Last Chance Pharmacotherapy Review Webinar

Gastrointestinal Disorders

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Conflicts of Interest

- I have no conflicts to disclose.

Objectives

- Evaluate updated safety and efficacy data for drugs used in the treatment of gastroesophageal reflux disease.
- Apply the current guideline treatment recommendations for nonvariceal upper gastrointestinal bleeding.
- Interpret the current guideline treatment recommendations for chronic Hepatitis B and Hepatitis C infection.
- Differentiate the treatment options for the major complications of alcoholic liver disease.
- Predict interventions for preventing NSAID-associated peptic ulcer disease in patients with risk factors.
- Summarize the role and adverse effects of drugs used in the treatment of inflammatory bowel disease.

Viral Hepatitis

Overview

Pathogens

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D (Delta)
- Hepatitis E
- Hepatitis G

- Various modes of transmission
- Acute infection
  - ≤ 6 months
- Chronic infection
  - ≥ 6 months
- Virus specific treatment and prevention

Practice Case #1

- V.K. is a 38-year-old man who recently immigrated to the United States from China 12 months ago. He is seen today in clinic with abdominal pain for the last 4 weeks, malaise, and his eyes turning yellow and feeling itchy.
- He reports a history of his eyes "turning yellow" in last year and feeling like he had the flu ,which seemed to get better and go way. He currently reports occasional alcohol use and no IVDA.
- Physical exam reveal right upper quadrant tenderness without rebound, no fluid wave, scleral icterus bilaterally, jaundice. He is otherwise healthy and has no physical exam findings of hepatitis.
- Laboratory results oreveal (+) HBsAg, (+) HBsAg, (-) anti-HBe, AST 950 IU/L, ALT 866 IU/L, and HBV DNA 108,000 IU/ml. Scr 1 mg/dl, BUN 12 mg/dl.

Hepatitis B (HBV)

- DNA Virus, Genotypes A-H
- Transmission
  - Parenteral: IVDA, transfusion, needlestick
  - Bodily fluids: saliva, semen, vaginal fluids
  - Sexual contact: heterosexual partners of infected persons, homosexuals, prostitutes
  - Perinatal

Hepatitis B

Detection

- Signs/Symptoms
- LFTs: ALT most sensitive for hepatocyte damage
- Serologies

Serologies: Need to distinguish if HBV is:

- HBeAg (+) or (-)
- HBeAg (-) denotes presence of the "YMDD" mutation" of the DNA polymerase
- Referred to as "precore mutants"
- More difficult to treat and monitor

Chronic Hepatitis B

- **Progression to chronicity**
  - 5-10% of adults with acute HBV
  - 20-50% children < 5 years old
  - 90% neonates

Chronic HBV Infection	Inactive HBV Carrier State
· **HBsAg positive > 6 months** · **Serum HBV DNA 20,000 IU/mL (105 copies/mL), lower values 2000–20,000 IU/mL (104–105 copies/mL) are often observed in HBeAg-negative chronic hepatitis B** · **Persistent/intermittent elevation of AST/ALT** · **Chronic hepatitis and moderate-severe necroinflammation on biopsy**	· **HBsAg positive > 6 months** · **HBeAg negative, anti-HbeAg positive** · **Serum HBV DNA < 2000 IU/mL (104 copies/mL)** · **Persistently normal AST/ALT; absence of significant hepatitis on biopsy**

Who needs Treatment?

Chronic HBV

- Disease > 6 months
- ↑ LFTs (> 1-2 x ULN)
- HBV DNA > 20,000 IU/ml
- Inflammation on Bx

No treatment

- Inactive carriers
- Decompensated cirrhosis*
- Normal LFTs

Hepatology 2009;50:1–36

HBV Treatment

Reverse transcriptase inhibitors

- Entecavir or Tenofovir preferred (HBeAg + or -)
- Adefovir
- Lamivudine and telbivudine not recommended 1st line
- Minimum of 1 year

Interferon-alfa

- Can be used first line but is poorly tolerated
- Effects may be longer lasting
- LFTs increase initially

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1. How should V. K.'s hepatitis B infection be managed at this time?

   A. Initiate lamivudine
   B. Initiate tenofovir
   C. Administer hepatitis B vaccine
   D. Initiate interferon-alpha

Practice Case #1 Answer

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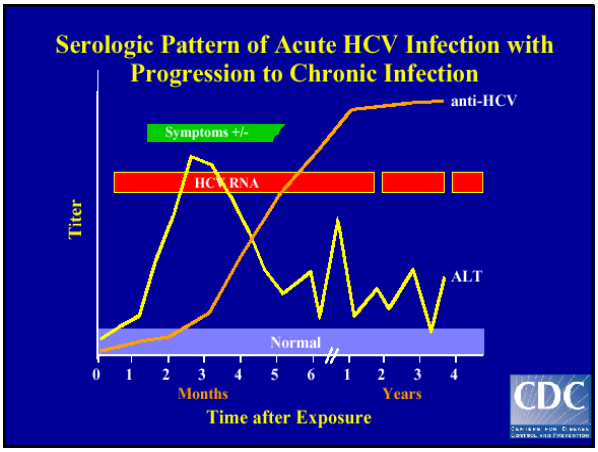
- J.G. is a 48-year-old woman with a history of heroin use who is admitted to the hospital with altered mental status, jaundice, abdominal swelling, shortness of breath and pruritis. Physical exam reveals jaundice, tense ascites with a positive fluid wave, asterixis, 3 + pitting lower extremity edema, and crackles on lung exam. She smokes 1 pack per day and reports her last heroin use as yesterday. Laboratory results reveal (+) anti-HCV, HCV RNA 100,00 copies/ml, AST 159 IU/L, ALT 250 IU/L, albumin 2 g/L, INR 3.6.

