Hepatitis, Peptic Ulcer Disease And Other Gastrointestinal Problems

Brian Desmond, M.D.
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51 y.o. male with Elevated LFT’s

51 yo male seen for routine PE. No current c/o. Takes no medications

PMH: splenectomy 25 yo due to trauma. Smokes ½ ppd, works as a painting contractor. ETOH rare, denies history of drug use or known transfusions

PE normal, no stigmata of liver dz

Labs: AST 72 U/L, ALT 66 U/L, ALK PHOS 120 U/L; NORMAL CBC, BILI. labs 3 years prior elevation of liver enzymes < 2x nl

HEPATITIS

- INFECTIOUS: Viral, bacterial, mycobacterial, fungal
- TOXIC: Alcohol, acetaminophen, mushroom poisoning, other drugs
- METABOLIC: Shock, passive congestion, hemochromatosis, Wilson’s disease, fatty liver
- IMMUNOLOGIC: Auto-immune hepatitis

HEPATITIS

Acute vs Chronic

- Viral: Hep A and B, CMV, HIV, Mono
- Toxic: mushroom, acetaminophen, other drugs
- Shock
- Alcohol

- Viral B and C
- Alcohol
- Medications, herbs
- Passive congestion, hemochromatosis, Wilson’s disease, NAFLD, A1-AT deficiency
- Auto-immune
HEPATITIS A

• Transmission is fecal/oral
• Incubation period: 2-6 weeks
• Course of disease: Children - disease often mild, usually anicteric; Adults - more often symptomatic with jaundice
• 99% fully recover, develop lifetime immunity
• Fulminant hepatitis is rare
• No chronic hepatitis, or cirrhosis

SEROLOGY HEPATITIS A

- ALT
- Anti HAV
- IgM anti-HAV

Months after exposure

HEPATITIS A VACCINE

• Pre-exposure prophylaxis for travelers to high risk areas.
• Universal vaccination of infants

ADULTS  1.0 ml @ 0 and 6 months
CHILDREN (Over 1 year old) 0.5 ml @ 0, and 6 months

HEPATITIS B

• 350 million persons infected globally
• 600,000 deaths annually due to complications
• 1 million person in the US infected
• Incidence US 11.5 cases / 100,000 1985 to 1.6 cases / 100,000 in 2006
• TRANSMISSION: Blood borne- vertical, transfusion, IVDU, needle stick/splash
  Sexual contact- multiple sexual partners, homosexual men
• INCUBATION PERIOD: 45 - 160 days
Course of Disease

- 95% of adults have self limited disease
- 1/3 of those have clinical illness
- 5-10% become chronic carriers
- Flu like prodrome, jaundice
- 10% immune complex, “serum sickness”
- Fulminant Hepatitis
- Chronic Hep B - HBsAg positive > 6 months

HBV Serology

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HbcAb</th>
<th>HBsAb</th>
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<tbody>
<tr>
<td>Vaccine</td>
<td>neg</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td>Immune past HBV</td>
<td>neg</td>
<td>pos</td>
<td>pos</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Acute or chronic HBV</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
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<tr>
<td>HBV infection</td>
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<tr>
<td>Resolved HBV infection</td>
<td>neg</td>
<td>pos</td>
<td>neg</td>
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<tr>
<td>False positive core</td>
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<td></td>
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<tr>
<td>Low level chronic</td>
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<tr>
<td>Resolving acute infection</td>
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</table>

Complications of Chronic Hepatitis B

- Chronic active hepatitis
- Cirrhosis and liver failure
- Transmission
- Hepatocellular Ca
**Prevention-HepB Vaccine**

- Children/adolescents
- Contacts HepBAg+
- Injection drug users
- Multiple sexual partners (>1/6mos)
- Men having sex with men
- Persons recently diagnosed with STI
- Pts with HIV
- Hemodialysis pts
- Health care/Public safety workers with blood exposure
- Clients and staff at institutions for developmentally disabled/inmates
- Travelers @ risk
- Chronic liver disease

**Treatment of Chronic Hep B**

- Goal to limit progression and prevent complications
- Alpha interferon – (PEG IFN-2a)
- Lamivudine (Epivir)
- Adefovir Dipivoxil (Hepsera)
- Entecavir
- Telbivudine
- Tenofovir
- Vaccination of family members
- Patient Education: ETOH abstinence
  - Sexual behavior
  - Toothbrushes, razors, etc.

