“Gastroenterology for Dummies” is a set of concise, practical guidelines and checklists for the management of common problems in gastroenterology and hepatology. The guidelines are not rigid and do not apply to all situations. They are intended to provide the clinician, especially trainees, easy access to basic information needed in day-to-day decision making and care.

Editor
William R. Brown, M.D.

Contributors to 2010-2011
Kevin Rufner, M.D.
Ariana Wallack, M.D.
Miranda Ku, M.D.
Hill Harris, M.D.
# TABLE OF CONTENTS

## ESOPHAGUS
- Gastroesophageal Reflux Disease (GERD)  
  - Indications for endoscopy in patients with GERD 6  
  - Endoscopic grading of GERD 6  
  - Barrett’s esophagus 6  
  - Gastroesophageal varices 8  
  - Factors that favor increased risk of bleeding 8  
  - Endoscopic screening for varices 8  
  - Gastric varices – classification 8  
  - Prophylaxis of variceal bleeding – EVL vs. beta blockers 8  
  - Octreotide in acute variceal hemorrhage 9  
  - Instructions for use of the Sengstaken-Blakemore tube 9  
  - Eosinophilic esophagitis 11

## STOMACH AND DUODENUM
- Peptic Ulcer Disease 12  
  - Predictors of risk of re-bleeding from a peptic ulcer 12  
  - IV proton pump inhibitors 12  
  - Erythromycin for emptying the stomach before endoscopy 12  
  - *Helicobacter pylori* 13  
  - Indications for checking fasting gastrin level 14  
  - Gastric Polyps 14

## SMALL INTESTINE AND COLON
- Irritable Bowel Syndrome 15  
  - Rome III criteria 16  
  - Recommended laboratory investigations in suspected IBS 16  
  - Drugs that may be useful in the treatment of IBS 17  
  - Dietary modifications 18  
  - Alarm signals 18  
- Diarrhea and Gas 19  
  - Acute diarrhea 19  
  - Fecal leukocytes in intestinal infections 22  
  - Travelers’ diarrhea 22  
  - Chronic diarrhea 22  
  - Stool osmolality in distinguishing osmotic from secretory diarrheas 23  
  - Celiac Sprue 24  
  - Sensitivity and specificity of serologic tests in celiac sprue 24  
  - Disorders associated with celiac sprue 25  
  - Causes of intestinal villous atrophy that may resemble celiac sprue 25
Considerations in failure to respond to a gluten-free diet or to deteriorate when on a gluten-free diet 25
Chronic Inflammatory Bowel Diseases 26
Treatment overview for Crohn’s disease 26
Monitoring of hematologic and liver markers in azathioprine treatment of Crohn’s disease 27
Managing azathioprine therapy with TPMT testing 28
5-aminosalicylic acid drugs and site of activity 28
Treatment overview for ulcerative colitis 29
Cyclosporine in severe ulcerative colitis 29
Inflammatory bowel disease drugs in pregnancy 29
C. difficile-induced Colitis-Treatment 30
Anal fissures 32
Ogilvie’s Syndrome 32
Colonic Neoplasms 33
Indications for colonoscopy and appropriate intervals 33
Amsterdam II criteria of HNPCC 34
Classification of colonic cancer 34
Dukes’ classification 34
American Joint Committee on Cancer (TNM classification) 35

PANCREAS
Conditions that predispose to acute pancreatitis 35
Acute non-gallstone pancreatitis 36
Examples of drug-induced pancreatitis 37
Sphincter of Oddi Dysfunction 38
Cystic Lesions of the Pancreas 39
Enzyme products for the treatment of chronic pancreatitis 40
Most common pancreatic endocrine tumors 40

HEPATOBILIARY
Evaluation of Abnormal Liver Function Tests 41
Algorithm for elevated AST/ALT 41
Algorithm for elevated alkaline phosphatase 42
Algorithm for elevated Bilirubin 42
Pearls in interpretation of Abnormal LFTs 43
Liver Biopsy 43
Use of liver biopsy in clinical practice 43
Complications of liver biopsy 43
Acute Liver Failure 44

Kings College criteria 44
Intensive care of acute liver failure 44
Liver Transplantation
  Initial transplant work-up
  Contraindications to liver transplantation
  Immunosuppressive therapy
  Complications of liver transplantation
Hepatitis B
  Interpretation of hepatitis B serologies
  Recommendations for treatment
  Comparison of treatment medications
Hepatitis C
  Considerations before treatment
  Algorithm for the management of chronic hepatitis C
  Evaluation of treatment
  Drug dosing and adjustment
  Use of GM-CSF during HCV treatment
  Use of erythropoietin during HCV treatment
Cirrhosis
  Child-Turcotte-Pugh and MELD scoring systems
  Hepatic Encephalopathy
  Hepatorenal Syndrome
  Hepatocellular Carcinoma
  Spontaneous Bacterial Peritonitis
Ascites and Peritonitis
  Algorithm for evaluation of ascites
  TIPS contraindications
Alcoholic Hepatitis
  Criteria for treatment
  Treatment options
  Etoh content of alcoholic beverages
NALFD and NASH
  Etiology of NAFLD/NASH
  Treatments
Hemochromatosis
  Diagnostic criteria
  Management and phlebotomy protocols
  Family screening
Wilson’s Disease
  Diagnostic tests
  Management and therapeutic options
Autoimmune Hepatitis
  Diagnostic criteria
  Indications for treatment
Liver Disease in Pregnancy
  Physiologic changes in LFTs during pregnancy
  Liver disorders stratified by gestational age
Drug-Induced Liver Disease 63
   A clinicopathologic classification of drug-induced liver disease 63
   Treatment of acetaminophen toxicity 64
   Alternative therapies implicated in hepatotoxicity 65
Evaluation of Liver Mass 66
   Radiographic findings of liver masses 66
   Algorithm for evaluation of liver mass 66
Pyogenic and Amoebic Liver Abscess 67

GENERAL 67
Guidelines for the Evaluation and Treatment of Osteoporosis/Osteomalacia in Gastrointestinal and Hepatobiliary Diseases
ESOPHAGUS

Gastroesophageal Reflux Disease (GERD)

- Indications for Endoscopy in Patients with GERD

  Warning signs: Dysphagia, weight loss, odynophagia, iron deficiency anemia, hematemesis, early satiety

  Extra-esophageal manifestations of GERD: Asthma, hoarseness, cough, choking, aspiration, sinus disease

  “Chronic” GERD: > 5 yrs or onset after age 50 (at risk for Barrett’s Esophagus, so called “Screening for Barrett’s”)

  Before consideration of surgical anti-reflux procedure

  Failure to respond to acid-suppression therapy in suspected GERD

- Endoscopic grading of GERD. The Los Angeles Grading Scheme.

  Grade A  One (or more) mucosal breaks no longer than 5 mm that do not extend between the tops of two mucosal folds.

  Grade B  One (or more) mucosal breaks more than 5 mm long that do not extend between the tops of two mucosal folds.

  Grade C  One (or more) mucosal breaks that is continuous between the tops of two or more mucosal folds but involve <75% of the esophageal circumference.

  Grade D  One (or more) mucosal breaks that involve at least 75% of the esophageal circumference.

- Barrett’s esophagus

  Categories

  a) Inlet patch Barrett’s: proximal esophageal patch of mucosa, usually located below the crycopharyngeus muscle.

  b) Short-segment Barrett’s: circumferential or “tongue” less than 2-3 cm in length

  c) Long-Segment Barrett’s: >2-3 cm in length
### Gastroenterology societies’ recommendations for endoscopic screening and surveillance

<table>
<thead>
<tr>
<th>Disease State</th>
<th>ASGE</th>
<th>ACG</th>
<th>AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Patients with frequent, longstanding GERD (&gt;5 yr, especially men &gt;50 yr.)</td>
<td>Patients with chronic GERD symptoms</td>
<td>Screening not recommended because of lack of evidence</td>
</tr>
<tr>
<td>No dysplasia</td>
<td>Repeat at 1 year to confirm no dysplasia, then every 3-5 years</td>
<td>Repeat endoscopy to confirm no dysplasia, then every 3 years</td>
<td>Repeat at 1 year to confirm no dysplasia, then every 5 years</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>Repeat at 6 mo. If LGD confirmed, yearly as long as dysplasia persists</td>
<td>Repeat endoscopy yearly until no dysplasia found on 2 successive biopsies</td>
<td>Repeat EGD twice within first year. If LGD persists, EGD yearly</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>Confirm histology, repeat endoscopy to exclude cancer, then consider ablative therapy, esophagectomy, or intensive surveillance every 3 months, depending on individual situation</td>
<td>Confirm histology and repeat endoscopy to exclude cancer; if HGD present, surveillance biopsies at 3 mo intervals or intervention based on results and patient’s status</td>
<td>Confirm histology; repeat endoscopy to exclude cancer; consider patient status, expertise of surgeons and gastroenterologists, focality of dysplasia; consider intensive surveillance (q 3 m first 2 yrs, then q 6 m indefinitely), ablation or esophagectomy</td>
</tr>
</tbody>
</table>

### Surveillance technique

4-quadrant biopsy specimens every 2 cm throughout the involved esophagus (every 1 cm for high-grade dysplasia). “Jumbo” forceps and “twist and suck” technique preferred.
Gastroesophageal Varices

- Factors that favor increased risk of bleeding from esophageal varices
  - Large varices
  - Advanced Child-Pugh class
  - Red wale markings
  *With these conditions present, the risk of bleeding within two years is about 30-60%

- Endoscopic screening for varices

  **Who should be screened?**
  All newly diagnosed cirrhotics and all other cirrhotics who are medically stable, willing to be treated prophylactically, and would benefit from medical or endoscopic therapies.

- Gastric varices--classification
  - Type 1 (GOV1). Extend from esophageal varices to lesser curvature. Should be treated like esophageal varices (ligation)
  - Type 2 (GOV2). Extend from esophageal varices to the fundus
  - Isolated type 1 (IGV1). Located in the fundus
  - Isolated type 2 (IGV2). Located in a part of the stomach other than the fundus

- Prophylaxis of variceal bleeding

  **AASLD guidelines for prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis**

  - For patients with cirrhosis and no varices, β blockers not recommended
  - If no varices seen on EGD repeat in 2-3 years
  - If small varices seen, repeat every 1-2 years

---

**Primary prophylaxis--patients who have not bled**

<table>
<thead>
<tr>
<th>Criteria for increased bleeding present*</th>
<th>Criteria not present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small varices</td>
<td>Non-selective β blocker</td>
</tr>
<tr>
<td>Medium-large varices (&gt;5 mm)</td>
<td>β-blocker or ligation**</td>
</tr>
</tbody>
</table>
Secondary prophylaxis—patients who have recovered from a bleed
Combination of β-blocker and ligation is best option. Consider TIPS in Child A/B cirrhotics

*Child B/C or red wale marks on varices

**Repeat ligation: 1-2 weeks until obliteration; first surveillance 1-3 months after obliteration, then every 6-12 months to check for recurrence

- **Octreotide and antibiotics in acute variceal hemorrhage**
  
  Octreotide: 50 μg IV bolus followed by 50-100 μg/hr continuous infusion for 72 hr
  Antibiotics: Fluoroquinolone (400 mg bid orally) or ceftriaxone (1 g /day IV) for 7 days

- **Instructions for use of the Sengstaken-Blakemore tube**

  1. **Insertion and maintenance of the tube**

    a. If possible, have the patient intubated and on mechanical respiration (passage of the tube often is painful, aspiration is a definite risk during passage of the tube and after, and variceal bleeder patients often are agitated and difficult to sedate). If the patient is not on the ventilator, position him/her on the left side.

    b. If the S-B tube does not have an esophageal aspiration port (so-called Minnesota modification), attach a nasogastric tube to the S-B tube with sutures--distal end just above the proximal end of the esophageal balloon.

    c. Test the integrity of the esophageal balloon and gastric balloon by inflating them and placing them under water. (Inflate the gastric balloon with about 500 ml.)

    d. Deflate the balloons.

    e. Lubricate the balloons well.

    f. If the S-B tube is to be passed nasally, anesthetize the nostril and oropharynx with topical agent; if it is to be passed orally, anesthetize the oropharynx and insert a bite block or oral airway. A Savary guidewire can be placed through the tube to stiffen it in order to ease passage if needed.
g. Insert the tube through the nostril or mouth to at least the 50 cm mark. Inject air through the gastric suction port and auscultate over the stomach (for presumptive evident that the tube has been properly inserted).

h. Irrigate the gastric suction port well and attach to suction.

i. Connect the esophageal suction port (or the attached N-G tube) to suction.

j. Inflate the gastric balloon with 50 ml increments of air (total of 250-300ml) and withdraw until resistance is encountered. Obtain and personally review STAT chest X-ray film (include upper abdomen), to assure proper position of the tube and balloon.

k. Secure the tube by taping it to the face guard of a football helmet or to a triangle of tongue blades placed about the mouth (Denver Health method). Use of a pulley-weight system traction on the tube is discouraged because if the gastric balloon should deflate, the esophageal balloon (if inflated) could be pulled up and obstruct the airway.

l. If bleeding seems to stop after inflation of the gastric balloon, do not inflate the esophageal balloon. (Bleeding from esophageal varices often stops when the gastric balloon only is inflated since gastric varices are “fed from below”.) If esophageal bleeding continues (as indicated by continual aspiration of blood through the esophageal aspiration port), inflate the esophageal balloon to 30-45 mm Hg. Monitor the pressure in the esophageal balloon by attaching its port to a sphygmomanometer; check pressure every 30-60 minutes. It may be advisable to deflate the esophageal balloon for 5 minutes every 6 hours.

