

NURSING 813 - APPLIED DRUG THERAPY
PEPTIC ULCER DISEASE
GASTROESOPHAGEAL REFLUX DISEASE (GERD)
NAUSEA AND VOMITING

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LEARNING OBJECTIVES:

1. To be able to rationally select appropriate drug therapy for PUD, GERD, and Nausea/Vomiting.
2. To understand the impact of age, concurrent disease, and other factors affecting the choice or dose of medication for these disorders.
3. Describe alternative therapies based on such variables as toxicity, noncompliance, and economic constraints.
4. To devise an appropriate monitoring plan after therapy has been selected.
5. To understand the available GI drugs to the extent that one is able to monitor for adverse effects and drug interactions, provide patient education, and dose in a skilled manner.

I. PEPTIC ULCER DISEASE

Epidemiology:

- 10% U.S. lifetime incidence, 1% annual incidence
- Duodenal Ulcer (DU) > Gastric Ulcer (GU)
- Men = Women
- Age of onset:
 - DU -- 25-55 (avg. 40), although as many as 1/3 may be >60
 - GU -- Peak incidence 60-70 yrs. female, 70-80 yrs. male

Presentation Features: GU vs DU^a:

<u>Feature</u>	<u>GU</u>	<u>DU</u>
Epigastric Pain	++	+++
Episodic Pain	0	++
Pain at Night	++	+++
Pain Relieved by food	+	++
Pain assoc. w/eating	+	0
Anorexia	++	+
Nausea/Vomiting	+++	++
Heartburn	0	++
Bloating/Belching	++	++
Ulcer Recurrence	++	+++

+++ consistent, ++ frequent, + infrequent, 0 rare

^aAdapted from: Pharmacotherapy: A Pathophysiological Approach; DiPiro JT et al eds.

Clinical Course:

- Periods of exacerbations and remissions
- Untreated patients may become asymptomatic
- Treatment accelerates healing, but most ulcers will heal on their own
- GU heals slower
- Rapid, frequent recurrences -- 50-90% w/in 1 year
 - *Helicobacter pylori* -- primary factor
 - NSAIDS -- must do careful history
 - Cigarettes

Treatment and Therapeutic Goals:

- 1) Anti-infective therapy aimed at *Helicobacter pylori*
 - Documented infection
 - Recurrence
 - Ulcer unrelated to drugs (NSAIDS) or ZE

- 2) "No acid -- No ulcer"
1^o focus: decreasing acid secretion
 - H₂-antagonists, proton pump inhibitors,
 - antacids: don't actually reduce acid secretion, neutralizes acid

- 3) Cytoprotection: enhancement of gastric defense mechanisms
 - sucralfate, bismuth, antacids

- 4) Goals:
 - a) Promote ulcer healing
 - b) Relieve ulcer pain
 - c) Prevent ulcer complications
 - d) Prevent recurrences

General Treatment Measures:

- Stop smoking
- Eliminate ulcerogenic medication
- Minimize alcohol intake
- Avoid foods that exacerbate symptoms
 - Bland diet: not necessary, alter diet based on symptoms only
- Drug Therapy
 - Anti-infectives
 - Bismuth Subsalicylate, Flagyl, Amoxicillin or Tetracycline
 - Clarithromycin
 - Proton Pump Inhibitors
 - H₂Receptor Antagonists (H₂RAs)
 - Famotidine, Ranitidine, Nizatidine, Cimetidine
 - Cytoprotective agents
 - Sucralfate
 - Bismuth
 - Antacids
 - Proton Pump Inhibitors
 - Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

Recurrent Ulcers:

- Recall that PUD is a chronic disorder characterized by frequent recurrence
- As many as 90% of DU and GU recur within 1 year of initial healing
- Factors that influence recurrence include: cigarette smoking, NSAIDS, acid hypersecretion, noncompliance, and *H. pylori* infection
- *H. pylori* of primary importance
- Strategies for management of recurrent ulcers:
 - Explore and treat for *H. pylori* !!
 - Maintenance therapy ? - is there a role?
- Candidates for maintenance therapy (low dose H₂RAs or Sucralfate 1 gm BID):
 - Should never consider without investigating &/or treating *H. pylori*
 - Potential candidates:
 - Severe symptoms
 - Continue to smoke or require use of NSAIDS
 - Recurrent ulcer despite treated or ruled out *H. pylori*
- PPI's now considered safe for maintenance