Hepatitis C (HCV)

Transmission	Laboratory
▪ Transfusions, needlesticks, IVDA ▪ Sexual contact ▪ Perinatal ▪ #1 reason for liver transplant ▪ 60-80% progress to chronic disease	▫ HCV RNA (copies/ml) ▫ Genotyping ▪ Genotypes 1-6 ▪ Genotypes 1-3 most common in US ▪ Subtypes ▫ Anti-HCV antibody ▫ Liver biopsy ▫ ALT- best for monitoring



Hepatitis C Testing

- Test if :
  - Suspected exposure
  - HIV Infection
  - IV Drug Abuse
  - Clotting factors before 1987 or blood before 1992
  - Hemodialysis
  - Abnormal ALT
  - Organ transplant prior to 1992
  - Adults born between 1945-1965

Who needs Treatment?

Chronic HCV

- Disease > 6 months
- ↑ LFTs (> 2-3 x ULN) → can treat if WNL
- Positive Serum HCV antibody
- Detectable HCV RNA
- Moderate to severe fibrosis/Inflammation on biopsy

No treatment

- Contraindications to interferon
- Decompensated cirrhosis

Hepatology 2011;54:1433–44.

Treatment of Chronic Hepatitis C

- First line:
  - Genotype 1 :Pegylated interferon + ribavirin + telaprevir OR boceprevir
  - Genotypes 2 and 3 :Pegylated interferon + ribavirin
- Pegylated Interferon Dosing:
  - Pegasys: 180ug SQ Weekly
  - Peg Intron: 1-1.5 ug/kg/week SQ
- Ribavirin orally in 2 divided doses:
  - Dose differs based on genotype, weight, and interferon product

Direct Acting Antivirals (DAAs)

	Telapravir (Incivek®)	Boceprevir (Victrelis®)
FDA Approved indication	• Chronic HCV therapy (genotype 1) in combination with PEG-INf alfa and ribavirin in patients with compensated liver disease • Not studied in Child-Pugh class B or C	• chronic HCV genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

Direct Acting Antivirals (DAAs)

	Telapravir (Incivek®)	Boceprevir (Victrelis®)
Dose	• 750 mg three times daily for 12 weeks plus PEG-INF followed by PEG-INF and ribavirin x 12 weeks if undetectable HCV RNA at week 4 and 12. • 375 mg tablets • Give doses 7-9 hours apart; give with meal that has at least 20 g fat ingested 20 minutes prior • Take missed doses if within 4 hours	• 800 mg orally three times daily starting after 4 weeks of PEG-INF and ribavirin • 200 mg capsules • Give doses 7-9 hours apart; give with meal or light snack • Take missed doses if within 2 hours

DAA Safety

- Both contraindicated in pregnancy and in male partners of pregnant women
- Telaprevir
  - Rash (up to 56%) maculopapular/eczematous
  - DRESS, Stevens Johnson Syndrome
  - Anemia, pruritis, nausea
- Boceprevir
  - Anemia, neutropenia, fatigue, dysgeusia

DAA Drug Interactions

- **Both are potent CYP 3A4/5 inhibitors**
- **Several CYP3A4 substrates or inducers are contraindicated**

Telaprevir	Boceprevir
Alfuzosin	Alfuzosin
Rifampin	Rifampin
Dihydroergotamine,ergonovine, ergotamine,methylergonovine	Dihydroergotamine,ergonovine, ergotamine,methylergonovine
Cisapride St. John's Wort Pimozide Tadalafil, sildenafil Oral triazolam or midazolam	Cisapride St. John's Wort Pimozide Drosperinone
Atorvastatin, lovastatin, simvastatin	lovastatin, simvastatin Carbamazepine, phenytoin, phenobarbital

DAA Drug Interactions

- **May narrow therapeutic index drugs must be adjusted**
- **Must check prescribing information**

- Antiarrthymics (amiodarone, fleicanide, profafenone)
- Digoxin
- Warafin
- Bosentan
- Azole antifungals
- Colchicine
- Clarithromycin
- Rifabutin
- DHP calcium channel blockers
- Dexamethasone
- Inhaled budesonide and fluticasone
- Methadone
- Cyclosporine/tacrolimus

Ribavirin

- **Adjust dose based on:**
  - Weight
  - Hemoglobin
  - Presence of cardiac history
- Fetal abnormalities (category X)
- Hemolytic Anemia (20-25%)

Treatment of Chronic HCV

Parameter	Definition
Rapid virologic response (RVR)	Undetectable HCV RNA at week 4 of treatment
Early virologic response (EVR)	> 2-log reduction in HCV RNA compared with baseline or undetectable HCV RNA at 12 weeks
End of treatment response (ETR)	Undetectable HCV RNA at the end of a 24- or 48-week course depending on genotype
Sustained virologic response (SVR)	Undetectable HCV RNA 24 weeks after finishing treatment
Breakthrough	Reappearance of HCV RNA while on treatment
Relapse	Reappearance of HCV RNA after finishing a course of treatment
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy
Null responder	Failure to decrease HCV RNA by < 2 log after 24 weeks of therapy
Partial responder	Decrease in HCV RNA by > 2 log after 24 weeks of therapy but HCV RNA still detectable

HEPATOLOGY, Vol. 49, No. 4, 2009

Chronic Hepatitis C Treatment Duration

- Genotype 1:
  - It depends…..
- Genotypes 2 and 3: 24 weeks

Chronic Hepatitis C Treatment Duration

Regimen	Patient Group	HCV RNA TW* 8	HCV RNA TW 24	Recommendation
PEG-INF+ Ribavirin + Boceprevir	Previously untreated	Undetectable	Undetectable	Continue all 3 drugs for 28 weeks total
		Detectable	Undetectable	1. Continue all 3 drugs for a total of 36 weeks. 2. Then continue PEG-INF and ribavirin for through TW 48
	Previous partial responders or relapsers	Undetectable	Undetectable	Continue all 3 drugs for 36 weeks total
		Detectable	Undetectable	1. Continue all 3 drugs for a total of 36 weeks. 2. Then continue PEG-INF and ribavirin for through week 48
	Patients with HCV RNA > 100 IU/ml at week 12 or detectable HCV RNA at week 24	NA	NA	1. Discontinue all 3 drugs