Removal of the tube

Do not leave either the gastric or the esophageal balloon continually inflated for more than 24 hours! (Necrosis and rupture of the esophagus or gastroesophageal junction are serious risks.) If bleeding has apparently stopped, deflate the balloon(s) and observe. If bleeding recurs, re-inflate the balloon(s) or initiate other measures for control of the bleeding.
Eosinophilic Esophagitis

- Endoscopic findings:
  1. Longitudinal furrowing, “trachealization” (concentric rings), white plaques or exudates (eosinophilic abscesses)

- Histology:
  1. 15> eosinophils/hpf in proximal as well as distal esophagus

- Treatment:
  1. Trial of one month PPI bid initially is recommended by some
  2. Food elimination diets may be useful
  3. Fluticasone 220 ug, two puffs bid swallowed, is commonly used
  4. Oral viscous budesonide has been used successfully
STOMACH AND DUODENUM

Peptic Ulcer Disease

- Predictors of risk of re-bleeding from a peptic ulcer

<table>
<thead>
<tr>
<th>Finding</th>
<th>Rate of re-bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spurting vessel</td>
<td>90</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>50</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>25</td>
</tr>
<tr>
<td>Red dot base</td>
<td>10</td>
</tr>
<tr>
<td>Clear ulcer base</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

- IV proton pump inhibitors

1. If active bleeding is evident or suspected, give IV esomeprazole or pantoprazole 80 mg bolus, then 8 mg/hr.

- Erythromycin for emptying the stomach before endoscopy in upper GI bleeding

1. Some advocate giving 250 mg in 50 mL NS over 5 min, then endoscope after 20 min.
2. Others advocate giving 3 mg/kg IV over 20-30 min, then endoscope after about one hour, because of concern that more rapid infusion may cause phlebitis.

*Since there usually is a considerable delay in getting the erythromycin from pharmacies, it should be ordered *STAT* as soon as one believes an upper GI bleeder will have be endoscoped. Tell the team to hold at bedside until you instruct them to give it. Once you decide patient needs EGD, give the erythromycin.*
- *Helicobacter pylori*

1. Diagnostic tests for *H. pylori*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>88-99</td>
<td>86-95</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>90-97</td>
<td>90-100</td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid urease assay</td>
<td>89-98</td>
<td>93-98</td>
</tr>
<tr>
<td>Histology</td>
<td>93-99</td>
<td>95-99</td>
</tr>
<tr>
<td>Culture</td>
<td>77-92</td>
<td>100</td>
</tr>
</tbody>
</table>

2. Treatment regimens for *H. Pylori eradication*

- **First Line—Triple Therapy (10-14 days)**
  - PPI BID
  - Amoxicillin 1000 mg BID (metronidazole 500 BID if patient is penicillin allergic)
  - Clarithromycin 500mg BID

- **First Line—Quadruple Therapy (14 days)**
  - PPI BID
  - Bismuth subsalicylate (Pepto-Bismol) 2 tabs QID
  - Metronidazole 500 mg TID
  - Tetracycline 500 mg TID

  Note: Some evidence indicates that adding bismuth to triple therapy increases its effectiveness.

- **Sequential Therapy (may increase effectiveness, but not proven)**
  - First five days: PPI BID plus amoxicillin 1 g BID
  - Next five days: PPI BID plus clarithromycin 500 mg BID and metronidazole 500 mg tid

- **“Salvage” Therapy**
  - PPI BID plus
  - Amoxicillin 1 g BID plus either
    - Levofoxacin 500 mg/day (10 days)
    - or
    - Rifabutin 300 mg/day (10 days)
    - or
    - Furazolidone 200-400 mg/day (10 days)
3. **Documentation of *H. pylori* eradication**

It is advisable to document that treatment for *H. pylori* infection has eradicated the bacteria. Stool antigen testing, urea breath test or rapid urea assay may be used. **Important**: These tests should not be performed sooner than four weeks after the cessation of antibiotic treatment and not sooner than one-two weeks after the cessation of proton pump inhibitor treatment.

**Important**: Failed therapy in an ulcer patient almost always leads to recurrence of the ulcer. In patients who have had a bleeding or perforated ulcer, eradication of *H. pylori* must be documented before H2 blockers or PPI are discontinued.

- **Indications for checking fasting gastrin level.** (PPI should be discontinued for at least 1 wk, and atrophic gastritis should be excluded, as in both these circumstances, hypergastrinemia may be the results of gastric hypochlorhydria.)
  - Multiple duodenal or gastric ulcers
  - Recurrent or non-responsive-to-treatment ulcers
  - Hypercalcemia (evaluation for MEN1; 25% of gastrinoma patients have MEN1)
  - Strong family history of peptic ulcer disease
  - Family history of endocrine tumors
  - Postoperative recurrence of peptic ulcer
  - Before elective ulcer surgery
  - Chronic unexplained diarrhea of secretory type

### Gastric Polyps

<table>
<thead>
<tr>
<th>Type</th>
<th>Prevalence (of polyps)</th>
<th>Location</th>
<th>Pathology</th>
<th>Malignant Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic</td>
<td>70 – 90%</td>
<td>Mostly antrum</td>
<td>Associated w/ <em>H. pylori</em>, atrophic gastritis. Polyp should be removed completely. Sample surrounding gastric tissue to eval for <em>H. pylori</em> infection.</td>
<td>0.6 – 4.5%</td>
</tr>
<tr>
<td>Fundic Gland</td>
<td>13-77%</td>
<td>Fundus, upper body</td>
<td>Highly assoc w/ PPI use but not w/ <em>H. pylori</em> infection. If multiple FGPs present in young patient consider FAP.</td>
<td>Low risk without FAP. If present with FAP, 30-50% risk.</td>
</tr>
<tr>
<td>Adenoma</td>
<td>0.5-3.75% Western countries; 9-27% China, Japan</td>
<td>Usually antrum</td>
<td>Premalignant. Assoc w/ chronic atrophic, metaplastic gastritis. Polyp should be completely excised. If &gt;2 cm, 50% contain adenoca.* May be sporadic or with FAP.</td>
<td>Higher risk with larger size; up to 50% if &gt;2 cm.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Peutz-Jeghers (Hamartoma)</td>
<td>&lt;1%</td>
<td>Random</td>
<td>Generally no risk of surrounding gastritis.</td>
<td>Minimal – none.</td>
</tr>
</tbody>
</table>

* Excise by multiple forceps biopsies if <5 mm, by snare polypectomy if >5 mm. Biopsy the surrounding mucosa for metaplasia. Endoscopic surveillance: one year. If no recurrence, then every 3-5 years; more frequently if polyp is atypical histologically or if surrounding metaplasia is present. Strongly consider colonoscopy to evaluate for colonic polyps.

**SMALL INTESTINE AND COLON**

**Irritable Bowel Syndrome**

- **Definition:** Abdominal discomfort or pain associated with a change in bowel habits for at least 3 months (in the absence of any organic cause).

- **Epidemiology:** 1 in 5 US adults, women>men, <50 yrs old, lower SES groups.

- **Symptoms:**
  1. *Abdominal pain*
     a. Bloating or feeling of abdominal distention
     b. Crampy, variable intensity, periodic exacerbations
     c. Exacerbated by physiologic stress
     d. Alleviated by flatus/BM
  2. *Stool alterations*
     a. Diarrhea
        frequent loose stools, small to large volume
        usually occurs in morning and after meals
        most preceded by urgency, cramping
        associated with fecal incontinence, feeling of lack of complete evacuation
     b. Constipation
        - hard, pellet-shaped stools
        - interludes of normal BMs or diarrhea
c. **Other GI symptoms**

d. GERD, dyspepsia, non-cardiac chest pain, nausea, dysphagia, early satiety

3. **Extraintestinal symptoms**
   a. sexual dysfunction, dysmenorrhea, dyspareunia, urinary frequency/urgency, fibromyalgia

- **Updated Rome III Criteria 2006 (Not validated)**
  1. Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following (3,3,2):
     a. Improvement with defecation
     b. Onset associated with a change in frequency of stool
     c. Onset associated with a change in form (appearance) of stool

- **Supportive symptoms not part of ROME III:**
  1. Abnormal stool passage (straining, urgency, feeling of incomplete evacuation)
  2. Passage of mucus

- **Three general patterns exist:**
  1. diarrhea-predominant (diarrhea 25%, constipation <5%)
  2. constipation-predominant (constipation >25%, diarrhea <25%)
  3. mixed (diarrhea >25%, constipation >25%).

- **Recommended investigations in patients suspected of having IBS**
  1. All patients:
     a. CBC, chem 7, ESR
  2. Patients with persistent or severe diarrhea:
     a. stool cultures, *C. difficile* toxin, ova and parasites
     b. anti-tissue transglutaminase IgA antibody
     c. malabsorption screen (fecal fat, serum B12, red cell folate, plasma ferritin)
     d. 24-hr stool volume for stool osmolality and electrolytes
     e. fecal fat and laxative screen
     f. colonoscopy w/ biopsy for microscopic colitis (age-appropriate) and inspection of distal terminal ileum
     g. EGD w/ duodenal biopsies for celiac disease if malabsorptive features
     d. sTSH
  3. Patients with constipation, severe rectal urgency or fecal incontinence:
     a. colonoscopy (if >50)
     b. colonic transit study using Sitz marker technique or Smart pill
     c. anorectal function tests, e.g., manometry or motility w/ balloon expulsion
     d. endoanal ultrasonography
e. defecography (to evaluate for enterocele or rectocele)
f. look for responsible medications (opiates, calcium-channel blockers, anticholenergics)

4. Patients with pain–predominant symptoms:
   a. abdominal films
   b. amylase, liver tests if suspect pancreatic/biliary disease
   c. CT (low yield if no alarm symptoms)

5. *Summary of recommendations by American College of Gastroenterology Task Force on IBS:
   a. Do not check TSH in the absence of alarm features
   b. Do not check stool O&P in the absence of alarm features
   c. Do not check abdominal imaging in the absence of alarm features
   d. Do perform serological screen for celiac disease in IBS-D and IBS-M patients
   e. Do not perform lactose tolerance test. Just ask about association between lactose ingestion and IBS symptoms.
   f. Do not perform breath testing for small intestinal bacterial overgrowth
   g. Do perform abdominal imaging in any patient over age 50 to screen for colorectal cancer

- **Drugs that may be useful in the treatment of IBS**
  1. *Antispasmodics* (not convincing evidence supporting their efficacy yet per the AGA, but often used first-line)
     a. Anticholenergics:
        a. Dicyclomine hydrochloride (Bentyl) 10-20 mg tid before meals and qhs
        b. Hyoscyamine (Levsin) 0.125-0.25 mg qid
  2. *Antidiarrheal agents*
     a. Loperamide hydrochloride (Imodium) 2-8 mg/day in divided doses*
     b. Diphenoxylate hydrochloride (Lomotil) 2-6 pills/day
     c. Cholestyramine 1-3 packets/day, 30 min a.c.
        *Only loperamide has been studied, in several small RCTs
  3. *Dietary fiber*
     a. Benefiber (less gas-producing), Citrucel, Metamucil
     b. Gradually titrate upward to avoid excessive gas, bloating, distention
     c. Very little benefit over placebo
4. **Probiotics**
   a. Lactobacilli alone not effective
   b. Bifidobacteria alone or combinations of probiotics has some efficacy
   c. VSL #3 may be effective

5. **Antibiotics**
   a. Rifaximin 400 mg tid x 10-14 days. Improves bloating and global symptoms

6. **Laxatives**
   a. Osmotic laxatives (magnesium citrate or sodium phosphate)
   b. Hyperosmotic laxative (polyethylene glycol [Miralax] 17-34 g daily)
   c. Stimulant laxatives (bisacodyl, senna). Increase intestinal motor activity but may lead to hypokalemia, protein-losing enteropathy, salt overload. (Avoid regular use of stimulant laxatives.)