H. pylori Treatment Recommendations:

- Positive Arguments
 - *H. pylori* associated with virtually all non-NSAID ulcers
 - Eradication promotes ulcer healing
 - Eradication decreases recurrence
 - Natural history of PUD is altered
- NIH Consensus Conference recommendations (JAMA 1994;272:65-9)
 - Ulcer patients with *H. pylori* infections require treatment with antimicrobial agents in addition to antisecretory drugs - upon first presentation or recurrence.
 - The value in treating nonulcerative dyspepsia patients with *H. pylori* infections remains undecided.
 - The interesting relationship between *H. pylori* and gastric cancer requires further exploration.
 - A comprehensive economic analysis should be conducted to examine the cost effectiveness of treating *H. pylori* infection.
 - Do recommendations go far enough?? -- in general treatment approaches

have evolved faster than formal guidelines

- Diagnosis of *H. pylori*

- Diagnostic testing should only be performed if treatment is intended
- HP infxn is common, most individuals asymptomatic, treatment of infxn is of proven value only for PUD and mucosa-associated lymphoid tissue (MALT)
- HP is classified as a definite carcinogen by WHO – however no benefit to treatment ever demonstrated for general population.
- Endoscopic biopsy – (CLOtest, Pyloritek, and Hp-fast) performed in micro lab – Pyloritek read in 1 hr; others 24 hr – false negative results may be seen in recent UGI bleeding, and patients on PPI's, H2's and antibiotics
- Histology – can document presence of HP and allows evaluation of the underlying gastritis. May be less sensitive in pts taking antisecretory meds
- Culture – difficult, time consuming and expensive – usually impracticable
- Serology -- blood test for IgG antibody for *H. pylori*, good sensitivity and specificity, can't determine if infection eradicated – good alternative for patients receiving antisecretory medication
- Office based Whole blood tests – simple and low cost – may be performed inappropriately or unnecessarily.
- Breath test for urease activity -- commercially available (Meretek UBT^R, Tri-Med) –high accuracy and reproducibility – delay 4 wk after completion of eradication Rx.
- Presumptive diagnosis -- not consistent with NIH guidelines but could make a good case for it

Summary of Diagnostic Tests¹

Test	Sensitivity	Specificity	Approx. Cost
In-office, serum	88-94%	74-88%	\$10-30
In-office, whole blood	67-88%	75-91%	\$10-30
Lab, serum ELISA	86-94%	78-95%	\$40-100
Urea Breath Test	90-96%	88-98%	\$250-350 (TriMed) \$20-65 (UBT)
Biopsy urease test	88-95%	95-100%	\$6-20 (plus endosc.)
Histology	93-96%	98-99%	\$60-250
Culture	80-98%	100%	\$150

¹Adapted from Am J Gastroenterology 1998;93(12):2330-2338

- Recommendation from Am. College of Gastroenterology: “When endoscopy indicated, the test of first choice is a urease test on an antral biopsy. If a biopsy urease test is negative, *H. Pylori* infection may be

diagnosed by histology or serology. . . . When endoscopy is not performed, an office-based serological test is the least expensive means of evaluating evidence of H. Pylori infection. A urea breath test is the best nonendoscopic test for documenting H. Pylori infection.

- Triple Therapy Regimens (1st generation treatment)
 - Minimum of 2 weeks of therapy
 - Metronidazole 250 TID plus Bismuth 2 tabs AC & hs plus TCN 500 QID **or** Amoxicillin 250-500 QID
 - Tetracycline regimens more effective than amoxicillin
 - Eradication rates generally 80-95%

- Dual Therapy Regimens – for historical reference only – cannot be recommended
 - Omeprazole 20 mg BID plus Amoxicillin 1gm BID/TID X 2 weeks - (30-90% eradication)
 - Omeprazole 20mg BID + Clarithromycin 500 mg BID/TID X 2 weeks -- increased eradication rates (70-90%)

- One week regimens (3rd generation treatment)
 - Metronidazole 500 mg BID, Omeprazole 20 mg BID, Clarithromycin 250-500 mg BID for 1 week ("MOC")
 - Metronidazole 500 mg BID, Omeprazole 20 mg BID, Amoxicillin 1 gm BID for 1 week ("MOA")

- FDA Approved agents: 5 regimens approved, 3 can't be recommended – not triple

Suggested Regimens for the Treatment of H. Pylori infection²

PPI (L 30 or O 20) + Amoxicillin 1gm + Clarithromycin 500mg - EACH BID X 14 days

PPI (L30 or O 20) + metronidazole 500mg + Clarithromycin 500mg - EACH BID X 14 days

RBC 400mg + Clarithromycin 500mg + Amoxicillin 1gm or Metronidazole 500mg or TCN 500mg – EACH BID X 14 days

Pepto-Bismol 525mg QID + Metronidazole 500mg TID + TCN 500 mg QID + PPI (L30 or O20) QD – X 14 days

Pepto-Bismol 525mg QID + Metronidazole 250mg QID + TCN 500mg QID + H2RA – X 14 days with H2RA continued additional 2 weeks

²Adapted from Am J Gastroenterology 1998;93(12):2330-2338.

