and 1 year. Transfusion of > 3 units of platelets significantly associated with elevated 30 day mortality.
  - Subramanian K et al. Red blood cell transfusion is associated with further bleeding and fresh-frozen plasma with mortality in nonvariceal upper gastrointestinal bleeding. Transfusion 2015 Dec 31
LARGER PEPTIC ULCER SIZE ASSOCIATED WITH WORSE BLEEDING OUTCOMES

- Factors affecting longer term (30 day) outcomes are not well studied.
- Study: Prospective cohort, 1264 pts, endoscopy proven peptic ulcer. Outcomes: 30 day re-bleeding, mortality and need for surgery.
- Results: 18% re-bled, 7% required surgery, 7% died. Ulcers > 10 mm associated with re-bleeding, and with need for surgery, and 30 day mortality.

  Camus et al. Independent risk factors of 30-day outcomes in 1264 patients with peptic ulcer bleeding in the USA: Large ulcers do worse. Aliment Pharmacol Ther 2016 Mar 22
SECOND LOOK ENDOSCOPY?

- Not part of current guidelines
- Study: Taiwan, 316 pts, prospective study
- Second look a day 2 (78 pts) or 3 (228 pts)
- Predictors for re-bleeding: initial hemostasis with epinephrine alone and hypoalbuminemia
- Used Forrest Classification of endoscopic findings to create a score to predict early re-bleeding
- Not ready for clinical use... yet.

  Cheng et al. Risk factors determining the need for second-look endoscopy for peptic ulcer bleeding after endoscopic hemostasis and proton pump inhibitor infusion. Endosc Int Open 2016 Feb 8;
HOSPITAL VOLUME AND OUTCOMES OF BLEEDING ULCERS IN ELDERLY PATIENTS

- Advanced age is associated with worse outcomes in GIBL
- Study: Japan, retrospective, 14569 pts, > 80 yo, 1073 hospitals, 2010-2012.
  - Low volume (< 5 cases/year), moderate (5-9 cases/year), high volume (> 9 cases/year)
  - Cost and LOS lower for high volume ($716 less and 5 days shorter). No mortality benefit was shown.
WEEKEND OUTCOMES FOR BLEEDING

- Weekend admission associated with worse clinical outcomes for various conditions. Data for those admitted with GI bleeds are variable.
- Study: retrospective, 85928 pts, 2000-2011
  - 15983 (19%) admitted on weekend
  - Results: more likely to have delayed endoscopy, higher in-patient mortality (OR 2.4; CI 1.5-3.9), more likely to be admitted to ICU, longer LOS, higher hospital costs
  - Conclusion: associated with increased mortality, ICU admit, delay in procedure, longer LOS, more costly