7. **Selective C-2 chloride channel activator**
   a. Lubiprostone (Amitiza) 8-24 µg bid

8. **Antidepressants**
   a. TCAs have more supportive evidence than SSRIs/SNRIs and are shown to improve abdominal pain. TCAs often cause constipation so are best suited for diarrhea-predominant IBS. SSRIs/SNRIs ok for either type.
   b. Imipramine hydrochloride (Tofranil) 10-100 mg qhs
   c. Desipramine (Norpramin) 50-100mg qhs
   d. Amitryptyline hydrochloride (Elavil) 25-75 mg qhs
   e. Nortriptyline hydrochloride (Pamelor) 25-75mg qhs

- **Dietary Modification (not proven to reduce IBS symptoms):**
  1. Eliminate foods that can exacerbate symptoms, e.g., coffee, chocolate, dairy products and sugar substitutes (or others if determined from exclusion diet and food diary). In mild constipation-predominant IBS consider a trial of fiber and/or osmotic laxative. Evaluate for lactose intolerance. If excessive gas/bloating present, advise against carbonated beverages, beans, gum chewing, excess fats. Avoid fructose-containing foods and drinks (high-fructose corn syrup).

- **Alarm symptoms and signs:** hematochezia, weight loss greater than 10 pounds, family history of colonic cancer, recurring fever, anemia, nocturnal awakenings due to symptoms, and chronic, severe diarrhea. Progressive symptoms and onset of symptoms after age 50 also suggest an organic disease.
**Diarrhea**

**Definition:** Loose or watery stools, increased stool frequency (normal is <3/d and >1 q 3 d), or excessive volume of stool. Normal stool volume <200 g/day.

- **Acute Diarrhea (<2wks)**
  1. Often due to viruses, bacteria, protozoa, food poisoning, or drugs.
  2. Evaluation indicated in the following:
     a. Profuse watery diarrhea with signs of hypovolemia
     b. Passage of many small-volume stools containing blood/mucus
     c. Bloody diarrhea
     d. Temperature ≥38.5°C (101.3°F)
     e. Passage of ≥6 unformed stools per 24 hours or a duration >48 hours
     f. Severe abdominal pain
     g. Recent use of antibiotics or in hospitalized patients
     h. ≥70 years, immunocompromised
     i. Systemic illness + diarrhea, especially in pregnancy

3. **Major causes:**
   a. Non inflammatory
      - Viral disease (rotavirus, Norwalk virus, cytomegalovirus, herpes simplex virus). Most common cause of acute infectious gastroenteritis.
      - Bacterial toxin-mediated disease (Nontyphoidal Salmonella, *S. aureus*, *Bacillus cereus*, *Clostridium perfringens*, *Listeria monocytogenese*)
      - Protozoal disease (*Giardia lamblia*, *Cryptosporidium*)
      - Medication-induced
        - Mg antacids, antibiotics, laxatives, colchicine, lactulose, metformin
      - Dietary intolerance
      - Disaccharidase deficiency
   
   b. Inflammatory, typically bloody
      - Most common cause: *E. coli* O157:H7
      - Invasive bacterial disease (Shigella, Salmonella, Campylobacter, Yersina, Vibrio, *C. Difficile*, Enterohemorrhagic E. Coli O157)
      - Protozoal disease (*Entamoeba histolytica*, *Strongyloides stercoralis*)
      - Mesenteric ischemia
      - Radiation colitis
      - Inflammatory bowel disease
<table>
<thead>
<tr>
<th>Symptom characteristic</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset within 6 hours</td>
<td><em>S. aureus, Bacillus cereus</em> (preformed toxin)</td>
</tr>
<tr>
<td>Onset between 8-16 hours</td>
<td><em>Clostridium perfringens</em></td>
</tr>
<tr>
<td>Onset after 16 hours</td>
<td>Viral or bacterial</td>
</tr>
<tr>
<td>Associated with fever, headache, myalgias, stiff neck</td>
<td><em>Listeria monocytogenes</em> (especially in pregnant women)</td>
</tr>
<tr>
<td>Recent antibiotics use, hospitalization, nursing home</td>
<td><em>Clostridium difficile</em></td>
</tr>
</tbody>
</table>

- **Diagnosis**
  1. Stool studies
     a. Occult blood
     b. Leukocytes (sensitivity 70%, specificity 50% in predicting inflammatory diarrhea)
     c. Lactoferrin latex agglutination assay - marker for fecal leukocytes, not widely available (sensitivity 90-100%, specificity 90-100%)
     d. Culture (*Salmonella, Shigella, Campylobacter*) – should be obtained in the following patients:
        - Immunocompromised
        - Serious comorbidities
        - Severe, inflammatory (bloody) diarrhea
        - Underlying inflammatory bowel disease
        - Food handlers
     e. Ova and parasites – should be obtained in the following patients:
        - Persistent diarrhea – *Giardia, Cryptosporidium, Entamoeba histolytica*
        - Persistent diarrhea with history of exposure to infants in daycare – *Giardia, Cryptosporidium*
        - Diarrhea in men who have sex with men or AIDS patients (*Giardia, Entamoeba, Isospora belli, Microsporidia, Cryptosporidium, MAC*)
        - Community waterborne outbreak (*Giardia, Cryptosporidium*)
        - Blood diarrhea without fecal leukocytes (intestinal amebiasis)
        - Send on consecutive days as O&P shed intermittently
  2. Endoscopy – may assist in the following scenarios:
     a. Distinguishing IBD from infectious colitis
     b. Diagnosing *C. diff* colitis and documenting presence of pseudomembranes in toxic patients while awaiting *C. diff* toxin assays
     c. Immunocompromised patients to rule out CMV colitis
     d. Rule out ischemic colitis if CT is non-diagnostic
• Treatment
  1. Oral rehydration – water, salt, sugar
  2. **Empiric antibiotic therapy**
     a. May result in shortened duration of illness, particularly in severely ill patients
     b. Fluoroquinolones less helpful in eradicating Salmonella infection
     c. Avoid use in enterohemorrhagic *E. coli* (EHEC) infection suspected due to risk of hemolytic-uremic syndrome (HUS). EHEC infection characterized by bloody diarrhea, abdominal pain, absence of fever.
     d. *C. difficile* – based on clinical history. Treat with metronidazole, vancomycin or rifaximin
     e. *Listeria monocytogenes* – Ampicillin/gentamicin versus Bactrim
     f. Indications to treat:
        Moderate to severe travelers’ diarrhea with > 4 stools/day + fever, blood/pus/mucus in stools
        Immunocompromised, elderly individuals
        >8 stools/day, signs/symptoms of dehydration, symptoms >1 week, likely need for hospitalization
     g. Specific antibiotic therapy:
        Ciprofloxacin 500mg PO BID, Norfloxacin 400mg PO BID, Levofloxacin 500mg PO QD, Rifaximin 200mg PO TID x 3-5 days, Azithromycin 1g (single dose), Erythromycin 500mg PO BID x 5d
  3. Symptomatic therapy
     a. Loperamide (Imodium)*
        Low grade or no fever, no bloody stools
        Two tabs (4 mg) for first dose, 2 mg per loose stool thereafter, not to exceed 16 mg/day x ≤2 days
     b. Diphenoxylate (Lomotil)
        2 tabs (4 mg) PO QID x ≤2 days
     c. Bismuth salicylate (Pepto-Bismol)
        30 ml (2 tabs) PO q 30 minutes x 8 doses max/day
        Not as good as loperamide in head-to-head trials, but may be used if dysentery suspected (where loperamide can’t be used)
  4. Probiotics
     a. Useful in travelers’ diarrhea only
  5. Dietary recommendations
     a. Avoid dairy products (lactose malabsorption may develop post-infection and last for several weeks)
     b. Boiled starches and cereals, bananas, boiled vegetables, crackers, soup
• Fecal leukocytes in intestinal infections
  1. Present: Shigella, Campylobacter, Enteroinvasive/Enterohemorrhagic E. coli
  2. Variable: Salmonella, Yersinia, V. parahaemolyticus, C. difficile, Aeromonas
  3. Absent: V. cholerae, Enterotoxigenic/Enteropathogenic E. coli, Rotavirus, Norwalk virus, Giardia lamblia, Entamoeba histolytica, Staphylococcus aureus, Clostridium perfringens, Bacillus cereus

• Travelers’ diarrhea
  1. Up to 50% of travelers to developing countries affected within first 2 weeks. 10-20% of travelers have onset of diarrhea after returning home.
  2. Travelers’ diarrhea may be an important etiologic feature in the development of IBS.
  3. Common etiologies include: Shigella, Salmonella, Yersinia, E. coli, S. aureus, Bacillus cereus, C. difficile, Listeria, Rotavirus, Norwalk virus, Giardia and Entamoeba histolytica.
  4. Prophylaxis
     a. Bismuth subsalicylate (2 tabs ac and qhs [8 tabs daily])
     b. Ciprofloxacin 500 mg QD, norfloxacin 400 mg QD, or ofloxacin 300 mg PO QD, rifaximin 200 mg QD

• Treatment of dysentery
  1. Loperamide or bismuth subsalicylate plus azithromycin 500 mg PO QD, or
  2. Fluoroquinolone (ciprofloxacin 500 PO BID, levofloxacin 500 mg PO QD, or norfloxacin 400 mg PO BID), or
  3. Rifaximin 200 mg PO TID, for 3-5 days

• Chronic Diarrhea (>4 wks)
  1. Often due to IBS, IBD, malabsorption or parasitic infection. Also consider laxative abuse, cancer, alcohol, endocrine abnormalities, neuroendocrine tumors, food allergy and medications.
  2. Initial Evaluation of Chronic Diarrhea:
     a. Send stool specimen for fecal leukocytes, occult blood, sudan stain, O and P, electrolytes, and pH (<5.3 suggests carbohydrate malabsorption), laxative screen.
     b. Consider 72-hr collection for stool weight and quantitative fat. Normal daily stool fat is <7g/day on 100g/day diet.
     c. CBC, ESR, TSH
     d. Review the medication list
e. If above unrevealing and diarrhea significant and or alarm symptoms (weight loss, positive occult blood, increased age) proceed to colonoscopy. Biopsy to evaluate for microscopic colitis even if mucosa appears normal. Also consider EGD with small bowel biopsy to evaluate for celiac disease, intestinal lymphoma, Whipple’s disease or giardiasis.

f. Consider an empiric trial of metronidazole for treatment of possible small bowel bacterial overgrowth or giardiasis, or cholestyramine, for treatment of possible bile colt malabsorption.