**HEPATITIS C**

- Approximately 3 million persons in US
- Most are not yet identified
- Of those diagnosed, most have not been treated
- Transmission : Blood borne
  - Sexual contact
- Incubation period : 2 - 22 weeks

**Risk Factors for Hepatitis C**

- Injection drug users, tatoos, cocaine
- People with multiple sexual partners
- Babies born to infected mothers
- Hemodialysis patients
- People who received blood products before 1992
- Sexual contacts of infected person
**Course of Disease Hep C**

- **Acute**: Majority are asymptomatic
  - One third develop jaundice
  - Not associated with fulminant disease
- **Chronic**: 85% develop chronic hepatitis
  - Approximately 20% will develop cirrhosis

**Serology of Hepatitis C**

- EIA Antibody test
- Quantitative PCR RNA viral load
- Genotyping: subtypes 1, 2, 3...

**Treatment of Hepatitis C**

- Pegalated interferon plus Ribavirin
- PEG IF + ribavirin + ?others
- Patient Education: ETOH abstinence
  - Sexual behavior
  - Toothbrush, razors, etc.
- Hepatitis A, B vaccines

**Treatment Response Rates**

![Treatment Response by Genotype and Duration of Therapy]

- Geno 1 - 12 months
- Geno 2,3 - 6 months
HEPATITIS D

- Transmission: blood borne (IVDU)
- Serology: RIA - HDV antibody
- Course of disease: “tag along hepatitis”
  - Acute: coinfection with HBV required
  - Fulminant: coinfection or carrier
  - Chronic: infection in chronic HBV may result in CAH

HEPATITIS E

- Transmission: fecal/oral
- Epidemiology: Indian subcontinent
  - South central Asia, Middle East
  - Mexico
- Course of Disease:
  - Acute: moderate to severe disease
  - 1% - 2% mortality
  - No chronic or carrier state
- Vaccine is being field tested

51 y.o Male Initial Lab Results

Results:
- HBAg negative
- HCAb positive
- Normal Iron and transferrin

Recommendations

A. Vaccinate against HepB, HepA
B. Test spouse
C. Advise alcohol abstinence
D. Obtain quantitative HCV RNA, genotype
E. Refer to GI / obtain liver biopsy
ALCOHOLIC HEPATITIS

• Can be acute or chronic ingestion
• Clinical: jaundice, tender hepatomegaly, leukocytosis, fever, vomiting
• Laboratory: AST/ALT ratio 2:1
  Transaminase elevation < 300
  Alkaline phosphatase < 400
  Bilirubin elevated
• Elevated MCV
• Treatment: abstinence, nutrition, high index of suspicion for SBP (ANC > 250)

TOXIC HEPATITIS

• Industrial: Carbon tetrachloride
• Ingestion: Aminita mushrooms
• Medications: many

Medications

• Acetaminophen
• Antibiotics
  – Ciprofloxin, Sulfamethoxazole, Nitrofurantoin, Amoxicillin-clavulanic acid
  – Isoniazid
  – Ketoconazole, Fluconazole, Terbinafine
• Anticonvulsants
  – Phenytoin, Carbamazepine
• Statins
  – Simvastatin, Lovastatin, atorvastatin, Pravastatin, Rosuvastatin
• NSAID
• Anti-dysrhythmics
  – Amiodarone

Medications

• Sulfonylureas
  – Glypizide, Glyburide
• Glitazones
  – Pioglitazone, Rosiglitazone
• Antiretrovirals
  – Protease inhibitors
  – Nucleoside analogs
• Niacin
  – Glitazones
**Herbs**
- Chaparral leaf
- Germander
- Alchemilla
- Germander
- Senna
- Shark cartilage
- Ma huang
- Ji bu huan
- Mistletoe
- Kava

**Drugs/Others**
- Anabolic steroids
- Cocaine
- MDMA, ecstasy
- Angel dust (Phencyclidine)
- Glues/solvents
  - Toluene, chloroform, trichloroethylene

**METABOLIC HEPATITIS**
- Hemochromatosis
  - Iron deposition in liver and other organs
- Fatty Liver: Steatohepatitis
- Wilson’s Disease
  - Copper deposition in liver, brain
- Alpha 1- AT deficiency
- Ischemic hepatitis, passive congestion

**Hemochromatosis**
- Most common genetic disorder in adults
- Autosomal recessive
- Prevalence: 1 in 400 in US
- Inappropriate iron absorption leads to cirrhosis, HCC, diabetes, heart disease
- HFE detects mutation C282Y, H63D
- Variable penetrance
**Hemochromatosis**

- **Diagnosis:** Serum transferrin saturation greater than 50% (often elevated ferritin)
- **Genetic markers:** HFE Gene C282Y, H63D mutation
- **Treatment:** Phlebotomy to maintain ferritin < 50ug/L