- Other issues
 - The ability to recommend triple therapy regimens for 7-10 days depends

on further US studies

- Adverse effects with MOC/MOA tend to be fewer; compliance is increased; and medication costs are less
- 2 weeks of MOC or MOA not statistically significant increase eradication over 1 wk
- H2RAs do not contribute to HP eradication but provide more rapid symptom relief
- Regimens with a PPI may contribute to both ulcer healing and symptom relief. Lansoprazole 30 mg BID may be substituted for omeprazole - \geq activity

- Cost comparison

- Conventional triple therapy (two weeks) = \$90
- Omeprazole plus amoxicillin and metronidazole (two weeks) = \$120
- Maintenance therapy with H2's (1 year) = \$400

H₂RAs:

- Competitively & Reversibly bind histamine type 2 receptors on the parietal cell
- Most frequently prescribed agents for PUD
- Potency variances between agents but all equally effective at equipotent doses
 - Relative potencies: Cimetidine (1), Ranitidine (4-10), Nizatidine (4-10), Famotidine (20-50)
- Regimens
 - Multiple daily dosing VS Nighttime dosing: no real efficacy difference
 - Optimal time of administration

Usual H₂RA Dosing Schedules:

<u>Indication</u>	<u>C</u>	<u>F</u>	<u>N^a</u>	<u>R</u>
Ulcer Healing	300 QID	20 BID	150 BID	150 BID
	400 BID	40 HS	300 HS	300 HS
	800 HS			
Maintenance (DU)	400 HS	20 HS	150 HS	150 HS

C=Cimetidine, F=Famotidine, N=Nizatidine, R=Ranitidine;

^a Nizatidine does not have labeled indication for GU

- Need for adjustment of dosage for renal insufficiency
Cimetidine: CrCl < 50, Ranitidine < 40, Famotidine < 30

- Ideal duration of treatment

- 4-6 weeks usually advocated for DU
- 8 weeks may be preferred in elderly or smokers

- 8-12 weeks for patients with GU

- Adverse Effects of H₂RAs:

- Generally quite safe and well tolerated
- Rare incidence of hematological toxicity with all
- Subtle differences between agents
 - Cimetidine greater potential for CNS toxicity
 - High dose, long term cimetidine ass. w/anti-adrenergic effects
 - All can elevate transaminases - esp. large IV doses of ranitidine

- Drug Interactions

- Cimetidine >> Ranitidine > Famotidine = Nizatidine
- Cytochrome P-450 enzyme system
 - Few drugs of significant concern
 - Narrow therapeutic index: warfarin, phenytoin, theophylline
- All reduce absorption of ketoconazole (Nizoral)

- Cost for 1 months supply:

Agent	Dosage	AWP	Generic	OTC
Cimetidine (Tagamet)	300 QID	\$102.30	\$83.71	
	400 BID	\$84.85	\$69.54	~\$35
	800 HS	\$75.20	\$62.57	
Famotidine (Pepcid)	20 BID	\$86.16N/A		~\$36
	40 HS	\$83.24		
Nizatidine (Axid)	150 BID	\$86.60N/A		
	300 HS	\$83.78		
Ranitidine (Zantac)	150 BID	\$95.66N/A		
	300 HS	\$86.26		

- Choice of an H₂RA:

- Clinical Experience: C=R>F>N
- Efficacy: C=F=N=R
- Potency - Beware of marketing ploys!
- Adverse Effects - All well tolerated, C slightly more potential for side effects
- Drug Interactions
 - Not an issue for about 94% of patients
 - Need to monitor carefully for patients on cimetidine
- Dosing Convenience - Famotidine slightly better - but all can be given QD
- Cost: R>F=N>C -- all quite similar, check with local pharmacists
 - May be single most important factor
 - Most H₂'s now available in generic form (Pepcid 4/2001)
 - All OTC versions are cheaper at an equal dose -- good option

Antacids:

- Reduce acidity by neutralizing secreted gastric acid
- Equally effective as H₂RAs but many disadvantages
 - Unacceptable side effects -- most commonly altered bowel function
 - Intensive dosing schedule is inconvenient
 - Newer data, however, suggests QID dosing may be equally effective
 - Optimal dosing remains to be established
- Agents utilized:
 - Calcium Carbonate: **NOT** appropriate for more than occasional "prn" use
 - May produce systemic complications from hypercalcemia
 - Leads to rebound hypersecretion of acid
 - Sodium Bicarbonate: **NOT** recommended for long-term use because of its tendency to produce systemic alkalosis
 - Magnesium Salts (primarily magnesium hydroxide): High incidence of diarrhea
 - Aluminum Salts (primarily aluminum hydroxide): Can cause constipation
 - Combination of magnesium and aluminum salts: Most appropriate
 - Diarrhea and constipation tend to balance (diarrhea may predominate)
 - Effective long-term
 - Available in concentrated forms (i.e. Mylanta, Maalox)
- Drug Interactions:
 - Often overlooked in patients regimen
 - Can alter absorption of many drugs when given concurrently
- Place of Antacids for PUD: PRN symptomatic relief

Sucralfate:

- Aluminum salt of a sulfated disaccharide -- only 3-5% absorbed
 - Forms a protective barrier on the ulcer crater -- inhibits back diffusion of H⁺ ions, pepsin, and bile salts
- Efficacy in the treatment of DU equal to H₂RAs
- Regimen

- 2gm BID appears equally effective as the standard 1 gm QID for treatment
- 1gm BID recommended for maintenance therapy
- Administered on an empty stomach - generally before meals
- If patient finds the large tablet difficult to swallow, it is now available in suspension form

- Role of combination therapy with H₂RAs
 - Permits two different mechanisms to provide ulcer relief
 - However, the combination offers **no clear advantage** over either agent alone
 - Primary result is **doubling the cost** of therapy.

- Adverse Effects
 - Minor and occur in <5% of patients (little if any systemic absorption)
 - Constipation is most common (2%)

- Drug Interactions
 - Concurrent administration may interfere with absorption of phenytoin, digoxin, theophylline, warfarin, ciprofloxacin, and norfloxacin
 - Significance not well quantified
 - Avoid simply by separating administration times

- Cost of therapy (1 month therapy)
 - Sucralfate (Carafate) 1 gm QID = \$85.06 (AWP)
 - Suspension " = \$87.06 (AWP)

- Sucralfate VS H₂RAs:
 - Comparable efficacy (DU) – maybe less effective for GU
 - Comparable cost
 - Sucralfate is non-systemic - good alternative for patient at risk of side effects
 - No effect on pH - may be desirable in selected patients
 - Slightly less convenient dosing (if use BID)

Other Cytoprotective Agents

- Misoprostil (Cytotec)
 - Indicated for the prevention of NSAID-induced GU
 - Using an expensive drug to treat a drug related problem
 - Limited role in selected patients
 - No real role in the management of PUD

- Bismuth Salts (in U.S. limited to Bismuth Subsalicylate (Pepto-Bismol)
 - Bismuth salts (Colloidal Bismuth Subcitrate [CBS]) used commonly in Europe
 - Effective agents for PUD -- similar efficacy

- Lower recurrence rates -- related to suppression of *H. pylori*
- Bismuth Subsalicylate in doses of 525 mg QID is probably as effective as CBS
- Cautions: neuro toxicity increased if used >8 weeks, salicylate toxicity is possible with concurrent use of ASA, black stools
- Role in management of PUD linked to *H. pylori* in U.S.

Proton Pump Inhibitor: Omeprazole –“O” (Prilosec), Lanzoprazole – “L” (Prevacid), Rabeprazole – “R” (Aciphex), Pantoprazole – “P” (Protonix)