3. **Selected Chronic Diarrhea States**:
   a. **Dumping Syndrome**: Occurs after gastrectomy and/or vagotomy when rapid emptying of hyperosmolar gastric content into the small bowel obligates large amounts of fluid and enteric neuropeptides to be secreted. Early dumping symptoms occur <30 min after eating (diarrhea, orthostasis, flushing, nausea, abdominal pain). Late dumping (hours after eating) is due to rapid carbohydrate emptying into the small bowel, with physiologic hyperinsulinemia and resulting hypoglycemia (anxiety, tremulousness, palpitations, diaphoresis).

b. **Ileostomy Diarrhea**: Typical stool output through an end ileostomy is 500 g. Large resections of the TI can result in malabsorption of B12, bile salts and various nutrients.

c. **Diabetic Diarrhea**: 20% of chronic diabetics have diarrhea. Usually other symptoms of autonomic neuropathy are present. Treatment options include clonidine, oxybutynin, cholestyramine, opiates and trial of antibiotics for possible small bowel bacterial overgrowth.

d. If suspect small bowel malabsorption of carbohydrates use the D-xylose test where D-xylose is ingested and then blood and urine collected 5 hr later. Decreased serum/urinary levels suggest intestinal malabsorption.

4. **Stool osmolality in distinguishing osmotic from secretory diarrheas**

   a. Fecal \((Na^+ + K^+) \times 2 = \) approximate stool osmolality (mOsm/Kg)
   b. 290 mOsm/Kg – calculated stool osmolality = fecal osmotic gap
   c. Gap < 50 usually is due to a secretory diarrhea, > 125 usually to an osmotic diarrhea.
   d. If stool osmolality is <290mOsm/kg than the stool has been diluted (by urine or water)

**Intestinal Gas**

Much of intestinal gas consists of CO₂, H₂ and methane produced by the fermentation of malabsorbed carbohydrates. Common gas-producing food are these:

<table>
<thead>
<tr>
<th>Food</th>
<th>Malabsorbed Carbohydrate</th>
</tr>
</thead>
</table>

23
Dairy products (milk, ice cream, cottage cheese, yogurt)  Lactose
Soft drinks (not “diet” drinks), honey  Fructose
Legumes (baked beans, soy beans)  Melitose, stachyose
Dietetic candies and chewing gum  Mannitol, sorbitol, xylitol

Celiac Sprue

- **Epidemiology:** 1 per 100-300 people in North America.

- **Clinical Presentation:** Episodic diarrhea, weight loss, malabsorption, anemia (most common presentation), flatulence, abdominal pain. Diarrhea present in only 50% and is malabsorptive. Lab abnormalities also may include macrocytic anemia (folic acid deficiency), coagulopathy (vitamin K deficiency), hypocalcemia or elevated alkaline phosphatase (vitamin D deficiency) and hypertransaminasemia. Enteropathy often results in lactose intolerance. Half of all cases present atypically or silently.

- **Diagnosis:**
  1. Histological changes (villous atrophy of small intestine and increased numbers of intraepithelial lymphocytes)
  2. Clinical/pathological changes gluten-dependent
  3. Serum tests are for screening only, not diagnosis

- **Endoscopic findings:**
  1. Normal, scalloped or ridged folds, smooth tubular surface

- **Histologic findings**
  1. Varying degrees of villous atrophy
  2. Increased intraepithelial lymphocytes
  3. Crypt hyperplasia
  4. More severe proximally (duodenum)
  5. Takes several months to improve once patient is on gluten-free diet
  6. Improve distally to proximally

- **Sensitivity and specificity of serologic tests in celiac sprue**

<table>
<thead>
<tr>
<th>Serum Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA tissue transglutaminase Ab**</td>
<td>90-98%</td>
<td>94-97%</td>
</tr>
<tr>
<td>IgA endomyosial Ab*</td>
<td>85-88%</td>
<td>97-100%</td>
</tr>
<tr>
<td>IgA anti-gliadin antibodies**</td>
<td>75-90%</td>
<td>82-95%</td>
</tr>
<tr>
<td>IgG anti-gliadin antibodies**</td>
<td>69-85%</td>
<td>79-90%</td>
</tr>
</tbody>
</table>

* wide variation in values from various laboratories
**may be normal in serum IgA deficiency
• Disorders associated with celiac sprue

Dermatitis herpetiformis
Insulin-dependent diabetes mellitus
Autoimmune thyroid disease
Sjogren’s disease
IgA deficiency
Epilepsy with cerebral calcification
Inflammatory bowel disease
Microscopic colitis

IgA mesangial nephropathy
Rheumatoid arthritis
Sarcoidosis
Down syndrome
Bird-fancier’s lung
Fibrosing alveolitis
Recurrent pericarditis
Idiopathic pulmonary hemosiderosis

• Causes of intestinal villous atrophy that may resemble celiac sprue

Post-gastroenteritis
Giardiasis (in the setting of hypogammaglobulinemia)
Tropical sprue
Whipple’s disease
Peptic duodenitis (including Zollinger-Ellison syndrome)
Crohn’s disease
Drug-induced enteritis (NSAIDs)

Small intestinal bacterial overgrowth
Eosinophilic enteritis
Radiation or cytotoxic chemotherapy
Severe malnutrition
Diffuse small intestinal lymphoma
Graft versus host disease
Hypogammaglobulinemia
Alpha chain disease

1. Treatment
   a. Gluten free diet: 70% of patients have symptomatic improvement within 2 wk. Adherence decreases the risk of disease-associated neoplasms (especially T-cell lymphoma).
   b. Avoid dairy products for 3-6 mo as patients often have secondary lactose intolerance.
   c. IV corticosteroids rarely are needed, for critically ill patients with acute celiac crisis.

2. Considerations in failure to respond to a gluten-free diet or to deteriorate when on a gluten-free diet
   a. Non-adherence to the gluten-free diet or inadvertent gluten ingestion (check anti-tissue transglutaminase IgA Antibody)
   b. Development of small intestinal lymphoma
   c. Refractory sprue (treat with corticosteroids, azathioprine/cyclosporine and/or TPN
   d. Collagenous sprue or collagenous colitis
   e. Unsuspected concurrent disease such as pancreatic insufficiency
   f. Development of diffuse intestinal ulceration (ulcerative jejunoileitis)
Chronic Inflammatory Bowel Diseases

- **Treatment Overview for Crohn’s Disease:**
  
  Four main considerations in deciding which therapies to initiate:
  
  1. **Classification of severity/extent of disease and potential for complications** (the following predict a more severe course: previous operations, penetrating disease, fistulizing disease, smoking history, multifocal and larger areas of small bowel involvement). Also, try to determine if symptoms are due to inflammatory activity as opposed to fibrostenotic areas.
  
  2. **Efficacy of therapy** (understanding that there is a high rate of placebo response [30%] in trials, possibly as a result of IBS symptom overlap)
  
  3. **Potential side effects of therapy** (infectious and malignant complications)
  
  4. **Is therapy being used for induction of remission or maintenance of remission?**

  a. For induction of remission in mild-to-moderate disease, three possibilities:
     
     - **Budesonide (Entecort)**- may be preferable in ileo-colonic disease, if colonic disease is limited to the right colon. Remember, budesonide is not a maintenance medication, even though its side-effect profile is more favorable than that of more systemic steroids.
     
     - **5-ASA drug**-(choice dependent on location of disease), but preferable in left-colonic disease. Can be used as a maintenance medication if patient has a response. Efficacy of these drugs, especially in small bowel disease, has been severely questioned in past decade.
     
     - **Antibiotics**- efficacy unclear but may be tried in mild to moderate colonic disease. Maintenance option with antibiotics is limited due to side effects.

  b. For induction of moderate-to-severe or severe-to-fulminant disease the two main therapies are:
     
     - A systemic steroid (either oral prednisone or parenteral Solumedrol) This choice usually depends on whether patient is hospitalized. The tapering of these steroids should be based on symptoms and not automatic. Steroids are not maintenance therapies.
     
     - **Anti-TNF therapy** (infliximab, adalimumab, certilizumab)- These therapies would typically be used in patients who are failing induction with steroids. Anti-TNF therapies can be used both for induction of remission and maintenance of remission. Check Tb and Hep B status prior to initiation.

  c. For maintenance of remission of mild-to-moderate disease the choices include:
- 5-ASA drug - Aminosalicylate therapy is safe and may be an effective maintenance strategy in patients who respond to it. However, whether this therapy is effective in the long-term is unknown, and there is no evidence that it changes the natural course of Crohn’s disease.
- Azathioprine or 6-MP - effectiveness in maintenance of remission is better established.
- For maintenance of remission in moderate-to-severe or severe-to-fulminant disease the options include: Azathioprine alone - Attempt to achieve a dose of 2.5 mg/kg, but dose can be increased, depending on white blood cell count. Typically the choice in patient who is naïve to immunomodulators.
- Anti-TNF therapy alone - Would be choice in patients who failed to maintain remission with azathioprine or in a patient who has a high risk of future complications. In the SONIC trial, anti-TNF therapy alone was more effective than azathioprine therapy alone in maintaining remission.
- Combination of anti-TNF therapy and azathioprine - In the SONIC trial, combination was more effective in maintaining remission than either therapy alone. Decision to use combination therapy must be weighed against the potential increase in infectious and malignant complications.

Perianal Fistula: Usually a combination of medical and surgical therapy is desirable. The best approach can be decided upon with the aid of MRI, endoscopic ultrasound or exam-under-anesthesia.
- Superficial fistula - Fistulotomy and short course of antibiotics. If this fails, then non-cutting seton with addition of immunomodulator or anti-TNF therapy.
- More complex fistula with or without abscess - Antibiotics, non-cutting seton and immunomodulator therapy or anti-TNF therapy. Patients with more complex perianal disease usually require maintenance with immunomodulator or anti-TNF therapy.

- **Step-down approach.** The early use of highly effective but potentially more toxic treatment strategies early in the course (biologics first for induction and or maintenance, then, after remission obtained, transition to immunomodulators or 5-ASA for maintenance.)
- **Step-up approach.** A sequential treatment strategy beginning with less toxic and, often, less effective treatments as first line (see above).
- **Suggested monitoring of hematologic and liver markers in azathioprine treatment of Crohn’s disease**
  1. Check CBC and LFTs before starting the drug, then:
     a. Check CBC weekly for one month, then monthly for the first year and quarterly thereafter.
b. Check LFTs after 1-2 months, then quarterly thereafter. Try to avoid the WBC going below 4000.

- **Managing azathioprine therapy with TPMT testing:**
  1. Azathioprine (Imuran) is a pro-drug, converted to 6-MP. Depending on the activity of the enzyme thiopurine methyltransferase (TPMT), 6-MP is metabolized to 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPN). Patients who have low or absent TPMT can shunt 6-MP to 6-TGN, which, at high levels, is associated with increased bone marrow toxicity (and increased efficacy). 6-TGN levels >235 are associated with therapeutic response. High 6-MMPN levels are associated with hepatotoxicity. Pancreatitis in 7% of patients treated with azathioprine is idiosyncratic.
  2. Pre-treatment TPMT genotyping:
     a. If low, avoid thiopurines
     b. If intermediate, use lower dose azathioprine, expecting full therapeutic response
     c. If normal, give full initial dose azathioprine.
     d. If high, higher dose azathioprine may be need to get a therapeutic response.
     e. (Metabolite testing does not replace lab monitoring for toxicity!)
  3. **Summary of management with TPMT testing**

     Step 1: Consider TPMT genetics testing (Pre-treatment). Genotypic analysis can predict a patient’s ability to metabolize thiopurine drugs and identify patients at increased risk for myelotoxicity. Knowing the TPMT genotype may decrease risk, allow tailored starting dose and shorten time to response.

     | TPMT genotype          | %   | Patients Interpretation          |
     |------------------------|-----|----------------------------------|
     | Homozygous (nml/increased) | 89% | Decreased risk, ?increase dose   |
     | Heterozygous (intermediate) | 11% | At risk, ?decrease dose          |
     | Homozygous (low/none)    | 0.3%| High risk, no treatment          |

     Step 2: Metabolite testing (during treatment)
     a. Can help guide dosing, check patient’s compliance, avoid overdosing.
     b. 6-TGN desired range: 230-400
     c. Lower level suggests underdosing or nonadherence, or preferential metabolism via an alternative pathway.
     d. Higher level may prompt concern for leukopenia.
     e. 6-MMPN desired range:<5700 may prompt concern for hepatotoxicity.

- **5-aminosalicylic acid drugs and site of activity**
### Treatment overview for ulcerative colitis

Often depends on the severity and site of the colitis.

1. **Proctitis**—limited to the rectum in 30% of patients. Start with 5-ASA suppository q hs until patient is in remission. If disease recurs leave on maintenance. For more severe disease add steroid foam.