*TW = Treatment Week

Chronic Hepatitis C Treatment Duration

	Patient Group	HCV RNA Week 4	HCV RNA Week 12	Recommendation
PEG-INF + Ribavirin + Telaprevir	Treatment naive or prior relapse	Undetectable	Undetectable	1. Continue all 3 drugs for 12 weeks 2. Then treat with PEG-INF and ribavirin for an additional 12 weeks (24 weeks total)
		Detectable (1000 IU/ml or less)	Detectable (1000 IU/ml or less)	1. Continue all 3 drugs for 12 weeks 2. Then treat with PEG-INF and ribavirin for an additional 36 weeks (48 weeks total)
	All patients	≥1000 IU/ml	≥1000 IU/ml	1. Discontinue all 3 drugs at week 12
	Detectable HCV RNA at 24 weeks	NA	NA	1. Discontinue PEG-INF and ribavirin

Practice Case #2

- J.G. is a 48-year-old woman with a history of heroin use who is admitted to the hospital with altered mental status, jaundice, abdominal swelling, shortness of breath and pruritis. Physical exam reveals jaundice, tense ascties with a positive fluid wave, asterixis, 3 + pitting lower extremity edema, and crackles on lung exam. She smokes 1 pack per day and reports her last heroin use as yesterday. Laboratory results reveal (+) anti-HCV, HCV RNA 100,000 copies/ml, AST 159 IU/L, ALT 250 IU/L, albumin 2 g/L, INR 3.6.

2. How should J.G.'s hepatitis C infection be managed at this time?

   A. No treatment is recommended
   B. Tenofovir
   C. Pegylated interferon
   D. Pegylated interferon + ribavirin

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Practice Case #3

- D.H. is a 58-year-old man who is seen in hepatology clinic today for a recent diagnosis of HCV infection. He received a diagnosis 8 months ago and recently switched jobs so his treatment has been delayed. He is now seen today to initiate therapy. He has a history of alcohol and intravenous drug use, with no use in the last year. He also has a history of BPH.
- He smokes 1/2 pack per day and reports no alcohol or illicit drug use in the last year. Laboratory results reveal (+) anti-HCV, HCV RNA 350,00 copies/ml, AST 290 IU/L, ALT 450 IU/L, albumin 3.4 g/L, INR 1.2. Hct 39%, Hgb 13.3 g/dl, Platelets 190 x 10^3, HCV genotype 1a. Scr 0.9 mg/dl.
- Physical exam reveals absence of jaundice or ascites, and is otherwise normal.
- Current medications include tamsulosin 0.4 mg daily, acetaminophen as needed.

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- Current medications include tamsulosin 0.4 mg daily, acetaminophen as needed.

3. How should D.H.'s hepatitis C infection be managed at this time?

A. No treatment is recommended
B. Pegylated interferon + ribavirin
C. Boceprevir + pegylated interferon
D. Telaprevir + pegylated interferon + ribavirin

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Gastroesophageal Reflux Disease

GERD

Updated Definition

- *"symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung."*
  - AGA guidelines (Am J Gastroenterol 2013; 108:308 – 328).

- Symptoms without erosions = NERD
- Symptoms with erosions = ERD

Guideline Evidence Grading

GRADE Category of Evidence	Definition
High	Further research was unlikely to change the authors ' confidence in the estimate of the effect
Moderate	Further research would be likely to have an impact on the confidence in the estimate of effect
Low	Further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate).
Strength	**Definition**
Strong	Desirable effects of an intervention clearly outweigh the undesirable effects
Conditional	There is uncertainty about the trade-offs

Am J Gastroenterol 2013; 108:308 – 328

Practice Case #4

- B. Z. is a 68-year-old man with a past medical history of Type 2 diabetes for 5 years, Hypertension, and GERD who presents for follow-up 6 weeks after initiating treatment for GERD. His initial symptoms included intermittent postprandial regurgitation and heartburn 5-6 days per week, often occurring 4-5 times throughout the day.
- An Upper GI endoscopy performed at that time was reported as normal. His symptoms have improved but are still present 3-4 days per week on average, with heartburn episode occurring 2-3 times throughout the day. He states that his symptoms are interfering with his daily routine.
- He currently takes enteric coated aspirin 81mg daily, metformin 1000 mg twice daily, hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, and lansoprazole 15 mg once daily in the morning. He does not drink alcohol or use tobacco. He works as a software engineer and is 5 ft 10 inches tall and weighs 235 pounds. He currently follows an exercise regimen and has lost 5 pound in the last month.

Treatment of GERD

- Nonpharmacologic/Lifestyle modifications
  - Targeted
- Antacids
- Acid suppression (as needed or scheduled)
  - Proton Pump Inhibitors
  - Histamine-2 Receptor Antagonists
- Promotility Agents
- Proper patient education
- Surgical intervention

GERD Guidelines 2013 Summary

Area	Recommendation (Strength/Evidence)
Diagnosis	• Empiric therapy with a PPI is recommended if typical symptoms of heartburn or regurgitation (Strong/Mod) • Screening for *H. pylori* is NOT recommended (Strong/Low)
NonPharm	• Weight loss if overweight or recent weight gain (Cond/Mod) • Elevate head of bed/avoid meals 2-3 hours prior to bedtime if nocturnal symptoms (Cond/Low) • Routine global elimination of food triggers NOT recommended (Cond/Low)

Am J Gastroenterol 2013; 108:308 – 328;