- Significantly reduce gastric acid by interfering with the activity of H^+/K^+ -ATPase
- Profound, but reversible, long-acting suppression of gastric acid - persists 1 to 3 days after D/C of drug - despite a 1 hr half-life
- Indications: (newer agents don't have all indications)
 - Short-term treatment of active DU - usually 4 weeks
 - GERD (more later)
 - Severe erosive esophagitis
 - Hypersecretory conditions - i.e. Zollinger-Ellison
 - Combination therapy for *H. pylori*
 - Maintenance therapy
- Regimens:
 - 20 mg O, 30 mg L, 20mg R, 40mg P Q AM orally usually for 4 weeks
 - Slightly faster healing rates compared to H₂RAs (DU & GU)
 - Resistant or refractory ulcers may respond to 40 mg/day
 - Omeprazole granules in capsule - release is pH dependent (>6) - swallow whole; Lansoprazole may be sprinkled on applesauce or mixed with apple juice for tube administration
 - Potency L30 >O20 >L15 = R20 = P40
- Safety:
 - Short-term adverse event rates are similar to H₂RAs
 - Long-term - profound acid suppression leads to hypergastrinemia - possibly increases risk of gastric carcinoid tumors (never seen in humans!)
- Drug Interactions:
 - Also inhibits cytochrome P-450 system - may inhibit metabolism of phenytoin, diazepam, and warfarin
 - pH increase may affect absorption of some meds - esp. ketoconazole
- Cost of Therapy (1 month):
 - 20 mg R QD and 30 mg L QD are about \$115/month, O20 = \$125 and P40 is least expensive @ \$94/month
 - May, however, be overall less costly if assume 4 weeks vs 6 weeks for H₂RAs

- Role in management of PUD:
 - Reasonable choice as first line agent
 - Drawbacks: cost compared to H₂'s
 - No rationale for combo Rx with an H₂RA (no add'l acid suppression)
- Comparison of PPI's – little to differentiate
 - Experience – greater with O and L
 - Potency – unlikely an issue, potentially affects cost (i.e. L15)
 - Safety – drug interactions a minor issue with O, otherwise no difference
 - Overall – all essentially equivalent

Recommendations: Management of PUD:

- First consideration: eradication of *H. pylori* - cure the infection, heal the ulcer
 - Regimen should contain 2 antibiotics + acid suppression
- Concentrate primarily on H₂RAs (6-8 wks), Sucralfate (6-8 wks), and PPIs (4 wks)
- Treatment of NSAID GU takes longer – minimum 8 weeks H₂, 4-6 week PPI – PPI's best choice
- Stick with one H₂RA -- little reason to switch back and forth
 - May want to avoid cimetidine but lower cost alone may be enough to override this suggestion due to only modest disadvantages
 - Famotidine may be reasonable choice - but again, these agents are quite similar!
- Sucralfate ideal for patients who you want to avoid systemic absorption (pregnancy), BID regimen make it a good alternative to H₂RAs
- PPIs: in many circumstances may indeed be the most cost effective choice due to shorter duration and improved efficacy - all available agents are good – Pantoprazole is least costly
- Antacids: primary role is in PRN symptomatic use
- Bismuth - role limited to suspected *H. pylori* infection in U.S.
- Consider *H. pylori* for any DU or for a GU when NSAIDS not involved especially when there is recurrence after initially successful therapy.

Monitoring:

- Remember epidemiology regarding age of presentation - refer very young or very old for work-up of other disease
- When prescribing an H₂RA, adjust dose for renal insufficiency, be aware of

- potentially greater rate of CNS side effects in elderly (esp. w/ cimetidine)
- Always review patients regimen for potentially interacting drugs
- Look for lifestyle modifications: food, drugs, cigarettes
- Frequent recurrences - refer for investigation of possible *H. pylori* infection

II. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Definitions:

- GERD: Any symptomatic clinical condition or histological alteration that results in episodes of reflux
- REFLUX ESOPHAGITIS: Inflammation of the esophagus that occurs secondary to refluxed material

Defensive Mechanisms vs Aggressive Factors:

- Normal defensive mechanisms: (Therapy aimed at maximizing these)
 - Anatomic factors
 - Lower esophageal sphincter tone
 - esophageal clearing
 - mucosal resistance
 - gastric emptying
- Aggressive factors: (Therapy aimed at minimizing these)
 - Gastric acid
 - pepsin
 - bile acids
 - pancreatic enzymes

Presenting Symptoms:

- Hallmark symptom = "Heartburn"
 - Described as substernal sensation of warmth or burning
 - Waxing and waning
 - Aggravated by activities that potentiate reflux
 - No age or sex related differences in incidence
 - Important note: Occurs in healthy individuals as well
- Other symptoms include: regurgitation, dysphasia, bleeding, chest pain

Evaluation:

- Patients with classic symptoms do not require invasive endoscopic evaluation
- Evaluate endoscopy in patients when:
 - Uncertain diagnosis or atypical presentation
 - Patient fails to respond to treatment
 - Symptoms include “warning” signs (below)
- Warning Symptoms Suggesting Complicated GERD
 - Dysphasia
 - Bleeding
 - Weight Loss
 - Choking (acid causing coughing, SOB, or hoarseness)
 - Chest Pain

Goals of Therapy:

- Alleviate/eliminate the patients symptoms
- Decrease the frequency and duration of GE reflux
- Promote healing of injured mucosa
- Prevent the development of complications