2. **Left-sided colitis**—For mild-to-moderate disease start with 5-ASA enema +/- steroid enema. Add an oral 5-ASA drug for inadequate response. Oral prednisone or budesonide can be added for more severe disease.

3. **Pancolitis**—For mild-to-moderate disease start with a 5-ASA oral drug. Add prednisone for inadequate response or severe disease. For steroid-Refractory disease considers azathioprine or infliximab.

4. **Severe colitis**: Start with bowel rest, TPN and IV steroids. Add broad-spectrum antibiotics if no response or disease is fulminant (high fever, leukocytosis with left shift and/or megacolon). In severe disease unresponsive to IV steroids consider IV cyclosporine or anti-TNF therapy. Have a low threshold for colectomy.

### Cyclosporine use in severe ulcerative colitis

1. Start at 2-2.5 mg/kg/day IV, continue for 10-14 days (target blood level 250-300).

2. When patient’s condition is stable, convert to oral; conversion is usually double the IV dose.

### Inflammatory bowel disease drugs in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Use Category</th>
<th>Usual Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>B</td>
<td>Doses differ according to brand</td>
<td>Sulfasalazine and mesalamine can be used safely in oral and topical forms. (Only olsalazine is categorized as Class C).</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>B</td>
<td>Variable</td>
<td>Effective in inducing but not in</td>
</tr>
<tr>
<td>Drug</td>
<td>Classification</td>
<td>Dosage</td>
<td>Remarks</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Budesonide</td>
<td>C</td>
<td>9mg/d</td>
<td>Probably safe in ileocolonic Crohn’s disease but not controlled data available.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>5-10 mg/kg IV</td>
<td>Seems safe based on limited data.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>Weight-based IV</td>
<td>Justified in active disease refractory to other oral or topical agents. Can cause small-for-gestational-age births.</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>B</td>
<td>250-500 mg tid</td>
<td>Seems safe, but use is limited to 2d and 3d trimesters because of potential mutagenicity in the first trimester.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td></td>
<td>Contraindicated owing to teratogenicity.</td>
</tr>
</tbody>
</table>

**C. difficile-induced Colitis-Treatment**

- **Indications for treatment**
  1. Symptoms (diarrhea, abd pain, n/v) + positive diagnostic assay
  2. Symptoms + high clinical suspicion
  3. No treatment if asymptomatic but toxin assay (+)

- **Specific treatment**
  1. Antimicrobial agents (if symptoms are severe or persistent)
  2. Vancomycin and metronidazole are equally effective
  3. Vancomycin is preferred in pregnant patients
  4. No need to check stool toxin assay after treatment in order to ensure eradication as test may be positive up to 6 weeks
  5. If on antibiotics for treatment of other infections, continue *C. diff* treatment during course of other infection tx plus an additional 7 days

- **Oral agents:** (preferred)
  1. Vancomycin 125 mg PO qid x 14 days
  2. Metronidazole 500 mg PO tid x 14 days
  3. Rifaximin 400mg PO tid x 14 days

- **Parenteral agent:** (to be used only until oral agents are tolerated)
  1. Metronidazole 500 mg IV q8h
  2. No effect of IV vanc on bowel

- **Alternative treatments (only as adjunctive therapy in relapsing disease, not first-line treatment)**
  1. Anion-exchange resin: Cholestyramine 4-g packet PO tid x 5-10 days (can bind antibiotics, so should be given 2-3 hours after antibiotics)
2. Alter fecal flora: Lactinex (Lactobacillus): 1-g packet PO qid x 7-14 days
3. IV gamma globulin
4. Fecal bacteriotherapy

- Treatment of recurrences
  1. Need to distinguish recurrence/relapse from reinfection with same or different C. diff strain
  2. Initial recurrence/relapse: Occurs in 10-25% of patients. Confirm diagnosis with stool toxin assay. Withhold antibiotics if symptoms are mild.
  3. 14-day course of metronidazole 500 mg tid or vancomycin 250 qid or rifaximin 400mg tid
  4. Second recurrence
     a. Tapered-pulsed vancomycin
        ▪ 125 mg qid for 1 week
        ▪ 125 mg bid for 1 week
        ▪ 125 mg qd for 1 week
        ▪ 125 mg qod for 1 week
        ▪ 125 mg Q3 days for 2 weeks
     b. Intermittent antibiotics
  5. Third of subsequent recurrence: Tapered-pulsed vancomycin Plus Saccharomyces boulardii (Florastor) 500 mg (2 X 250 mg caps) bid or cholestyramine 4 g bid or IV gamma globulin IG (400mg/kg-2 doses 1 week apart)

- Severe C.diff associated colitis
  1. IV antibiotics, supportive care, hospitalization
  2. Oral vancomycin 500mg po qid plus IV flagyl 500mg tid
  3. Surgery
     a. For toxic megacolon, perforation or impending perforation, necrotizing colitis, worsening/refractory septicemia
     b. Subtotal colectomy with ileostomy
     c. Consider early surgery if: age >65, WBC >20,000, elevated lactate
Anal Fissures

- **Characteristics**
  1. Tear in the lining of the anal canal distal to the dentate line, which most commonly occurs in the posterior midline.
  2. Majority are caused by trauma to the anal canal (such as passage of hard stool). Less common causes: Crohn’s disease, TB, leukemia.
  3. A midline sentinel skin tag is often associated with chronic anal fissure. Acute anal fissure presents as acute laceration.
  4. 90% are mid-posterior; 10% anterior.
  5. Any not anterior or posterior may be Crohn’s disease.
  6. Initial tear then leads to cycle of repeated injury contributed by ischemia.
  7. Pain is secondary to spasm of exposed internal sphincter muscle.
  8. Presentation is tearing pain with passage of bowel movement associated with some rectal bleeding.
  9. Full colonoscopy if rectal bleeding. Flex sig okay if age <50 and no family history of colorectal cancer.

- **Treatment**
  1. Fiber, stool softeners:
  2. Nitroglycerin (increases blood flow and reduces pressure at the internal anal sphincter, associated with headache)
  3. Nifedipine
     a. 0.2% gel bid or 20 mg po bid
     b. 2-5% lidocaine ointment or hydrocortisone can be used pre-BMs; Sitz baths can be used after BMs.
  4. Other: Botulinum toxin (injection into anal sphincter, two injections of 0.2cc, 20 units each, into each side of fissure)
  5. Last Resort: Surgery: lateral sphincterotomy. Successful but may result in fecal incontinence.

Ogilvie’s Syndrome

- **Definition** - acute colonic pseudobstruction with gross dilation of cecum and R colon sometimes extending to rectum in the absence of a mechanical blockage.

- **Contributing factors**
  1. Recent surgery, general anesthesia
  2. Chronic obstructive pulmonary disease
  3. Underlying neurological disease (Parkinson’s, Alzheimers, spinal cord injury, MS)
  4. Medications (antidepressants, antipsychotics, opiates)
  5. Diabetes
  6. Congestive heart failure
  7. Uremia
  8. Infection
  9. Hip fracture
10. Metabolic imbalance (hypokalemia, hypocalcemia, hypomagnesemia)
11. Severe medical illness

- **Treatment**
  1. Supportive care, removal of precipitants (correct electrolyte abnormalities, treat infection/CHF, stop opiates & anticholingergics, etc.)
  2. Place NGT and rectal tubes
  3. Keep NPO, start IVF
  4. Positioning – prone, elevate hips, R and L lateral decubitus q 1 hour
  5. **Neostigmine protocol**
     - mg IV over 3 min. Continuous cardiac monitoring because of the risk of severe bradycardia. Can repeat if first dose is not effective. Response in ~80%. Keep atropine at bedside in case of severe bradycardia. Should respond within 5 minutes.
  6. **Erythromycin – 250mg IV q8hr**
     - 2.0 mg IV over 3 min. Continuous cardiac monitoring because of the risk of severe bradycardia. Can repeat if first dose is not effective. Response in ~80%. Keep atropine at bedside in case of severe bradycardia. Should respond within 5 minutes.
  7. Endoscopic decompression +/- placement of decompression tube if:
     - a. Supportive measures, medications fail
     - b. Cecal diameter is 11-13cm
     - c. Clinical deterioration
     - d. Do not use bowel preps, just water enemas if need be
     - e. Use water, not air insufflation
  8. If endoscopic decompression fails, may need percutaneous cecostomy tube placement or percutaneous endoscopic colostomy.

**Colonic Neoplasms**
- **Indications for colonoscopy and appropriate intervals (recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer 2008)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
</tr>
<tr>
<td>1) Average risk</td>
<td>10 y (begin at age 50y)</td>
</tr>
<tr>
<td>2) <strong>Moderate risk</strong></td>
<td></td>
</tr>
<tr>
<td>One first-degree relative (FDR) with cancer/adenomas at age ≥60y or 2 second-degree relatives (SDR) with cancer</td>
<td>10 y (begin at 40y)</td>
</tr>
<tr>
<td>≥2 FDR with cancer (or adenomas) or 1 FDR diagnosed at age &lt;60 y</td>
<td>5 y (begin at age 40y or 10 y younger, whichever is earlier)</td>
</tr>
<tr>
<td><strong>3) High Risk</strong></td>
<td></td>
</tr>
<tr>
<td>HNPCC</td>
<td>1-2 y (begin at age 20-25 or 10y younger)</td>
</tr>
<tr>
<td>Genetic diagnosis or suspected FAP</td>
<td>Colectomy if gene positive (begin age 10-12)</td>
</tr>
</tbody>
</table>
### Postadenoma resection
- 1-2 tubular adenomas of <1cm with LGD
- 3-10 adenomas or adenoma, or 1 adenoma >=1cm or any with villous features or HGD
- >10 adenomas
- flat adenomas removed in piecemeal fashion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tissue Involvement</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>limited to the mucosa</td>
<td>90%</td>
</tr>
<tr>
<td>B1</td>
<td>confined to the muscularis propria</td>
<td>80%</td>
</tr>
<tr>
<td>B2</td>
<td>through the muscularis</td>
<td>60%</td>
</tr>
</tbody>
</table>

### Postcancer resection
Clear colon, then in 1 yr, then 3y, then 5y

### Inflammatory bowel disease: chronic ulcerative colitis or Crohn’s colitis
- Pancolitis
- >8 years: 1-2 years
- >12 years: yearly

### Amsterdam II criteria for diagnosis of HNPCC (Lynch syndrome) (1998)
1. (3) At least three relatives with a Lynch syndrome cancer (one must be a first-degree relative of other two)
2. (2) Colorectal cancer involving at least two generations
3. (1) One or more colorectal cancer cases before age 50 years
4. FAP has been excluded (The Amsterdam II criteria allow for any Lynch syndrome cancer (endometrial, ovarian, gastric, small bowel, upper urogenital or liver) to replace colonic cancer in the original criteria.