**FATTY LIVER**

- **Diagnosis:** Imaging studies, liver biopsy
- **NAFLD:** Non Alcoholic Fatty Liver Dz
- **NASH:** Non Alcoholic Steatohepatitis
- **Natural History:** 30% progress, 60% no change, 10% improvement
- **Treatment:** Weight loss, Gemfibrozil, Metformin, Thioglitazones, Rimonabant

**Risk factors in pts with NAFLD**

- Obesity (BMI>30 kg/m2) 30-100%
- Diabetes Mellitus type 2 10-75%
- Hyperlipidemia (esp TRIG) 20-92%
- FHx steatohepatitis and cryptogenic cirrhosis
- Insulin resistance underlies most cases

**Diffuse Steatosis on Non-Contrast CT**
Fatty Liver on Ultrasound

AUTOIMMUNE HEPATITIS

- Often a diagnosis of exclusion, biopsy
- Consider in young women with other autoimmune disorder - thyroditis, ulcerative colitis, or Sjogren’s syndrome.
- Elevated IgG; ANA positive in 80%; smooth muscle antibodies in 70%;
- Treatment with prednisone and azathioprine improves survival rates in patients with severe disease

Clinical Case

- 55 y/o male with 15 year history of intermittent heartburn, presents with daily symptoms for the past 6 months. Denies dysphagia, bleeding or weight loss.
Dyspepsia

- Exclude by history:
  - GERD
  - Irritable bowel syndrome
  - Biliary pain
  - Medication induced dyspepsia

- Risk factors for serious disease:
  - GERD
  - Age > 50 years
  - Dysphagia
  - Protracted vomiting
  - Anorexia/weight loss
  - Melena or anemia
  - Palpable mass

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GERD

- Diagnosis reliably made by typical symptoms and response to therapy. Diagnostic testing not typically indicated
- Remember very poor correlation between endoscopic findings and symptoms
- Testing (EGD) usually reserved for concern for stricture, Barrett’s metaplasia, adenocarcinoma, and to evaluate treatment failures.

GERD Treatment

- Healing related to potency of medication’s anti secretory effect
- Meta-analysis of 136 randomized controlled studies involving 35,978 patients healing rates at standard doses – PPI 83%, H2 antagonists 52%, placebo 8% (after 8-12 weeks)

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Differential Diagnosis of Dyspepsia</td>
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<tr>
<td>Diagnostic category</td>
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<tr>
<td>&quot;Functional&quot; dyspepsia†</td>
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<tr>
<td>Dyspepsia caused by structural or biochemical disease</td>
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<tr>
<td>Peptic ulcer disease</td>
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<tr>
<td>Reflux esophagitis</td>
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<tr>
<td>Gastric or esophageal cancer</td>
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<tr>
<td>Biliary tract disease</td>
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<tr>
<td>Gastroparesis</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Carbohydrate malabsorption (lactose, sorbitol, fructose, mannitol)</td>
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<td>Medications (see Table 4)</td>
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<tr>
<td>Infiltrative diseases of the stomach (Crohn’s disease, sarcoidosis)</td>
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<td>Metabolic disturbances (hypercalcemia, hyperkalemia)</td>
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<td>Hepatoma</td>
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<td>Ischemic bowel disease</td>
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<tr>
<td>Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)</td>
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<tr>
<td>Intestinal parasites (Giardia, Strongyloides)</td>
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<tr>
<td>Abdominal cancer, especially pancreatic cancer</td>
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</table>
**GERD TREATMENT**

- PPI’s now recommended first line
- PPI’s should be given 30-60 min ac
- Reducing fat, chocolate, coffee, alcohol, and peppermint intake
- Avoiding onions, citrus, tomato-based foods
- Smoking cessation, weight loss
- Avoid late meals, elevate head of bed

**Endoscopic Screening for Barrett’s**

Insufficient evidence of benefit to recommend screening in those with GERD
Replacement of squamous epithelium in the distal esophagus with metaplastic intestinal columnar epithelium
- ~10% of pts with GERD have Barrett’s
- 0.5-0.75% of pts per year with Barrett’s will develop cancer
- Most patients diagnosed with adenocarcinoma of the esophagus or stomach cardia don’t have Barrett’s

**Surgical Indications - GERD**

- Failed medical management
- Patient preference despite successful medical therapy
- Large hiatal hernia

**GERD Endoscopic Treatments**

- Stretta Procedure – radiofrequency heating of gastroesophageal junction
- Endocinch Procedure – endoscopic suture ligation GE junction
**PEPTIC ULCER DISEASE**

