Hepatitis, Peptic Ulcer Disease
And Other Gastrointestinal Problems

Brian Desmond, M.D.
March 25, 2013

HEPATITIS

Acute vs Chronic

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

• Viral Hepatitis B / C
• Alcohol
• Medications, herbs
• NAFLD, Hemochromatosis, Wilson’s disease, A1-AT deficiency, Passive congestion
• 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

Months after exposure
HEPATITIS A VACCINE

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

- HAVRIX and VAQTA Intramuscular vaccine - 2 dose schedule
- Twinrix Combination Hep A vaccine (pediatric dose) and Hep B (adult dose)
HEPATITIS B

- 350 million persons chronically infected globally
- 1 million deaths annually due to complications
- 1.25 million persons in the US chronically infected (5,000 deaths annually)
- 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td>neg</td>
<td>neg</td>
<td>pos</td>
</tr>
<tr>
<td><strong>Immune past HBV Infection</strong></td>
<td>neg</td>
<td>pos</td>
<td>pos</td>
</tr>
<tr>
<td><strong>Acute or chronic HBV infection</strong></td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td><strong>Resolved HBV infection</strong></td>
<td>neg</td>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td><strong>False positive core</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low level chronic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resolving acute infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</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

**Hepatitis B Vaccine Formulations**

- **Recombivax HB (Merck)**
  - 5 mcg/0.5 mL (pediatric)
  - 10 mcg/1 mL (adult)
  - 40 mcg/1 mL (dialysis)

- **Engerix-B (GSK)**
  - 10 mcg/0.5 mL (pediatric)
  - 20 mcg/1 mL (adult)
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, tattoos, 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
- ONE TIME UNIVERSAL SCREENING those born 1945 – 1965 ??
**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**

- Peglated interferon + ribavirin + telaprevir or boceprevir
- Oral combination Antiviral Therapy on the horizon
- Patient Education: ETOH abstinence
  - Sexual behavior
  - Toothbrush, razors, etc.
  - Hepatitis A, B vaccines

**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

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: Aminda mushrooms
- Medications: many

MEDICATIONS

- Acetaminophen
- Antibiotics
  – Ciprofloxin, Sulfa,
  Nitrofurantoin, Amoxicillin-clavulinic
  – Isoniazid
  – Ketoconazole,
  Fluconazole, Terbinatine
- Anticonvulsants
  – Phenytoin, Carbamazepine
- Statins
  – Simvastatin, Lovastatin,
  atorvastatin, Pravastatin, Rosuvastatin
- NSAID
- Anti-dysrhythmics
  – Amiodarone
Medications and Herbs

• Sulfonylureas
  – Glypizide, Glyburide
• Glitazones
  – Pioglitazone, Rosiglitazone
• Antiretrovirals
  – Protease inhibitors
  – Nucleoside analogues
• Niacin

Herbs

– Chaparral leaf
– Germander
– Alchemilla
– Senna
– Shark Cartilage
– Ma huang
– Ji bu huan
– Mistletoe
– Kava

METABOLIC HEPATITIS

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

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, “many tried, none have reached consensus” Gemfibrozil, Metformin, Thioglitzones, 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
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
**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

**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**

- PPI’s recommended first line
- PPI’s should be given 30-60 min ac once daily (except dexilant) Partial responders can increase PPI therapy to BID
- Avoid late meals (within 3 hours of bedtime), elevate head of bed
- Weight loss
- Other behaviors on an individual basis:
  - Reducing fat, chocolate, coffee, and peppermint intake
  - Avoiding irritants : onions, citrus,tomato-based foods
- Smoking cessation, alcohol cessation not recommended for GERD symptoms
Should one screen for Barrett’s?

Controversy Exists

ACG recommends screening for Barrett's
10%-15% of patients with GERD will have Barrett’s
The risk of esophageal adenocarcinoma is 30-40 x higher in patients with Barrett’s
Over 50 years old with GERD for more than 5 years. Surveillance every 2-3 years if no dysplasia detected on initial biopsies (likely to be extended with recent large studies on incidence of progression to cancer)

• CGA, AGAI do not recommend screening for Barrett’s
• Insufficient evidence that screening reduces the death rate from adenocarcinoma of the esophagus
• 0.12% - 0.13 % of pts with Barrett’s will develop cancer per year.
• Many or most patients diagnosed with adenocarcinoma of the esophagus or stomach cardia don’t have Barrett’s

Surgical Indications - GERD

• **Laposcopic Nissen Fundoplication**
• 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
**Dyspepsia**