GERD Guidelines 2013 Summary

Area	Recommendation (Strength/Evidence)
Treatment	• Erosive esophagitis = 8 week course of PPI; no major differences in products (Strong/High) • Use maintenance PPIs if return of symptoms or complications (Strong/Mod) • Bedtime H2RAs can be used if AM PPI and nighttime symptoms but development of tachyphylaxis occurs (Cond/Low) • Further testing needed prior to use of metoclopramide or baclofen (Cond/Mod)
Dosing	• Traditional PPIs 30-60 minutes prior to meals (Strong/Mod) • Newer PPIs offer dosing flexibility in relation to meals (Cond/Mod) • Initiate PPIs once daily prior to AM meal (Strong/Mod) • Twice daily PPIs if partial response to once daily and/or night time symptoms (Strong/low) • Twice daily if partial response to once daily or can switch to another PPI (Cond/Low)

Am J Gastroenterol 2013; 108:308 – 328;

PPI Safety Concerns

Adverse Effect	Prevention and Management
Risk of Fracture (Hip, wrist, spine)	• Concern for fractures should not affect decision to use PPIs except in patients with other know risk factors for hip fracture (Cond/Mod) • Patients with osteoporosis can remain on PPIs • Limit dose and duration • Ensuring adequate Calcium and Vitamin D • BMD screening if at risk for low bone mass • Weight bearing Exercise
Hypomagnesemia	• Re-evaluate need • Limit dose and duration • Consider baseline testing (diuretics, digoxin) • Supplementation

PPI Safety Concerns

Adverse Effect	Prevention and Management
Clostridium difficile associated diarrhea	• Re-evaluate need •Limit dose and duration • Evaluate for *C. difficile* if patient receiving PPI has diarrhea that is not improving. Have patients report diarrhea. •Report cases to Medwatch
Community acquired Pneumonia	• Short term use may increase risk; long term risk is not elevated (Cond/Mod) •Assess for vaccine status

Other PPIs Issues

- Switching of PPIs can be considered in patients with side effects (Cond/Low)
- Interaction with clopidogrel and PPIs is not considered significant (Strong/High)
- First step in refractory GERD is optimization of PPI therapy (Strong/Low)

Practice Case #4

- B. Z. is a 68-year-old man with a past medical history of Type 2 diabetes for 5 years, hypertension, and GERD who presents for follow-up 8 weeks after initiating treatment for GERD. His initial symptoms included intermittent postprandial regurgitation and heartburn 5-6 days per week, often occurring 4-5 times throughout the day. An Upper GI endoscopy performed at that time was reported as normal. His symptoms have improved but are still present 3-4 days per week on average, with heartburn episode occurring 2-3 times throughout the day. He states that his symptoms are interfering with his daily routine.
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4. Which treatment recommendation would be most appropriate for this patient?

A. Add ranitidine 300 mg at bedtime
B. Switch to pantoprazole 20 mg once daily
C. Increase lansoprazole to 15 mg twice daily
D. Add metoclopramide 10 mg four times daily

Practice Case #4 Answer

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5. Based on B.Z.s current GERD treatment which monitoring test could be performed at this visit?

A. Serum Calcium
B. Serum Magnesium
C. Stool culture
D. Dual x-ray absorpitometry

Practice Case #5 Answer

- B. Z. is a 68-year-old man with a past medical history of Type 2 diabetes for 5 years, hypertension, and GERD who presents for follow-up 8 weeks after initiating treatment for GERD. His initial symptoms included intermittent postprandial regurgitation and heartburn 5-6 days per week, often occurring 4-5 times throughout the day. An Upper GI endoscopy performed at that time was reported as normal. His symptoms have improved but are still present 3-4 days per week on average, with heartburn episode occurring 2-3 times throughout the day. He states that his symptoms are interfering with his daily routine.
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Ulcer Related Upper Gastrointestinal Bleeding

Practice Case #6

- C. Y. is a 55-year-old woman with a past medical history of seasonal allergies and sinusitis who presents to the Emergency Department with a 12 hour history of nausea with coffee ground emesis. She undergoes emergent endoscopy which reveals a 2 cm duodenal ulcer with an actively bleeding vessel. Electrocautery is performed on the vessel and biopsies are taken. A rapid urease test performed during the endoscopy is positive for *Helicobacter pylori* infection.
- She currently takes cetirizine 10 mg daily and fluticasone nasal spray daily. She reports an allergy to clarithromyin, which she reports as "GI discomfort". Renal and liver function are both within normal limits and hemoglobin in reported as 10 g/dl.

Peptic Ulcer Disease (PUD)

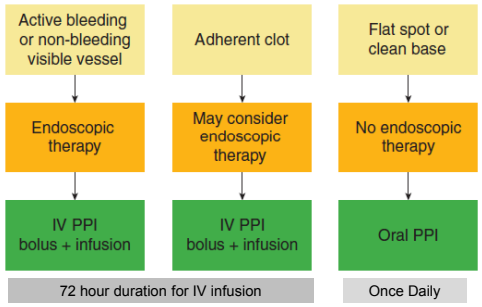
- Classification
  - Duodenal ulcer
  - Gastric ulcer
- Etiologies
  - *Helicobacter pylori* (carcinogen)
  - NSAIDs
- Symptoms
  - Epigastric pain, nausea, anorexia, belching
  - May be temporally related to food intake

Ulcer Related GI Bleeding

- Often referred to as NonVariceal
- "Overt"
  - Hematochezia
  - Melena
  - Hematemesis
- Pre-endoscopic Therapy
  - Erythromycin 250 mg IV (Conditional)
  - PPI Bolus/Infusion (80mg/8mg/hr)
  - No effects on outcomes!