### Bethesda Criteria (for identification of patients with colorectal tumors who should undergo testing for microsatellite instability)
1. Individuals with cancer in families that meet the Amsterdam criteria
2. Individuals with 2 HNPCC-related tumors, including synchronous and metachronous colorectal cancer or associated extra-colonic carcinoma (endometrial, ovarian, gastric, hepatobiliary, small bowel cancer, or transitional cell carcinoma of the renal pelvis or ureter
3. Individuals with colorectal cancer (CRC) and a first degree relative with CRC or HNPCC- related extracolonic cancer or a colorectal adenoma (one of the cancers diagnosed at age<45 and adenomas diagnosed <40)
4. Individuals with CRC or endometrial CA diagnosed at age <45
5. Individuals with right-sided CRC with an undifferentiated pattern on histopathology diagnosed at age <45
6. Individuals with signet-ring type CRC diagnosed at age <45
7. Individuals with adenomas diagnosed at age <40 years

### Classification of colonic cancer
1. Dukes’ classification (Astler-Coller modification)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tissue Involvement</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>limited to the mucosa</td>
<td>90%</td>
</tr>
<tr>
<td>B1</td>
<td>confined to the muscularis propria</td>
<td>80%</td>
</tr>
<tr>
<td>B2</td>
<td>through the muscularis</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>propria, into or through serosa</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>C1</td>
<td>same as B1 plus regional nodal metastases</td>
<td>40%</td>
</tr>
<tr>
<td>C2</td>
<td>same as B2 plus regional nodal metastases</td>
<td>40%</td>
</tr>
<tr>
<td>D</td>
<td>distant metastases</td>
<td>5%</td>
</tr>
</tbody>
</table>

- **American Joint Committee on Cancer (TNM Classification)**
  1. **Stage 0**
     a. Carcinoma in situ intraepithelial or invasion of lamina propria (Tis N0 M0)
  2. **Stage I**
     a. Tumor invades submucosa (T1 N0 M0) Dukes’ A
     b. Tumor invades muscularis propria (T2 N0 M0)
  3. **Stage II**
     a. Tumor invades thr
        ▪ Normal fecal blood loss: 0.5-1.5 ml/d
        ▪ 1 ml blood = 0.5 mg iron
        ▪ Maximum iron absorption (dietary), 3-4 mg/d
        ▪ Average menstrual iron loss, 15-20 mg/mo

**PANCREAS**

**Conditions that Predispose to Acute Pancreatitis**

- **Obstructive**
  1. Gallstones
  2. Tumors
  3. Parasites
  4. Duodenal diverticula
  5. Annular pancreas
  6. Choledochocele
- **Alcohol/other toxins/drugs**
  1. Ethyl alcohol
  2. Scorpion venom
  3. Methyl alcohol
  4. Organophosphorous insecticides
  5. Drugs (see table below)
- **Infectious**
- **Vascular**
1. Vasculitis
2. Embolic to pancreatic vessels
3. Hypotension

- **Trauma**
- **Post-ERCP**
- **Postoperative**
- **Controversial**
  1. Pancreas divisum
  2. Sphincter of Oddi dysfunction
- **Idiopathic**

**Acute Non-Gallstone Pancreatitis**

- **Ranson’s criteria**
  1. **On Admission:**
     - Age > 55
     - WBC > 16,000/mm³
     - Glucose > 200 mg/dL
     - LDH > 350 IU/L
     - AST > 250 IU/L
  2. **Within 48 hours:**
     - Hematocrit decrease > 10%
     - BUN rise > 5 mg/dL
     - Calcium < 8 mg/dL
     - Arterial pO₂ < 60 mm Hg
     - Base deficit > 4 mEq/L
     - Fluid sequestration > 6 L
  3. **Mortality rates by Ranson score:**
     - <3: 5-10%
     - 3-4: 15%-20%;
     - 5-6: 40%;
     - >7: >99%

- **CT criteria for severity of acute pancreatitis**

<table>
<thead>
<tr>
<th>Grade of acute pancreatitis</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A- Normal</td>
<td>0</td>
</tr>
<tr>
<td>B- Enlargement of the pancreas</td>
<td>1</td>
</tr>
<tr>
<td>C- Peripancreatic inflammation</td>
<td>2</td>
</tr>
<tr>
<td>D- Single fluid collection</td>
<td>3</td>
</tr>
<tr>
<td>E- Multiple fluid collections</td>
<td>4</td>
</tr>
</tbody>
</table>
Degree of necrosis
None 0
One-third of pancreas 2
One third to one-half of pancreas 4
More than one-half of pancreas 6

* CT severity index = Acute pancreatitis grade (0-6) plus degree of necrosis (0-6)
Mortality rates: 0-3 CT severity index, about 3%; 4-6, about 6%; 7-10, about 17%.

Examples of Drug-Induced Pancreatitis

- **Proven**
  L-asparaginase
  Azathioprine
  Didanosine
  Estrogens
  ACE inhibitors
  6-mercaptopurine
  Sulfasalazine
  Pentamidine
  Valproate

- **Probable**
  Protease inhibitors
  Acetaminophen
  5-Aminosalycilic acid
  Ergotamine
  Furosemide
  Isoniazide
  Procardiamide
  Rifampicin
  Thiazides

- **Possible/Questionable**
  Carbamazepine
  Corticosteroids
  Cimetidine
  Furadantin
  Metronidazole
  Minoceycline
  Piroxicam
  Ranitidine
  Tetracycline
Sphincter of Oddi Dysfunction

Biliary – Rome III criteria

- **Type I:** patients present with biliary-type pain; abnormal aminotransferases, bilirubin or alkaline phosphatase >2 times normal values documented on two or more occasions; a dilated bile duct greater than 8 mm diameter on ultrasound. ~65-95% have manometric evidence of biliary SOD.

- **Type II:** patients present with biliary-type pain and one of the previously mentioned laboratory or imaging abnormalities. ~50-63% have manometric evidence of biliary SOD.

- **Type III:** patients complain only of recurrent biliary-type pain and have none of the previously mentioned laboratory or imaging criteria. ~12-59% have manometric evidence of biliary SOD.

Pancreatic - criteria

- **Type I:** patients have all three of the following criteria: (a) elevation of pancreatic enzymes (more than 1.5 times the upper limit of normal) associated with pain; (b) a dilated pancreatic duct (greater than 6 mm in the head and more than 5 mm in the body by ERCP); and (c) delayed drainage of contrast after ERCP (more than nine minutes).

- **Type II:** patients have one or two of the above criteria.

- **Type III:** patients have none of the above criteria.

*In one study, abnormal manometry was found in 92, 58, and 35 Percent in groups I, II, and III, respectively.*
### Cystic Lesions of the Pancreas

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Sex</th>
<th>Age/Gender</th>
<th>Appearance</th>
<th>Histology/ cytology</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous cystadenoma</td>
<td>F</td>
<td>Middle Age</td>
<td>Macrocytic</td>
<td>Mucinous</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>F</td>
<td>Middle Age</td>
<td>Macrocytic</td>
<td>Malignant, mucinous</td>
<td>High</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td>Mixed d</td>
<td>Elderly, W=M</td>
<td>Mixed features of macrocystic and microcystic lesions; assoc. with dilated ducts</td>
<td>Mucinous (similar to mucinous cystic neoplasms)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>F</td>
<td>Middle Age</td>
<td>Microcystic or honeycombed lesion</td>
<td>Serous (PAS positive for glycogen)</td>
<td>Low</td>
</tr>
<tr>
<td>Cystic endocrine neoplasm</td>
<td>Mixed d</td>
<td>Middle Age</td>
<td>Variable appearance</td>
<td>Endocrine-like. Small cells with scant cytoplasm. Monomorphic nuclei with salt &amp; pepper chromatin</td>
<td>Low</td>
</tr>
<tr>
<td>Solid cystic pseudopapillary neoplasm</td>
<td>F</td>
<td>Young</td>
<td>Mixed solid and cystic</td>
<td>Endocrine-like</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Autoimmune Pancreatitisis—Diagnostic Criteria (Combined Mayo Clinic and Asian Consensus Criteria)

- **Histology**
  1. Lymphoplasmacytic infiltration with fibrosis and abundant IgG4-positive cell infiltration
- **Imaging**
  1. Diffuse, segmental or focal enlargement of the gland, with or without a mass or hypoattenuated rim
  2. Diffuse, segmental or focal pancreatic duct narrowing, with or without stenosis of the bile duct
- **Other organ involvement**
  1. Biliary strictures, parotid or lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis

- **Response to glucocorticoid therapy**
  1. Resolution of marked improvement of pancreatic or extrapancreatic manifestations

### Enzyme Products for the Treatment of Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Lipase content (USP Units)</th>
<th>Dose to treat pain</th>
<th>Dose to treat steatorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonenteric coated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viokase 8</td>
<td>8,000</td>
<td>8 with meals and at night</td>
</tr>
<tr>
<td>Viokase 16</td>
<td>16,000</td>
<td>4 with meals and at night</td>
</tr>
<tr>
<td><strong>Enteric coated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creon 5</td>
<td>5,000</td>
<td>NA</td>
</tr>
<tr>
<td>Creon 10</td>
<td>10,000</td>
<td>NA</td>
</tr>
<tr>
<td>Creon 20</td>
<td>20,000</td>
<td>NA</td>
</tr>
<tr>
<td>Pancrease MT10</td>
<td>10,000</td>
<td>NA</td>
</tr>
<tr>
<td>Pancrease MT16</td>
<td>16,000</td>
<td>NA</td>
</tr>
<tr>
<td>Pancrease MT 20</td>
<td>20,000</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Co-treatment with H-2 receptor antagonist or PPI required

#May not be effective for treatment of pain because the enzymes are released too far distally in the small bowel to inhibit CCK release

### Most Common Pancreatic Endocrine Tumors

<table>
<thead>
<tr>
<th>Tumor/Syndrome</th>
<th>Hormone causing symptoms</th>
<th>Primary symptoms or signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Gastrinoma, Z-E* syndrome</td>
<td>Gastrin</td>
<td>Abdominal pain, diarrhea, dysphagia-heartburn</td>
</tr>
<tr>
<td>VIPoma, Verner-Morrison</td>
<td>VIP#</td>
<td>Diarrhea, flushing</td>
</tr>
<tr>
<td>syndrome, WDHA, pancreatic cholera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>Dermatitis, weight loss, diarrhea</td>
</tr>
</tbody>
</table>

*Zollinger-Ellison syndrome

#Vasoactive intestinal peptide
HEPATOBILIARY

Evaluation of Abnormal Liver Function Tests
(“AGA Medical Position Statement: Evaluation of Liver Chemistry tests” Gastroenterology 2002; 123)

- Algorithm for elevated AST/ALT

```
Elevated ALT and AST <5 times normal
  History and Physical Examination*, Discontinue hepatotoxic medications
  Confirm abnormality if an error is suspected
  Liver Chemistries, PT, Albumin, CBC with platelets
  Hepatitis A, B and C Serologies**, Fe, TIBC, Ferritin

Negative serology, asymptomatic patient without hepatic decompensation
  Positive serologic evaluation
  Negative serology
  Consider ultrasound, ANA, α-smooth muscle Ab,
  ceruloplasmin, α1-antitrypsin

Abnormal results
  Liver biopsy

Negative serology
  Lifestyle modification
  Discontinue alcohol
  Stop hepatotoxic medications
  Weight loss
  Diabetes control

observation
  normal
  Repeat Liver Chemistries

abnormal
  Ultrasound and serologic evaluation; ANA,
  α-smooth muscle Ab, ceruloplasmin,
  α1-antitrypsin, α-fetoprotein and α-endomysial Ab

Liver biopsy

Positive Serology/Test
  Biopsy

Treat Accordingly
```
- Algorithm for elevated Alkaline Phosphatase

```
Elevated serum bilirubin

History and Physical Examination, Liver Chemistries

Unconjugated bilirubin
Normal Alk Phos, ALT, AST

Conjugated bilirubin
Abnormal Alk Phos, ALT, AST

Hemolysis Studies
Review Medications

RUQ ultrasound to assess ductal dilatation

present → ERCP or MRCP
absent → *Elevated ALT evaluation
Review medications, AMA,
ERCP or MRCP
liver biopsy
```

- Algorithm for elevated Bilirubin

```
Elevated serum alkaline phosphatase

History and Physical Examination

Normal bilirubin, ALT, AST

γ-GGT or 5'-nucleotidase

negative → Etiology is not hepatobiliary

positive → RUQ ultrasound, AMA

No ductal dilatation → Observation

Liver biopsy

Abnormal Liver Chemistries

RUQ ultrasound to assess ductal dilatation

Yes → ERCP

AMA

negative → Elevated alkaline phosphatase > 6 months

*Elevated ALT evaluation
liver biopsy
ERCP or MRCP
```
• Pearls in interpretation of Abnormal LFTs
  1. Do not rely on Bilirubin to determine obstructive or infiltrative hepatopathy as it frequently may lag behind or fail to elevate.
  2. Acute obstructive hepatopathy (e.g. choledocolithiasis) can present as hepatocellular or infiltrative patterns. Timing and clinical setting are key.
  3. Drugs may confound or modify any pattern of hepatopathy.
  4.