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

- Risk factors for serious disease:
  - Age > 55 years
  - Dysphagia,
  - Odynophagia
  - Protracted vomiting
  - Anorexia/weight loss
  - Melena or anemia
  - Palpable mass

**PEPTIC ULCER DISEASE**

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

**TABLE 1**

**Differential Diagnosis of Dyspepsia**

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Approximate prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Functional&quot; dyspepsia</td>
<td>Up to 60 percent</td>
</tr>
<tr>
<td>Dyspepsia caused by structural or biochemical disease</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>15 to 25 percent</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>5 to 15 percent</td>
</tr>
<tr>
<td>Gastric or esophageal cancer</td>
<td>&lt; 2 percent</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Rare</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Carbohydrate malabsorption (lactose, sorbitol, fructose, mannitol)</td>
<td>Rare</td>
</tr>
<tr>
<td>Medications (see Table 4)</td>
<td>Rare</td>
</tr>
<tr>
<td>Infiltrative diseases of the stomach (Crohn's disease, sarcoidosis)</td>
<td>Rare</td>
</tr>
<tr>
<td>Metabolic disturbances (hypercalcemia, hyperkalemia)</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Ischemic bowel disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)</td>
<td>Rare</td>
</tr>
<tr>
<td>Intestinal parasites (Giardia, Strongyloides)</td>
<td>Rare</td>
</tr>
<tr>
<td>Abdominal cancer, especially pancreatic cancer</td>
<td>Rare</td>
</tr>
</tbody>
</table>
**H. Pylori**

- Test and treat strategy validated
- Strongly associated with duodenal ulcer
- Eradication decreases PUD recurrence
- Eradication not convincing in relieving symptoms in “non ulcer dyspepsia”
- Associated with development of gastric cancer
- Associated with “MALT Lymphoma”

**H. Pylori - Testing**

- **Non Endoscopic**
  - **Serologic test**: inexpensive, not specific for current infection, not recommended for confirmation of eradication.
  - **Urea Breath Test**: High sensitivity and specificity, useful for confirmation, at least 4 weeks post treatment, avoid PPI’s x 2 weeks
  - **Fecal antigen test**: High sensitivity and specificity, useful for confirmation 4-6 weeks post treatment, avoid PPI’s x 2 weeks

- **Endoscopic**
  - **Urease based -CLO test**: rapid, inexpensive. Same caution regarding PPI’s and antibiotics
  - **Histology**: good sensitivity and specificity
  - **Culture**: cumbersome, not widely available and relatively insensitive

**H. Pylori - Treatment**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Days</th>
<th>% Eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20mg BID</td>
<td>14 days</td>
<td>80-85</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>Lansoprazole 30mg BID</td>
<td>10-14 days</td>
<td>86</td>
</tr>
<tr>
<td>Metronidazole 500mg 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>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine 300mg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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**
- 3 or more non formed stools daily for < 14 days
- 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 levaquin
- 1-5 days cipro, norfloxacin, or levaquin
- Stop offending antibiotics, metronidazole 500mg TID, vancomycin 125mg QID
- Metronidazole 500mg TID 10 days
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
**Crohn’s – Strictures, Fistulae**

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

**Treatment of IBD 5-Aminosalicylates**
- **Sulfasalazine (Azulfidine)** 500mg QID
- **Mesalamine**
  - Asacol (400mg,800mg) 800mg TID
  - Pentasa (250mg,500mg) 1000mg QID
  - Lialda (1.2g delay release) 2.4-4.8g Daily
  - Apriso (0.375g Ext release) 1.5g daily
  - Rowasa (4g/60cc enema susp) 4gm PR QHS
  - Canasa (1000mg rectal suppository) 1g PR QHS
- **Balsalazide (Colazal 750mg)** 2.25g TID
- **Olsalazine (Dipentum 250mg)** 500mg BID
**Treatment of IBD**

**Immunomodulators**
- 6 metcaptopurine 50mg QD (1.5 mg/kg/d)
- Azathioprine (Imuran) 50mg (2.5mg/kg/d)
- Budesonide (3mg) 9mg daily for 8 weeks
- Methotrexate 25 mg weekly
- Prednisone 20-40 mg daily
- Anti Tumor Necrosis Factor Agents
  - Adalimumab (Humira) 160mg sq week 0, 80mg week 2, then 40 mg q 2 weeks
  - Certolizumab (Cimzia) 400mg sq 0,2,4 , then every 4 weeks
  - Infliximab (Remicade) 5mg/kg IV 0, 2, 6 then q 8 wks

**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

**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”