Am J Gastroenterol 2012; 107:345–360;

Post Endoscopic Treatment



Am J Gastroenterol 2012; 107:345–360;

Post GI Bleeding Maintenance

- Treat for *H. pylori* if present
- Assess need for NSAIDs
- Assess need for aspirin
  - If secondary prevention resume within 1-3 days (max 7 days)
- Chronic PPI, including non-NSAID or non- *H. pylori*

Am J Gastroenterol 2012; 107:345–360;

Practice Case #6

- C. Y. is a 55-year-old woman with a past medical history of seasonal allergies and sinusitis who presents to the Emergency Department with a 12 hour history of nausea with coffee ground emesis. She undergoes emergent endoscopy which reveals a 2 cm duodenal ulcer with an actively bleeding vessel. Electrocautery is performed on the vessel and biopsies are taken. A rapid urease test performed during the endoscopy is positive for *Helicobacter pylori* infection.
- She currently takes cetirizine 10 mg daily and fluticasone nasal spray daily. She reports an allergy to clarithromyin, which she reports as "GI discomfort". Renal and liver function are both within normal limits and hemoglobin in reported as 10 g/dl.

6. Which treatment option is the best choice for treatment of C.Y.'s ulcer disease

A. Esomeprazole 80 mg intravenously, then 8mg/hour
B. Lansoprazole 15 mg orally once daily
C. Bismuth, tetracycline, metronidazole, and omeprazole
D. Ranitidine 75 mg intravenously 3 times daily

Practice Case #6 Answer

- C. Y. is a 55-year-old woman with a past medical history of seasonal allergies and sinusitis who presents to the Emergency Department with a 12 hour history of nausea with coffee ground emesis. She undergoes emergent endoscopy which reveals a 2 cm duodenal ulcer with an actively bleeding vessel. Electrocautery is performed on the vessel and biopsies are taken. A rapid urease test performed during the endoscopy is positive for *Helicobacter pylori* infection.
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Practice Case #7

- C R. P. is a 75-year-old man seen in clinic with chronic low back pain. His past medical history is significant for obstructive sleep apnea, atrial fibrillation, obesity, hypertension and dyslipidemia. He currently takes verapamil 240 mg daily, warfarin 5 mg daily, lisinopril 40 mg daily, and simvastatin 10 mg daily. He smokes 1/2 pack per day and consumes alcohol on a social basis.
- He does not require surgery, however her reports a chronic pain score of 7/10. His provider wishes to avoid narcotics as has had multiple falls and wished to initiate chronic high dose naproxen therapy.

Risk Factors for NSAID-induced GI Injury

Level of Risk	Specific Risk Factors
Low	No risk factors
Moderate (1-2 risk factors)	• Age > 65 years • High dose NSAID therapy • History of uncomplicated ulcer • Concurrent use of: ➢Aspirin (including low dose) or other NSAIDs ➢Corticosteroids ➢Anticoagulants
High	• History of complicated PUD •> 2 risk factors

Am J Gastroenterol 2009; 104:728 – 738

Prevention Strategies for NSAID induced PUD

- If *Low CV Risk* and:
  - Low GI Risk → NSAID (lowest dose of least ulcerogenic agent)
  - Moderate GI Risk → NSAID + PPI or Misoprostol
  - High GI Risk → COX-2 inhibitor + PPI or Misoprostol
- If *High CV Risk** and:
  - Low GI Risk → Naproxen + PPI or Misoprostol
  - Moderate GI Risk → Naproxen + PPI or Misoprostol
  - High GI Risk → Avoid NSAIDs or COX-2 Inhibitors

*need for ASA

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7. How would you assess this patients level of risk for NSAID induced gastrointestinal complications?

A. Low risk
B. Moderate risk
C. High Risk
D. Extreme risk

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8. What would be the preferred therapy for prevention of NSAID induced gastrointestinal injury in this patient?

A. Misoprostol 200 mcg twice daily
B. Lansoprazole 15 mg once daily
C. Switch to celecoxib 400 mg twice daily
D. Cimetidine 200mg twice daily

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Healing NSAID-Induced Ulcers

- Assess need for continued therapy
  - Stop NSAID if possible
  - Use lowest effective dose or COX-2 inhibitor
  - Alternate agents (disease dependent)
- PPIs most effective to date
  - Efficacious in preventing subsequent ulcers
  - Duration of therapy: 8-12 weeks
  - May need continually thereafter
- Risk factor modification

Inflammatory Bowel Disease

Practice Case #8

- S. H. is a 40 year old man who presents with a 2 week history of intermittent bloody stools 1-2 times per day, abdominal cramping, and tenesmus. He has no other past medical history and reports an allergy to shellfish. He currently takes no medications. A colonoscopy reveals superficial inflammation of the rectum extending approximately 14 cm consistent with mild ulcerative proctitis.

Clinical Differences

Clinical Findings	Ulcerative Colitis	Crohn's
Bowel Involvement	Confined to rectum and colon	May be anywhere from mouth to anus (mostly ileal)
Depth of Inflammation	Superficial	Possibly Transmural
Continuous Disease	Very Common	Rarely, "Cobblestone"
Fistula/Perforation Strictures	No	Yes
Malabsorption or Malnutrition	Rare	Yes, Often Vitamin Deficiencies
Perianal disease	No	Common

Disease Severity

Severity	Ulcerative Colitis	Crohn's
Mild	< 4 Stools/day No systemic disturbance	Tolerating oral intake No fever/abdominal pain No dehydration/Wt loss
Moderate	> 4 stools/day Minimal systemic disturbance	Failing treatment for mild (+) fever/abdominal pain (+) ↓ HCT, N/V, Wt loss
Severe	> 6 stools/day + blood Fever, ab pain, dehydration, ↑ ESR, ↓ HCT, ↑ WBC	Failing treatment for mod (+) fever/abdominal pain (+) ↓ HCT, N/V, Wt loss
Fulminant	>10 stools/day + blood Fever, ab pain, dehydration ↑ ESR, ↓ HCT, ↑ WBC Colonic dilation	Failed oral steroids Obstruction, abscess, cachexia, dehydration (+) fever/abdominal pain