<table>
<thead>
<tr>
<th>External Factors</th>
<th>Aggressive Factors</th>
<th>Defensive Factors</th>
<th>External Factors</th>
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<tbody>
<tr>
<td>Zollinger Ellison Syndrome</td>
<td>ACID PEPCIN</td>
<td>Mucus Secretion Bicarbonate production</td>
<td>Helicobacter pylori NSAID use</td>
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<tr>
<td></td>
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<td>Mucosal blood flow Cell mediators Prostaglandins</td>
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**H. Pylori**

- Test and treat strategy validated
- Strongly associated with duodenal ulcer
- Eradication decreases PUD recurrence
- Eradication not effective in relieving symptoms in “non ulcer dyspepsia”
- Associated with development of gastric cancer
**H. Pylori - Testing**

- CLO test – invasive, requires endoscopy
- Urea Breath Test – sensitive, office based testing may be inconsistent. Allow 4 weeks post treatment.
- Stool Antigen – high sensitivity and specificity. Allow at least 6-8 weeks post treatment.
- Serology – not reliable for post treatment

**H. Pylori - Treatment**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Days</th>
<th>% Eradication</th>
</tr>
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<tbody>
<tr>
<td>Omeprazole 20mg BID</td>
<td>14 days</td>
<td>80-85</td>
</tr>
<tr>
<td>Amoxicillin 1gm BID</td>
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<tr>
<td>Clarithromycin 500mg BID</td>
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<tr>
<td>Lansoprazole 30mg BID</td>
<td>10-14 days</td>
<td>86</td>
</tr>
<tr>
<td>Amoxicillin 1gm BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500mg BID</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>Bismuth Subsalicylate 525mg QID</td>
<td>14 days</td>
<td>80</td>
</tr>
<tr>
<td>Metronidazole 250mg QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline 500mg QID</td>
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<tr>
<td>Ranitidine 300mg BID</td>
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**Clinical Case**

- A healthy 27 y/o male presents with 4 days of acute watery diarrhea, with blood, fever to 102, cramping and nausea, without vomiting.
Diarrhea

**ACUTE**
- Viral
- Bacterial - food borne, person to person, antibiotic use, travel,
- Food poisoning
- Associated with other serious illness

**CHRONIC**
- Infectious
- Inflammatory Bowel
- Ischemic Bowel
- Irritable Bowel
- Microscopic colitis
- Collagenous colitis
- Celiac disease

Initial Assessment

- Dehydration (BP, P, skin turgor, mucus membranes, urination, oral intake)
- Duration and severity of illness
- Evidence of inflammation (fever, tenesmus, bleeding)

Identify Clinical Clues

- Clinical
  - Bloody diarrhea
  - Abdominal pain
  - Weight loss
  - Fecal WBC
- Epidemiologic
  - Food borne,
  - Recent antibiotics
  - Travel
  - Common source
  - Seasonal factors

Infectious Pathogens

**Viral**
- Norovirus
- Rotavirus
- Others “flu like”

**Parasites**
- Giardia
- E. Histolytica
- Cryptosporidium
- Isospora, cyclospora,

**Bacterial**
- Salmonella
- Campylobacter
- Shigella
- E.Coli (O157:H7)
- C. Difficile
- Vibrio, Yersinia, Listeria
Common Epidemiologic Factors

- Norovirus – winter outbreaks in families, nursing homes, schools, cruise ships, ingestion undercooked shellfish
- Salmonella – foodborne outbreaks, community acquired
- Campylobacter – community acquired, uncooked poultry
- Shigella – community acquired, person to person
- Shiga toxin producing E. coli – foodborne, especially undercooked hamburger or raw sprouts
- C. difficile – Nosocomial spread, antibiotic use
- Yersinia – community acquired, foodborne
- Giardia – Day care, waterborne transmission, travel
- Cryptosporidium – waterborne, travel, immunocompromised
- E. coli (enteropathic, etc) – travel

Empirical Antibiotic Therapy

- Moderate to severe traveler’s diarrhea
- Febrile, community-acquired if invasive disease suspected
- Severe nosocomial diarrhea, pending results of C. difficile toxin assay
- Suspected Giardia

- 1-5 days Cipro, norfloxacin, or levofloxacin
- 1-5 days cipro, norfloxacin, or levofloxacin
- Stop offending antibiotics, metronidazole 500mg TID, vancomycin 125mg QID
- Metronidazole 500mg TID 10 days

33 yo with bloody diarrhea

33 yo male presents with 4 weeks of loose stools with blood. 1-3 stools daily. Denies abdominal pain, fever, weight loss, recent travel or prior history of bleeding.