Liver Biopsy

• Use of liver biopsy in clinical practice

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Staging</th>
<th>Prognosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>-</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>-</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>+</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>+ +</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>AIH</td>
<td>+ +</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>AIH</td>
<td>++</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>PBC</td>
<td>++ (AMA-negative, ? overlap syndrome)</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>PSC</td>
<td>++ (small duct disease; overlap syndrome?)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>(+)</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>NAFLD/NASH</td>
<td>+ +</td>
<td>++</td>
<td>+ (+)</td>
</tr>
<tr>
<td>HCC</td>
<td>+ + (depends on size)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Other focal lesions</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>+ + + +</td>
<td>+ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>DILI</td>
<td>+ +</td>
<td>+</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>+ (+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-OLT</td>
<td>+ + + +</td>
<td>+ (+)</td>
<td>+ (+)</td>
</tr>
</tbody>
</table>

Complications of liver biopsy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate/100</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>&lt;0.5</td>
<td>Usually from bleeding complications</td>
</tr>
<tr>
<td>Pain</td>
<td>20</td>
<td>Chronic pain, Small intercostals windows</td>
</tr>
<tr>
<td>Hematoma/Bleeding</td>
<td>&lt;3</td>
<td>Coagulopathy, pt cooperation, multiple passes</td>
</tr>
<tr>
<td>Biloma/Infection</td>
<td>&lt;0.5</td>
<td>H/o or current cholangitis, ductal dilaton</td>
</tr>
<tr>
<td>Non-liver organ damage</td>
<td>&lt;0.01</td>
<td>Operator, lack of imaging guidance</td>
</tr>
</tbody>
</table>
Acute Liver Failure

- **King’s College Criteria**
  1. Acetaminophen toxicity
     a. Acidosis (pH <7.3) irrespective of HE grade or INR >6.5 plus creatinine >3.4 mg/dL in patients with grade III-IV HE.
     *PPV and NPV for mortality, 88% and 65%, respectively.

  2. Other causes of fulminant hepatic failure
     a. INR > 6.5 irrespective of HE grade, or any three of the following:
        Age <10 yr or >40 yr
        Non-A, non-B hepatitis or drug-induced disease
        Duration of jaundice before encephalopathy >7d
        INR > 3.5
        Bili >17.5 mg/dL
     *PPV and NPV for mortality, 79% and 50%, respectively.

- **Intensive care of acute liver failure**
Liver Transplantation

Initial transplant work-up

Laboratory:

<table>
<thead>
<tr>
<th>ANA</th>
<th>Hep A</th>
<th>TSH</th>
<th>CT Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMA</td>
<td>T&amp;S</td>
<td>AFP</td>
<td>Doppler U/S</td>
</tr>
<tr>
<td>ASMA</td>
<td>Coombes</td>
<td>RPR</td>
<td>CT Abdomen</td>
</tr>
</tbody>
</table>

Studies*:

- CT Brain
- Doppler U/S
- CT Abdomen

Consults*:

- Anesthesia
- Psychiatry
- Social Work
### Contraindications to liver transplantation

- **Sepsis/Infection**
  - Active Substance Abuse: (6 months abstinence with completion of rehab program)
- **Extrahepatic Cancer**
- **Extensive Portal Thrombosis** (Eval by CT scan; surgical consultation)
- **Severe Comorbidities** (Coronary artery disease, COPD, Pulm HTN, others)
- **HIV/AIDS**
- Porto-Pulmonary or Hepatopulmonary syndromes (criteria for exclusion greatly varies)
- Hepatoma (beyond Milan criteria) or extensive Cholangiocarcinoma

### Immunosuppressive therapy

<table>
<thead>
<tr>
<th>Drug:</th>
<th>Dose:</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Rejection:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solumedrol</td>
<td>Day 1-1gm, day2-3500mg, then Prednisone 40mg long taper</td>
<td></td>
</tr>
<tr>
<td>OKT3</td>
<td>5mg x~10d</td>
<td>Anaphylaxis, serum sickness, increased risk PTLD</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>22mg x3d</td>
<td>Lymphopenia, anaphylaxis, serum sickness</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>20mg x1</td>
<td>Protocols new; experience is limited</td>
</tr>
<tr>
<td><strong>Chronic Maintenance:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>~0.1mg/kg BID</td>
<td>Nephrotoxic, neurotoxic, DM, HTN, pancytopenia</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1mg BID</td>
<td>Diarrhea, leucopenia. Minimally nephrotoxic</td>
</tr>
<tr>
<td>Rapamune</td>
<td>2-10mg QD</td>
<td>↓nephrotoxic and cytopenia, Hepatic artery thrombosis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>8mg/kg BID</td>
<td>Nephrotoxic, neurotoxic, (similar to tacrolimus)</td>
</tr>
</tbody>
</table>

### Complications of liver transplantation

---

46
Hepatitis B

- **Interpretation of hepatitis B serologies**

<table>
<thead>
<tr>
<th>Stage</th>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcIgM</th>
<th>HBcIgG</th>
<th>HBeAg</th>
<th>HBeAb</th>
<th>DNA</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Follow; ± treat if DNA+ at 12 w</td>
</tr>
<tr>
<td>Acute-Window</td>
<td>±</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>Follow</td>
</tr>
<tr>
<td>Recovered</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>Protective/Immune</td>
</tr>
<tr>
<td>Immunized</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Protective/Immune</td>
</tr>
<tr>
<td>Chronic</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>With treat to goal inactive state</td>
</tr>
<tr>
<td>Chronic-Tolerant</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Follow LFTs</td>
</tr>
<tr>
<td>Chronic-Precore Mut-</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>Pre-core specific treatment, lifelong</td>
</tr>
<tr>
<td>Chronic-Inactive</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Carrier, observe</td>
</tr>
<tr>
<td>Isolated Core</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Only concern for liver transplant</td>
</tr>
<tr>
<td>Relapse on Treatment</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Check YMDD mutation</td>
</tr>
</tbody>
</table>

- **Recommendations for treatment**

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA (PCR)</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt;20,000 IU/mL</td>
<td>≤2 × ULN</td>
<td>Low efficacy with current treatment. Observe; consider treatment when ALT becomes elevated. Consider biopsy in persons &gt; 40 years, ALT persistently high normal-2× ULN, or with family history of HCC. Consider treatment if HBV DNA &gt;20,000 IU/mL and biopsy shows moderate/severe inflammation or significant fibrosis.</td>
</tr>
<tr>
<td>+</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;2 × ULN</td>
<td>Observe for 3-6 months and treat if no spontaneous HBeAg loss. Consider liver biopsy prior to treatment if compensated. Immediate treatment if liver or clinical decompensation. IFNα, pegIFNα, LAM, ADV, ETV, TDF or LdT may be used as initial therapy. ADV not preferred due to weak antiviral activity and high rate of resistance after 1 year. LAM and LdT not preferred due to high rate of drug resistance. End-point of treatment: Seroconversion from HBeAg to anti-HBe.</td>
</tr>
<tr>
<td></td>
<td>&gt;20,000 IU/mL*</td>
<td>≥2 × ULN</td>
<td>Duration of therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• IFNα: 16 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• PegIFNα: 48 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM/ADV/ETV/LdT/TDF: minimum 1 year, continue for at least 6 months after HBeAg seroconversion</td>
</tr>
<tr>
<td>−</td>
<td>&lt;20,000 IU/mL</td>
<td>≤2 × ULN</td>
<td>IFNα or pegIFNα, LAM, ADV, ETV, TDF or LdT may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance. ADV not preferred due to weak antiviral activity and high risk of resistance after 1 year. End-point of treatment: not defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• IFNα or pegIFNα: 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM/ADV/ETV/LdT/TDF: &gt; 1 year</td>
</tr>
<tr>
<td>−</td>
<td>&gt;2000 IU/mL</td>
<td>1–2 × ULN</td>
<td>Consider liver biopsy and treat if liver biopsy shows moderate/severe necroinflammation or significant fibrosis.</td>
</tr>
<tr>
<td>−</td>
<td>&lt;20,000 IU/mL</td>
<td>≤ULN</td>
<td>Observe, treat if HBV DNA or ALT becomes higher.</td>
</tr>
<tr>
<td>−</td>
<td>detectable</td>
<td></td>
<td>Compensated:</td>
</tr>
<tr>
<td>−</td>
<td>undetectable</td>
<td></td>
<td>HBV DNA &gt;2,000 IU/mL—treat. LAM/ADV/ETV/LdT/TDF may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance; ADV not preferred due to weak antiviral activity and high risk of resistance after 1 year. HBV DNA &lt;2,000 IU/mL—consider treatment if ALT elevated.</td>
</tr>
<tr>
<td>−</td>
<td>Cirrhosis</td>
<td></td>
<td>Decompensated: Coordination with transplant center, LAM (or LdT) + ADV, TDF or ETV preferred. Refer for liver transplant.</td>
</tr>
<tr>
<td>+/−</td>
<td>CIRHOSIS</td>
<td></td>
<td>Compensated: Observe.</td>
</tr>
<tr>
<td>+/−</td>
<td>CIRHOSIS</td>
<td></td>
<td>Decompensated: Refer for liver transplant.</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; IFNα, interferon alpha; pegIFNα, pegylated IFN-alpha; LAM, lamivudine; ADV, adefovir; ETV, entecavir; LdT, telbivudine; TDF, tenofovir disoproxil fumarate.

*Treatment may be considered in patients with HBV DNA 2,000-20,000 IU/mL, particularly if they are older or have cirrhosis. Although several studies including the REVEAL study showed a correlation between serum HBV DNA and clinical outcomes such as HCC, only patients with 1 or both samples at baseline and last follow-up

- **Comparison of treatment medications by medication**
Table 8. Responses to Approved Antiviral Therapies Among Treatment-Naive Patients with HBeAg-Positive Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Groups from Multiple Studies</th>
<th>Placebo/Control</th>
<th>Standard IFN-α 5 MU qd or 10 MU tid 12-24 wk</th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
<th>Telbivudine 600 mg qd 52 wk</th>
<th>Peg IFNα 180 mcg qw + Lamivudine 100 mg qw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBeAg DNA*</td>
<td>0%-17%</td>
<td>37%</td>
<td>40%-44%</td>
<td>21%</td>
<td>67%</td>
<td>76%</td>
<td>60%</td>
<td>25%</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>6%-12%</td>
<td>33%</td>
<td>17%-32%</td>
<td>24%</td>
<td>22%</td>
<td>na</td>
<td>26%</td>
<td>30%/34%†</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>4%-6%</td>
<td>Difference of 16%-21%</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
<td>22%</td>
<td>27%/32%†</td>
<td>24%/27%†</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>0%-1%</td>
<td>7.80%</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
<td>3.2%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>7%-24%</td>
<td>Difference of 41%-75%</td>
<td>48%</td>
<td>68%</td>
<td>68%</td>
<td>77%</td>
<td>39%</td>
<td>46%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>na</td>
<td>na</td>
<td>49%-56%</td>
<td>52%</td>
<td>72%</td>
<td>74%</td>
<td>65%</td>
<td>38%†</td>
</tr>
<tr>
<td>Durability of response</td>
<td>80%-90%</td>
<td>50%-80%§</td>
<td>-90%-90%§</td>
<td>69%§</td>
<td>na</td>
<td>-80%</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

*Hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/mL or 5-6 log copies/mL) in standard IFN-α studies and some lamivudine studies, and PCR assays (lower limit of detection approximately 50 IU/mL or 250 copies/mL) in other studies. na = not available.
†Responses at week 48/week 72 (24 weeks after stopping treatment).

Table 9. Responses to Approved Antiviral Therapies Among Treatment-Naive Patients with HBeAg-Negative Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Groups from Multiple Studies</th>
<th>Placebo/Control</th>
<th>Standard IFN-α 5 MU qd or 10 MU tid 6-12 mo</th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Telbivudine 600 mg qd 52 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
<th>Peg IFNα 180 mcg qw + Lamivudine 100 mg qw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBeAg DNA*</td>
<td>0%-20%</td>
<td>60%-70%</td>
<td>60%-73%</td>
<td>51%</td>
<td>90%</td>
<td>88%</td>
<td>93%</td>
<td>63%</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>10%-29%</td>
<td>60%-70%</td>
<td>60%-79%</td>
<td>72%</td>
<td>78%</td>
<td>74%</td>
<td>76%</td>
<td>38%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>33%</td>
<td>na</td>
<td>60%-66%</td>
<td>64%</td>
<td>70%</td>
<td>67%</td>
<td>72%</td>
<td>48%</td>
</tr>
<tr>
<td>Durability of response</td>
<td>Control</td>
<td>10%-20%</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>5%</td>
<td>3%</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

na = not available
*Hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/mL or 5-6 log copies/mL) in standard IFN-α studies and some lamivudine studies, and PCR assays (lower limit of detection approximately 50 IU/mL or 250 copies/mL) in other studies.
†Post-treatment nadir obtained at week 72.