IBD Treatment: Where to start

1. Disease: UC vs. CD
2. Severity: mild-severe or in remission
3. Extent and location of disease
4. Pick drug(s) based on
   - Onset of action
   - Effectiveness
   - Formulation
   - Adverse effects

Am J Gastroenterol 2004;99:1371–85 Am J Gastroenterol Gastroenterology 2009

IBD Treatment Guidelines

Severity	UC	Crohn's
Mild-Moderate	Aminosalicylate Budesonide	Aminosalicylate or Budesonide (ileal)
Moderate to Severe	Infliximab, Adalimumab OR Azathioprine/6-MP +/- Corticosteroid (short-term)	TNF-α inhibitor OR Azathioprine/6-MP OR Methotrexate +/- Corticosteroid (short-term) Natalizumab (last line)

Aminosalicylates

- Considered first line agents for mild-moderate UC and CD
- Possible mechanisms include anti-inflammatory and immunomodulatory effects
- Active component is 5-aminosalicylate, also referred to as 5-ASA or mesalamine
- Mesalamine must be delivered to the site of action, and has mostly topical effects

Aminosalicylates

- Sulfasalazine
  - Terminal ileum + Colon
  - Avoid if sulfa-allergic
- Mesalamine
  - Pentasa (small + large bowel)
  - Asacol, Lialda: (Terminal ileum + Colon)
  - Olsalazine, Balsalazide: (Colon)
  - Rowasa enema: (distal colon + rectum; splenic flexure)
  - Canasa suppository: (rectum)

Corticosteroids

- Patients with Moderate to Severe Disease
  - Systemic Oral
    - Prednisone
    - Budesonide: First line for CD ileal involvement or UC
  - Enemas/suppositories
  - IV: hospitalized patients
- Typical course for acute flare is 5-10 days
- No role in maintenance of remission

Biologic Therapies

Drug	Structure	Target	CD	UC	Induction	Maintenance
Infliximab	Chimeric	TNF-α	√	√	√	√
Adalimumab	Humanized	TNF-α	√	√	√	√
Certolizumab	Humanized with murine CDRs	TNF-α	√		√	√
Natalizumab	Humanized	α4-integrin	√		√	√

Biologic Therapies

- All indicated in Moderate to Severe Disease
- Drugs of choice for fistulizing disease
- May have steroid sparing effects
- Antibody development may occur
  - Loss of effectiveness
  - Increase in infusion related adverse effects
- Expensive

Immune Modulators

- **Azathioprine or 6-Mercaptopurine**
  - Steroid dependent patients with UC or CD
  - Combination therapy with biologics
  - Aminosalicylate failures
  - May result in steroid sparing effect
  - Check TPMT activity
  - Slow onset
- **Methotrexate**
  - Used mostly in steroid dependent CD or aminosalicylate failures
  - Slow onset

Key Safety Concerns in IBD

Drug(s)	Adverse Effects
TNF-alpha antagonists	• Risk of infection (screen for TB and Viral hepatitis) • Risk of Heart Failure and/or exacerbation • Hepatosplenic T-cell lymphoma when used with azathioprine or 6-MP in young male patients • Antibody formation
Antimotility agents	• Risk of toxic megacolon in active disease
Azathioprine/6MP	• Bone marrow suppression, pancreatitis, hypersensitivity • Need to check TPMT activity
Methotrexate	• Bone marrow suppression, pulmonary and hepatic toxicity
Corticosteroids	• Adrenal suppression, metabolic effects, infection
Natalizumab	• Progressive mutilfocal leukoencephalopathy

Practice Case #8

- S. H. is a 40 year old man who presents with a 2 week history of intermittent bloody stools 1-2 times per day, abdominal cramping, and tenesmus. He has no other past medical history and reports an allergy to shellfish. He currently takes no medications. A colonoscopy reveals superficial inflammation of the rectum extending approximately 14 cm consistent with mild ulcerative proctitis.

Practice Case #8

- S. H. is a 40 year old man who presents with a 2 week history of intermittent bloody stools 1-2 times per day, abdominal cramping, and tenesmus. He has no other past medical history and reports an allergy to shellfish. He currently takes no medications. A colonoscopy reveals superficial inflammation of the rectum extending approximately 14 cm consistent with mild ulcerative proctitis.

9. What would be the preferred therapy for treatment of S. H.'s ulcerative proctitis?

A. Anucort (hydrocortisone) suppository twice daily
B. Asacol (mesalamine) 800 mg orally twice daily
C. Pentasa (mesalamine) 500 mg orally four times daily
D. Canasa (mesalamine) suppository 1 g daily

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Twelve months later S.H. is admitted to the hospital with 6-7 bloody bowel movements per day, a temperature of 101 ºF, a heart rate of 110 bpm an ESR of 100 mm/hr, and a hemoglobin of 11 g/dl. A colonoscopy reveals extension of his ulcerative colitis to the proximal sigmoid colon with evidence of ongoing bleeding.

10. What would be the preferred therapy for treatment of S. H.'s ulcerative proctitis at this time?

A. Natalizumab 300 mg intravenously x 1 dose
B. Methylprednisolone 80 mg once daily intravenously
C. Rowasa (mesalamine) enema once daily
D. Colazal 1500 mg three times daily by mouth

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Practice Case #9

- P. R. is a 29 year old woman with a 2 year history of Crohn's Disease affecting both the ileum and colon who has been receiving sulfasalazine 4 g/day for the last 22 months. Due to adverse effects she has been non-adherent to her therapy. She presents today with 2-3 bloody stools per day, abdominal cramping, a CRP of 5 mg/L, and a 10 pound weight loss over the last 2 months.
- Upon exam she is also found to have an enterocutanous fistula on her left upper abdominal wall with active drainage. She reports no drug allergies and takes no other medications other than the sulfasalazine. She has no other past medical history.