PMH: no chronic medical conditions, no previous surgery
Medications: none
FHX: Mother and Father alive, no chronic medical problems 2 siblings healthy
Physical exam: Healthy male, VS wnl
HEENT: WNL
GI: Non tender, NABS, no organomegaly
Anoscopy: no hemorrhoids, erythematous mucosa

Inflammatory Bowel Disease

- Chronic relapsing inflammatory disorder of the gastrointestinal tract
- Ulcerative Colitis: primarily involves mucosal and submucosal layers of colon - involves rectum and extends proximally to involving all or part of colon
- Crohn’s: characterized by transmural inflammation, often discontinuous, may involve alimentary tract from mouth to anus
Epidemiology

- Reported in all regions of the world
- More common in developed countries - United States and Western Europe
- In US
  - Prevalence: ~ 1.3 million persons
  - Gender distribution:
    - Crohn’s – slight female predominance
    - UC – slight male predominance
    - Age distribution: bimodal

IBD – Family History

- 10-25% IBD patients have 1st degree relative with IBD
- Relatives of patients with UC / Crohn’s tend to get UC / Crohn’s
- 10% lifetime risk for siblings and offspring of patients with IBD

IBD - Pathogenesis

- Exact etiology is unknown
- Proposed mechanism:
  - Intestinal epithelial barrier is breached by genetic variation, ineffective response to injury, or external agents (NSAID)
  - Chronic intestinal inflammation stimulated by luminal bacteria
  - Activation of cell-mediated immune response with immune dysregulation

Clinical Presentation

- Ulcerative Colitis: abdominal pain, bloody diarrhea, occasional fever, weight loss, increased incidence of cancer, especially with pancolitis
- Crohn’s: abdominal pain (often RLQ), diarrhea (with or without blood) fever, weight loss, fistulae
  - Small bowel involvement - malabsorption of Vit B12, iron, folic acid, electrolytes, etc.
IBD - Lab Evaluation

- CBC, metabolic panel
- Elevated ESR, CRP
- Liver enzymes, albumin
- Stool – WBC’s, RBC’S
- Stool Cultures ova and parasites, bacterial, Clostridium Difficile

ULCERATIVE COLITIS

CROHN’S DISEASE

SP

T

U
Crohn’s – Strictures, Fistulæ

Extraintestinal Manifestations
- Arthropythy
- Dermatologic
- Liver
  - Peripheral migratory Arthropathy
  - Ankylosing spondylitis
  - Erythema nodosum
  - Pyoderma Gangrenosum
  - Hepatic steatosis
  - Primary Sclerosing Cholangitis

Treatment of IBD
- Aminosalicylates
- Corticosteroids/Budesonide
- Immunmodulators
- Antibiotics
- Anti-metabolites
- Biologic Modifiers
- Nutritional therapy

Factors Influencing Choice of Therapy
- Diagnosis- Crohn’s vs. UC
- Extent of disease
  - UC: proctitis vs left-sided colitis vs pancolitis
  - Crohn’s: colitis vs ileal vs small bowel
- Clinical Goal
  - Induction of remission vs maintenance
- Severity/ complications
  - Mild vs severe with or without complications
- Refractoriness
Probiotics

- Mechanism is tolerance restitution
  - Decreased TH-1, increased TH-2
  - Increase T suppressor cells
- Mesalamine 800mg tid vs *E. Coli* (O6:D5:H1)
  - 2 caps BID
- Gentamycin pre-treatment
- Remission: *E. Coli* 65%, mesalamine 75%
- Realpse: *E. Coli* 76%, mesalamine 73%
  - Rembaker Lancet, 1999

33 y.o. male Lab and Sigmoidoscopy results

CBC: WBC 7.2 normal differential, Hbg 14.2 mg/dl
ESR: 13
Stool culture: Negative bacterial pathogens, Ova and Parasites, and *C. Difficile* toxins
Sigmoidoscopy results: moderate inflammed friable mucosa to 20 cm, remaining mucosa to 65cm appeared normal. Biopsies at 10cm and 20 cm: mild active chronic proctitis. 30cm : normal mucosa.

33 y.o. with Ulcerative Proctitis

- Treatment Options
  - Oral aminosalicylates
  - Hydrocortisone enema
  - Rowasa enema
  - Oral corticosteroids
  - Immune modulators
  - Biologicals

Cancer Surveillance Recommendations

- Not recommended for distal proctitis
- Begin after 8-10 years for pancolitis
- Begin at 12-15 years for left-sided colitis
- Immediate in those with sclerosing cholangitis
- Surveillance interval q 1-3 years
- Biopsies taken every 10 cm and “suspicious areas”