Specific Aims of Treatment:

- Increasing lower esophageal sphincter (LES) pressure
- Enhancing esophageal acid clearance
- Improving gastric emptying
- Protecting the esophageal mucosa
- Decreasing the acidity of the refluxate
- Decreasing the gastric volume

Therapeutic Approach^a:

PHASE I:

- Elevate head of bed
- Change dietary habits – decrease fat, avoid certain foods
- Stop smoking
- Avoid potentially harmful medications
- Antacids and/or alginic acid (Gaviscon)
- OTC H₂RAs

PHASE IIa:

- Standard doses of H₂RAs
- Prokinetic Agents: Metoclopramide (Reglan, generic)
- Bethanechol
- Sucralfate

PHASE IIb:

- High dose H₂RA
- PPI

PHASE III:

- Antireflux surgery: Laparoscopic Nissen fundoplication

^aAdapted from Kitchin LI, Castell DO. Arch Int Med 1991;151:448-453

Antacids and Alginic Acid:

- Major aggressive factor = gastric acid -- antacids aimed at neutralizing acid, also impart some increased LES tone.
- Gaviscon contains **alginic acid** sodium bicarbonate, aluminum hydroxide, and magnesium trisilicate
 - Forms a viscous foam that floats on the surface of the gastric secretions
 - Mechanical barrier, mucosal protectant
 - Not a potent acid neutralizer, no effect on LES tone
- Antacids and Gaviscon equally effective in reducing the number and severity of GERD symptomatic episodes

H₂RAs:

- Like PUD, they are mainstays in treatment of GERD for mild-moderate symptoms; PPIs best choice for more severe disease
- May be superior to standard doses of antacids
- Likely no difference among agents (limited data on famotidine, little on nizatidine)
- Response appears to be dependant on:
 - The disease severity
 - Duration of therapy
 - The dose employed
- Prolonged courses generally required
- Dosing:
 - PHASE I: OTC Tagamet HB 100 mg tabs, up to 4/day
Pepcid AC 10mg, Zantac 75, or Axid AR 10mg, up to 2/day
 - PHASE IIa:
 - Cimetidine 400 mg QID or 800 mg BID
 - Ranitidine 150 mg BID - higher doses may be more effective
 - Famotidine 20 mg BID or 40 mg HS

- Continuous acid suppression may lead to improved healing rates but still inferior to PPIs

Proton Pump Inhibitors:

- Greater degree of acid inhibition than with standard doses of H₂RAs
- Significant advantage of PPI over cimetidine and ranitidine at 4 and 8 weeks
- 33 randomized trials involving > 3000 pts
 - sx relief seen in 27% placebo, 60% H₂RA, and 83% PPI
 - Esophagus healed 24% placebo, 50% H₂RA, 78% PPI
- Effective in patients who are refractory to H₂RAs
- Dosing
 - Initially 20 mg O/day for 4-8 weeks, may increase if severe to 40 mg
 - 30 mg L/day for 8 weeks
 - R20mg and P40mg likely similar efficacy (data?)

Bethanechol: May be classified as a prokinetic agent

- A cholinergic agonist: Increases LES tone and improves esophageal acid clearance
- Results in significant reduction in symptoms of reflux
- Decreases antacid usage and increases esophageal healing; overall limited efficacy
- Dose: 25 mg QID
- Cost (1 month): Urecholine^R = \$114.65 ! Generic = \$5.88 !
- Side Effects: (Well tolerated generally)
 - increased gastric acidity, abdominal cramps, diarrhea, blurred vision, and urinary frequency
- Relative contraindications: asthma, COPD, PUD
- Most useful in patients with documented abnormally low LES pressures

Prokinetic Agents: Metoclopramide & Cisapride (although not marketed anymore):

- Metoclopramide: Dopamine antagonist & a cholinergic agonist
- Cisapride: enhanced release of acetylcholine & serotonin type IV agonist

- Increase LES tone and accelerate gastric emptying
- Metoclopramide can significantly reduce symptoms in patients with GERD
- Esophageal healing appears NOT to be significantly effected although cisapride may be superior
- Dosage: Metoclopramide is given generally 10 mg QID
- Cost (1 month, AWP): Metoclopramide (Reglan) 10 mg QID - \$53.59 (generic) = \$20.82
- Metoclopramide Side Effects:
 - Significantly limit use of metoclopramide -- especially extrapyramidal toxicity
 - Other common SE include: somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea, and rash
 - It is a dopamine antagonist - all extrapyramidal reactions are a result of its effect on dopamine, also can exacerbate Parkinson's
- Cisapride:
 - Available only through an investigational limited-access program
 - Devoid of dopaminergic activity: no extrapyramidal toxicity
 - Improved efficacy compared to metoclopramide
 - DRUG INTERACTIONS -- SERIOUS !! – led to market withdrawal
 - Metabolized in liver via CYP3A4 isoenzym
 - Most problematic w/clarithromycin, erythromycin, and azole

antifungals

Treatment Recommendations:

- Current therapy involves a step-wise approach :
 - Mild esophagitis: lifestyle modification and antacids
 - Moderate disease: H₂RAs are mainstay of therapy
 - Refractory disease: higher doses of H₂RAs or use PPI
 - PPI preferred at least initially for refractory patients
 - Adjunctive therapy may include bethanechol or metoclopramide
- Alternate approach is to start with more aggressive therapy and “step-down” based on symptom control. Choice is left to practitioner as neither step-up or step-down has been demonstrated to be superior
- Care must be taken as with PUD not to simply add new classes of drugs on top of existing therapy -- usually only serves to increase cost
- For example: combination of H₂RAs, metoclopramide, and bethanechol may be inappropriate -- patient may achieve equal benefit from omeprazole alone while combination Rx leads to more side effects

- Many patients require maintenance therapy: H₂RA vs PPI
- Refractory patients: surgery more appealing option than in past with laparoscopic procedure

III. NAUSEA AND VOMITING

Complications:

- Metabolic Disturbances
- Dehydration and renal failure
- Mallory-Weiss tears, wound disruption
- Aspiration Pneumonias

Assessment:

- Always directed at the underlying pathophysiology
- Detailed history including: description of vomitus, volume, timing
- Unexplained vomiting may require significant work-up:
 - Serum chemistries, drug screening, hormone levels, abdominal X-rays, CT scans, endoscopy, GI emptying tests, manography, psychiatric assessment

Antiemetics:

- Many classes of agents -- some limited to post-operative use and/or use in chemotherapy induced nausea and vomiting -- our discussion limited to general use
- Antihistamines and Anticholinergics: used primarily in motion sickness
 - Most frequently used agents:
 - Dimenhydrinate (Dramamine, others) -- Adults 50-100 mg PO/IM/IV 30" prior to exposure and Q4 hr, Children 1.25 mg/kg PO/IM Q4-6 hrs (max. 300/day)
 - Meclizine (Antivert, Bonine) -- Adults 25-50 mg PO 1 hr prior to exposure & Q4-6 hr
 - Scopolamine (Transderm-Scop) -- Adults 4hr prior to exposure and Q 72 hr
 - Interrupt various visceral afferent pathways that stimulate nausea and vomiting
 - appropriate **only** for symptoms of a simple nature
 - Adverse effects: drowsiness, confusion, blurred vision, dry mouth, urinary retention
 - Particularly troubling in the elderly
- Phenothiazines: general use, motion sickness
 - Most frequently used agents:
 - Prochlorperazine (Compazine) -- Adults 5-10 mg PO/PR/IM/IV Q6-8 hr

- Promethazine (Phenergan) -- Adults 25 mg PO/PR/IM 30" prior to exposure and Q8-12 hr, Children 0.5 mg/kg PO 30" prior to exposure and Q8-12 hr
 - Most commonly prescribed class of antiemetics
 - Most likely block dopamine in the CTZ
 - Again most effective for use in patients with simple nausea and vomiting
 - Side effects: extrapyramidal, excessive sedation, hypotension
- Miscellaneous
- Trimethobenzamide (Tigan) -- Adults 250 mg PO Q6-8 hr or 200 mg PR/IM Q6-8 hr

Considerations in the treatment of Nausea and Vomiting:

- The suspected etiology of the symptoms
- The frequency, duration, and severity of the episodes
- The ability of the patient to use oral, rectal, injectable, or transdermal medications
- The success and tolerability of previous courses of antiemetics

Gastroenteritis

- Common: 35 million episodes/yr in U.S.
- Patients < 1 year of age account for 65% of hospitalizations & 85% of deaths
- Often refractory to anti-emetic therapy
- In pediatrics, education of parents is of major importance
 - >700 children die annually from dehydration from gastroenteritis
 - Aware of S/S: little or no urination, dark circles under eyes, sticky mouth, thirst, sunken fontanel in infants
 - Need to provide energy, water, and minerals in a clear liquid
 - Seek medical attention if any of the following occur along with vomiting: fever, severe headache, head injury, abdominal distention, abdominal pain, change in alertness, coughing or choking, toxic ingestion, or dehydration
- Dehydration:
 - Pt weight is a key assessment
 - Rehydration: AAP Guidelines (1985)
 - Rapid rehydration with oral glucose-electrolyte solution over 4-6hours
 - Restoration of diluted formula/milk after 6 hours
 - Lactose need not be eliminated
 - Solids reintroduced after successful rehydration