Practice Case #9

- P. R. is a 29 year old woman with a 2 year history of Crohn's Disease affecting both the ileum and colon who has been receiving sulfasalazine 4 g/day for the last 22 months. Due to adverse effects she has been non-adherent to her therapy. She presents today with 2-3 bloody stools per day, abdominal cramping, a CRP of 5 mg/L, and a 10 pound weight loss over the last 2 months. Upon exam she is also found to have an enterocutanous fistula on her left upper abdominal wall with active drainage. She reports no drug allergies and takes no other medications other than the sulfasalazine. She has no other past medical history.

11. What would be the preferred therapy for treatment of P.R.'s Crohn's Disease at this time?

A. Natalizumab 300 mg intravenously x 1 dose
B. Budesonide 9 mg orally once daily
C. Infliximab 5 mg/kg intravenously x 1 dose
D. Prednisone 40 mg orally once daily

Practice Case #9 Answer

- P. R. is a 29 year old woman with a 2 year history of Crohn's Disease affecting both the ileum and colon who has been receiving sulfasalazine 4 g/day for the last 22 months. Due to adverse effects she has been non-adherent to her therapy. She presents today with 2-3 bloody stools per day, abdominal cramping, a CRP of 5 mg/L, and a 10 pound weight loss over the last 2 months. Upon exam she is also found to have an enterocutanous fistula on her left upper abdominal wall with active drainage. She reports no drug allergies and takes no other medications other than the sulfasalazine. She has no other past medical history.

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Complications of Chronic Liver Disease

Complications of Cirrhosis

- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Spontaneous bacterial peritonitis

Ascites

- Treatment goals
  - Negative fluid and salt balance
- Diuretics
  - Loops
  - Spironolactone
  - 100 mg Spironolactone / 40 mg furosemide
- Monitoring
  - Weight (1kg/day: edema, 0.5 kg/day: no-edema)
  - Electrolytes

Hepatology 2009;49:2087–107 Am J Gastroenterol 2009;104:1802–29 .

Hepatic encephalopathy

- Remove/treat precipitating factors
  - Infection, drugs, electrolyte disturbances, constipation, bleeding
- Lactulose
  - Titrate to 2-4 loose BMs/day
  - Acute and maintenance
- Rifaximin 550mg twice daily (prevention)
  - Neomycin, metronidazole
  - Similar efficacy to lactulose
  - Renal insufficiency with neomycin
  - Acute and maintenance
  - Cost with rifaximin, plus use with lactulose

Gastroenterology 2001;120:726–48.

Variceal Bleeding

- Acute management
  - Fluid resuscitation
  - Octreotide IV continuous infusion x 5 days
  - Antibiotic x 7 days (FQ or 3rd Gen Cephalosporin)
- Primary prevention
  - Non selective B-blocker or band ligation
  - Med/large varices or small varices + high bleeding risk
- Secondary prevention
  - All patients with prior bleeding
  - Non selective B-blocker or band ligation (or combo)

Hepatology 2009;49:2087–107

Spontaneous Bacterial Peritonitis

- Diagnosis = 250 PMNs/mm^3 of ascitic fluid
- Treatment
  - 3rd gen Cephalosporin or FQ
  - Albumin: 1.5 g/kg on admission; 1 g/kg on hospital day 3 if Scr > 1 mg/dL, BUN >40 mg/dL, or T. bili. >4 mg/dL
- Primary Prevention
  - Ascitic fluid protein < 1.5 g/l + Scr > 1.2 mg/dl or BUN > 25 mg/dl or Na < 130 mEq/L or CP Score > 9 (T. bili. > 3 mg/dl)
  - Norfloxacin/ciprofloxacin, TMP/SMX
- Secondary prevention
  - All patients with prior episode

Hepatology 2009;49:2087–107 Am J Gastroenterol 2009;104:1802–29 .

Practice Case #10

- B.D. is a 51-year-old man with a 20 year history of alcohol abuse, illicit drug use, and asthma who presents to the clinic with complaints of abdominal swelling, jaundice, pruritis, intermittent nausea, and a 20 pound weight gain over the last 2 months. Physical exam reveals tense abdominal ascites with 2+ pitting lower extremity edema. Vital signs are Temp 98.9 F, HR 89 BPM, RR 16 breaths/min, BP 138/74. An oxygen saturation is reported as 92% on room air.
- Current labs include Scr 0.8 mg/dl, BUN 18 mg/dl, ALT 40 IU/L, AST 120 IU/L, and albumin 2.2 g/L, total bilirubin 1.8 mg/dl, Na 132 mEq/L, INR 1.3. A diagnostic paracentesis reveals no WBCs or and a fluid protein concentration of 1.1 g/L. He reports an allergy to penicillin, which results in a rash. Current medications include albuterol HFA MDI as needed and fluticasone/salmeterol DPI 500mcg/50mcg 1 inhalation twice daily.

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12. What would be the preferred therapy for treatment of B.D.'s ascites at this time?

A. Spironolcatone 400 mg orally once daily
B. Bumetanide 1 mg intravenously once daily
C. Furosemide 40 mg + metolazone 5 mg orally once daily
D. Furosemide 40 mg + Spironolcatone 100 mg orally once daily

Practice Case #10 Answer

- B.D. is a 51-year-old man with a 20 year history of alcohol abuse, illicit drug use, and asthma who presents to the clinic with complaints of abdominal swelling, jaundice, pruritis, intermittent nausea, and a 20 pound weight gain over the last 2 months. Physical exam reveals tense abdominal ascites with 2+ pitting lower extremity edema. Vital signs are Temp 98.9 F, HR 89 BPM, RR 16 breaths/min, BP 138/74. An oxygen saturation is reported as 92% on room air.
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13. B.D. is diagnosed with cirrhosis secondary to alcohol abuse and undergoes screening endoscopy, which reveals several large esophageal varices protruding into the lumen of the esophagus for which the patient undergoes band ligation. Which strategy is most appropriate to prevent or address this patient varices in the future?

A. Atenolol 50 mg once daily
B. Propranolol 10 mg three times daily
C. Nitroglycerin patch once daily
D. Intermittent band ligation

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- B.D. is a 51-year-old man with a 20 year history of alcohol abuse, illicit drug use, and asthma who presents to the clinic with complaints of abdominal swelling, jaundice, pruritis, intermittent nausea, and a 20 pound weight gain over the last 2 months. Physical exam reveals tense abdominal ascites with 2+ pitting lower extremity edema. Vital signs are Temp 98.9 F, HR 89 BPM, RR 16 breaths/min, BP 138/74. An oxygen saturation is reported as 92% on room air.
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14. What intervention should be made at this time regarding spontaneous bacterial peritonitis (SBP)?

A. No treatment or prevention is needed
B. Ceftriaxone 1 g intravenously
C. Ciprofloxacin 750 mg once weekly
D. Rifaximin 550mg twice daily

Practice Case #10 Answer

- B.D. is a 51-year-old man with a 20 year history of alcohol abuse, illicit drug use, and asthma who presents to the clinic with complaints of abdominal swelling, jaundice, pruritis, intermittent nausea, and a 20 pound weight gain over the last 2 months. Physical exam reveals tense abdominal ascites with 2+ pitting lower extremity edema. Vital signs are Temp 98.9 F, HR 89 BPM, RR 16 breaths/min, BP 138/74. An oxygen saturation is reported as 92% on room air.
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Review Question #1

- W. Y. is 66 year old woman with GERD who is receiving esomeprazole 20 once daily for GERD symptoms. She reports that she is satisfied with her treatment but does get occasional (once every 14-21 days) recurrent GERD symptoms following a large meal.

R1. What would be the best choice for treatment of these occasional symptoms when they occur?

A. Increase esomeprazole to 20 mg twice daily
B. Take an extra esomeprazole capsule when symptoms occur
C. Take TUMS when symptoms occur
D. Recommend weight loss to the patient

Review Answer #1

- W. Y. is 66 year old woman with GERD who is receiving esomeprazole 20 once daily for GERD symptoms. She reports that she is satisfied with her treatment but does get occasional (once every 14-21 days) recurrent GERD symptoms following a large meal.

R1. What would be the best choice for treatment of these occasional symptoms when they occur?

A. Increase esomeprazole to 20 mg twice daily
B. Take an extra esomeprazole capsule when symptoms occur
C. Take TUMS when symptoms occur
D. Recommend weight loss to the patient

Extra Question #1

E1. What baseline monitoring for toxicity should be performed for a 45 year old man who is otherwise healthy, but will be taking a proton pump inhibitor indefinitely for treatment of GERD?

A. Chest X-Ray
B. Stool culture for *Clostridium Difficile*
C. Bone Mineral density
D. No baseline treatment monitoring is required

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Review Question #2

A 65 year old male patient requires long term NSAID therapy for rheumatoid arthritis and is also taking low dose aspirin (81 mg/day) for cardiopotection.

R2. What is the preferred strategy to prevent gastrointestinal toxicity assuming he has an appropriate indication for the aspirin?

A. Use celecoxib with aspirin
B. Stop aspirin and start indomethacin
C. Start naproxen and a PPI
D. Add misoprostol and ibuprofen

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Extra Question #2

A 29 year old woman diagnosed with Crohn's Disease of moderate severity involving the terminal ileum. She presents with 1-3 bloody stools per day, a temperature of 100.3 F, and a heart rate of 85 BPM. She reports no allergies to medications and takes an oral contraceptive medication on a daily basis.

E2. What is the most appropriate initial therapy for this patient's Crohn's Disease?

A. Budesonide
B. Adalimumab
C. Olsalazine
D. Azathioprine

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Extra Question #3

A 49 year old man with a history of Child-Pugh Class C cirrhosis is admitted to the intensive care unit for upper gastrointestinal bleeding. A endoscopy reveals several moderate to large esophageal varices, which are subsequently banded.

E3. Which drug regimen is most appropriate to initiate for this patient at this time?

A. Nadolol
B. Octreotide + ciprofloxacin
C. Lansoprozole IV infusion
D. Octreotide

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Review Question #3

A 52 year old woman with a history of Child-Pugh Class B cirrhosis secondary to alcohol abuse is admitted to the general medicine floor for altered mental status. She has asterixis and alerted and oriented to only person, but not place or time. She has no evidence of infection or electrolyte disturbances and takes no other medications. Lactulose 15 ml twice daily is started and 24 hours later her symptoms are minimally improved. Her nurse reports one semi-sold bowel movement during this time period.

R3. What is the best course of action for treatment of this patient's encephalopathy?

A. Increase the lactulose dose to 30 ml twice daily
B. Increase the lactulose dose and frequency of administration
C. Add neomycin
D. Administer flumazenil

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Extra Question #4

A 57 year old man is new diagnosed with chronic hepatitis C virus infection and was started on pegylated interferon and ribavirin 2 weeks ago. He has no other past medical history.

E4. Which laboratory test should be monitored at this time for evidence of potential toxicity?

A. TSH
B. Calcium
C. Potassium
D. Complete blood count

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Review Question #4

R4. What is an appropriate duration of treatment for a patient with chronic hepatitis C virus (genotype 2) infection who is receiving pegylated interferon and ribavirin?

A. 12 weeks
B. 24 weeks
C. 48 weeks
D. 60 weeks

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