Diabetic Gastroparesis:

- Vomiting is common complication
- No good pharmacological therapy -- progressive disorder
- Symptomatic improvement from bethanechol or prokinetic agents

- stimulate gastric motility
- Prokinetic agents may be preferred (same doses as with GERD)

Motion Sickness:

- Effective drugs have strong CNS anticholinergic effects and act on receptors in the VC
- Phenothiazines are ineffective with the exception of promethazine which also has strong central anticholinergic actions
- Primary agents include scopolamine, and the antihistamines
 - Transdermal scopolamine patch is convenient, effective, and well tolerated
 - Cost is drawback: \$43.24/ 4 patches

Antiemetic Use in Pregnancy:

- More than 50% of pregnant women experience nausea and vomiting
- Hyperemesis gravidarum is a more serious complication sometimes requiring hospitalization for hydration and parenteral nutrition
- Teratogenicity is a major consideration in the use of antiemetic drugs during pregnancy
- If drug therapy is felt to be needed, cyclizine (Marezine), and meclizine (Antivert) are considered the drugs of choice

Antiemetic Use in Children:

- Most antiemetic research has been conducted on adults
- Unique differences with certain agents:
 - Metoclopramide - much greater incidence of extrapyramidal reactions
 - Phenothiazines - more likely to produce dystonias
 - Benzquinamide, cyclizine, and scopolamine not recommended <12 yrs
- Dimenhydramine has been utilized in all age groups
- Trimethobenzamide may be used in children (not newborns) PO or PR but not by injection

Patient Evaluation:

- Symptomatic relief may be unattainable until correction of the underlying problem
- If nausea and vomiting persist despite optimal doses of an antiemetic, an agent with a different mechanism may be substituted

- Always be on guard for potential fluid and electrolyte imbalances -- esp. in children

PATIENT CASE #1 DUODENAL ULCER

1. B.S. is a 64-year old CPA with a chief complaint of epigastric pain. B.S. reports that his pain is worse at night and that he achieves acute relief from food and antacids. The pain has been recurrent over the past 2 months. He reports no weight loss or change in bowel habits.

B.S.'s past medical history is unremarkable with the exception of osteoarthritis which is currently being treated "PRN" with ibuprofen. Other current medications include Nicoderm patch and Valium prn anxiety.

Be prepared to evaluate and discuss the following:

- A. Presentation -- S/S consistent with PUD
- B. Non-pharmacological treatment
- C. Devise a drug treatment and monitoring plan -- be prepared to discuss alternative therapeutic choices

PATIENT CASE #2
GERD

2. J.H. is a 51-year old obese LPN. She complains of severe retrosternal burning occurring several times per day. Her discomfort typically occurs at night or after a large meal. The symptoms are relieved by Mylanta.

J.H. is currently taking Procardia XL 60 mg for angina, Premarin 0.625 mg/day, and she smokes 1 1/2 packs per day.

Be prepared to evaluate and discuss the following:

- A. Factors in history that may contribute to her problem
- B. Potential Complications
- C. Lifestyle changes
- D. Stepwise approach to drug therapy management

PATIENT CASE #3
VOMITING -- DIABETIC GASTROPARESIS

3. K.R. is a 74-year old male with a history of poorly controlled NIDDM since the age of 40. He is currently maintained on Humulin 70/30 80 units Q AM, and 50 units Q PM. He presents to you with a 2-day history of persistent vomiting. His vomitus contains undigested food, despite not having eaten within 6-8 hours. He also complains of a "sick stomach" with putrid belching. Upon further questioning, you determine that she has had nausea for a prolonged for several weeks and reports a 12 # weight loss.

Upon referral to a radiologist, barium ingestion reveals gastric dilation and diminished peristalsis but no evidence of mechanical obstruction.

His past medical history is significant for Parkinson's currently controlled with Sinemet CR, mild hypertension treated with HCTZ 25 mg/day, hypercholesterolemia being treated with Questran 2 scoops BID.

Evaluate and discuss the following:

- A. Nonpharmacological interventions
- B. Pharmacological management and monitoring plan