Table 11. Comparison of Approved Treatments of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>IFNα</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+, normal ALT</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>HBeAg+, chronic hepatitis</td>
<td>Indicated</td>
<td>Indicated†</td>
<td>Indicated</td>
<td>Indicated</td>
<td>Indicated†</td>
</tr>
<tr>
<td>HBeAg+, chronic hepatitis</td>
<td>4-12 months§</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
</tr>
<tr>
<td>HBeAg–, chronic hepatitis</td>
<td>1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Side effects</td>
<td>Many</td>
<td>Negligible</td>
<td>Potential Nephrotoxicity</td>
<td>Negligible</td>
<td>Potential Nephrotoxicity</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>~20%, year 1</td>
<td>~70%, year 5</td>
<td>29%, year 5</td>
<td>~1% up to year 5‡</td>
<td>~25% up to year 2</td>
</tr>
<tr>
<td>Cost*</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

*Based on treatment duration of 1 year.
**Treatment for at least 12 months continuing for at least 6 months after anti-HBe seroconversion.
†PegIFN approved for 12 months.
§Entecavir resistance reported within year 1 in patients with prior lamivudine resistance.
Hepatitis C

- Considerations before treatment

<table>
<thead>
<tr>
<th>Table 10. Characteristics of Persons for Whom Therapy Is Widely Accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 18 years or older, and</td>
</tr>
<tr>
<td>• HCV RNA positive in serum, and</td>
</tr>
<tr>
<td>• Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and</td>
</tr>
<tr>
<td>• Compensated liver disease (total serum bilirubin &lt;1.5 g/dL; INR 1.5; serum albumin &gt;3.4, platelet count 75,000 mm² and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and</td>
</tr>
<tr>
<td>• Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm³ and serum creatinine &lt;1.5 mg/dL, and</td>
</tr>
<tr>
<td>• Willing to be treated and to adhere to treatment requirements, and</td>
</tr>
<tr>
<td>• No contraindications (Table 12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 12. Characteristics of Persons for Whom Therapy Is Currently Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major uncontrolled depressive illness</td>
</tr>
<tr>
<td>• Solid organ transplant (renal, heart, or lung)</td>
</tr>
<tr>
<td>• Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin</td>
</tr>
<tr>
<td>• Untreated thyroid disease</td>
</tr>
<tr>
<td>• Pregnant or unwilling to comply with adequate contraception</td>
</tr>
<tr>
<td>• Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• Age less than 2 years</td>
</tr>
<tr>
<td>• Known hypersensitivity to drugs used to treat HCV</td>
</tr>
</tbody>
</table>

- Algorithm for the management of chronic hepatitis C
- **Evaluation of treatment**
  - Check viral load in-treatment weeks 4, 12, 24, and 6 months post-treatment
### Drug dosing and adjustment

1. **Interferon alfa-2a (Intron-A):** If WBC <1.5, neutrophils <0.7 or platelets <50K, decrease to 1.5 MU TIW. If WBC <1.0, neutrophils <0.5 or platelets <25K, discontinue.

2. **Peginterferon alfa-2b (Peg-Intron):** If WBC <1.5, neutrophils <0.75 or platelets <80K, decrease dose by 50%. If WBC <1.0, neutrophils <0.5 or platelets <50K, discontinue.

3. **Peginterferon alfa-2a (Pegasys):** If neutrophils <0.75, decrease to 135 µg/wk. If neutrophils <0.5, suspend treatment until neutrophils >1.0, then resume at 90 µg/wk. If platelets <50K, decrease to 90 µg/wk. If platelets <25K, discontinue.

4. **Ribavirin:**
   - **No cardiac disease:** If hemoglobin <10, decrease to 600 mg/d. If hemoglobin <8.5, then discontinue.
   - **Cardiac disease:** If >2 gm/dL decrease in hemoglobin during any 4 wks of treatment, decrease to 600 mg/d. If hemoglobin <12 despite 4 wks at a reduced dose, discontinue.

### Use of GM-CSF during HCV treatment

---

#### Table 8. Virological Responses During Therapy and Definitions

<table>
<thead>
<tr>
<th>Virological Response</th>
<th>Definition</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virological response (RVR)</td>
<td>HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay</td>
<td>May allow shortening of course for genotypes 2&amp;3 and possibly genotype 1 with low viral load</td>
</tr>
<tr>
<td>Early virological response (EVR)</td>
<td>≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)</td>
<td>Predicts lack of SVR</td>
</tr>
<tr>
<td>End-of-treatment response (ETR)</td>
<td>HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment</td>
<td>Best predictor of a long-term response to treatment</td>
</tr>
<tr>
<td>Sustained virological response (SVR)</td>
<td>HCV RNA negative 24 weeks after cessation of treatment</td>
<td></td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of HCV RNA in serum while still on therapy</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Reappearance of HCV RNA in serum after therapy is discontinued</td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>Failure to clear HCV RNA from serum after 24 weeks of therapy</td>
<td></td>
</tr>
<tr>
<td>Null responder</td>
<td>Failure to decrease HCV RNA by &lt; 2 logs after 24 week of therapy</td>
<td></td>
</tr>
<tr>
<td>Partial responder</td>
<td>Two log decrease in HCV RNA but still HCV RNA positive at week 24</td>
<td></td>
</tr>
</tbody>
</table>

---

![Graph](image-url)
1. Consider using it if patients have cirrhosis or are post-liver transplant and require reduction in their interferon dose at any point.
2. Consider using in patients without cirrhosis who continue to have an absolute neutrophil count (ANC) <500 despite a dose reduction in interferon at any point.
3. Initiate G-CSF at a dose of 300 µg SQ once to thrice weekly in patients <70 kg, 480 µg SQ once to thrice weekly in patients >70 kg.
4. In patients who have had G-CSF started, check their CBC weekly until their ANC is stable, then Q 2 weeks. If their ANC is 500-1500, interferon should be up-titrated to full dose. If their ANC is >1500, G-CSF should be held and a CBC repeated in 2 weeks.
5. Contraindications to G-CSF treatment:
   - Acute myelocytic leukemia
   - Allergy to *E. coli*-derived proteins
   - Vasculitis
   - Cardiovascular disease
   - Autoimmune disease
   - Sepsis

- **Use of erythropoietin during HCV treatment**
  1. Consider using Epogen in patients who have stage 3 fibrosis, cirrhosis, heart disease or HIV, or are post-liver transplant, previous non-responders to HCV treatment, or African-Americans whose hemoglobin has fallen to <12 (men) or <11.0 (women) while on treatment.
  2. All patients should have iron stores, vitamin B-12, and folic acid evaluated.
  3. Start Epogen at 40,000 U SQ/wk. If the hemoglobin does not increase by 1 g/dL after 4 weeks, increase to 60,000 U SQ/wk; if there is no response after 4 weeks on this dose, cease Epogen treatment.
  4. If patients start Epogen and the hemoglobin reaches 16 (men) or 14 (women), withhold it. If the hemoglobin then falls to <15 (men) or <13 (women), resume Epogen at 20,000 U SQ/wk and titrate the dose by 5,000-10,000 U to maintain the hemoglobin level.
  5. In patients who have stage 0, 1, or 2 fibrosis consider using Epogen only if they have required a 50% reduction in their ribavirin dose and their hemoglobin has remained <11.5 (titrate as above).

**Cirrhosis**

- **Child-Turcotte-Pugh and MELD scoring systems**

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bili</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
<td>A = score total &lt;7 (1-year survival 100%)</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
<td>B = score total 7-9 (1-year survival 80%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>C = score total &gt;9</td>
</tr>
</tbody>
</table>
• **Hepatic Encephalopathy**

  1. **Grades of HE**
     a. Changes in behavior with minimal change in level of consciousness.
     b. Gross disorientation, drowsiness, asterixis, inappropriate behavior.
     c. Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
d. Comatose, unresponsive to pain, decorticate or decerebrate posturing.

  2. **Common precipitating factors**

<table>
<thead>
<tr>
<th>Nitrogenous encephalopathy</th>
<th>Non-nitrogenous encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia/azotemia</td>
<td>Sedatives, benzodiazepines</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Hypoxia, hypoglycemia</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Constipation</td>
<td>Anemia</td>
</tr>
<tr>
<td>Excessive dietary protein</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
</tbody>
</table>

  3. **Treatment**

Correct underlying precipitating factors

- Lactulose 30-45cc PO TID titrate to 2-4 BM daily, 300cc retention enemas q4-6 hrs
- Neomycin 1000-3000mg PO TID
- Rifaximin (with lactulose?) 400mg PO TID or 550mg PO BID

*Other options: Zinc, L-ornithine L-aspartate for refractory disease

• **Hepatorenal Syndrome**

  a. Two types of hepatorenal syndrome

  - **Type 1:** rapid and progressive reduction of renal function, defined by doubling of the initial serum creatinine to a level >2.5 mg/dl or a 50% reduction of the initial 24-hr creatinine clearance to a level <20 ml/min in less than two weeks.

  - **Type 2:** renal failure does not have such a rapidly progressive course.

  b. **Criteria for hepatorenal syndrome:**

  c. **Major Criteria** (all criteria must be present)

  - Chronic or acute liver disease with advanced hepatic failure and portal hypertension
  - Low glomerular filtration rate, as indicated by serum creatinine >1.5 mg/dl or 24-hr creatinine clearance of <40 ml/min.
  - Absence of shock, ongoing bacterial infection, current or recent treatment with nephrotoxic drugs, and ongoing fluid losses.
- No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander.
- Proteinuria <500 mg/dl and no ultrasonographic evidence of obstructive uropathy or parenchymal disease.

d. **Additional Criteria** (supportive, not required)
   - Urine volume <500 mL/day
   - Urine sodium <10 mEq/L
   - Urine osmolality greater than plasma osmolality
   - Urine red blood cells <50 per high-power field
   - Serum sodium concentration <130 mEq/L
• Hepatocellular Carcinoma
• Spontaneous Bacterial Peritonitis

(Runyon BA “AASLD Practice Guidelines: Management of Adult Patients with Ascites due to Cirrhosis: An Update,: Hepatology June 2009)

a. Treatment

- Ascitic fluid PMN counts > 250 cells/mm³: empiric antibiotic therapy, e.g., intravenous cefotaxime 2 g every 8 hours. Test for total protein, LDH, glucose, and gram stain to assist with the distinction of SBP from secondary peritonitis.

- Oral ofloxacin (400 mg BID) can be considered in lieu of IV cefotaxime in uncomplicated SBP (absence of shock/vomiting/HE/GIB/ileus).

- Ascitic fluid PMN counts < 250 cells/mm³ and signs/symptoms of infection (temperature<100°F, abdominal pain and/or tenderness): empiric antibiotic therapy, e.g., intravenous cefotaxime 2 g every 8 hours pending results of cultures.

- Patients with ascitic fluid PMN counts >250 cells/mm³ and clinical suspicion of SBP should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (UCHSC alternative: 50g (25% solution) IV BID)

b. Prophylaxis

- Cirrhotics hospitalized for GI hemorrhage: Regardless of the presence or absence of ascites, patients with cirrhosis should receive 7 days of antibiotics (e.g. quinolone or cephalosporin). Studies suggest a reduction in SBP and other infectious complications, increase in survival and possibly decreased rate of re-bleed.

- Cirrhotics with ascites hospitalized for other reasons: Consider SBP prophylaxis in hospitalized patients with an ascitic fluid protein concentration <1g/dL.

- Prior SBP: Patients who have survived an episode of SBP should receive indefinite prophylaxis with a daily quinolone (e.g. norfloxacin 400mg qd) or TMP/SMX double strength bid.
• **Ascites and Peritonitis**

**Algorithm for evaluation of ascites**

- **Ascites**
  - Serum Albumin, Ascites Albumin
  - WBC, Gram stain, Culture
  - SAAG ≥1.1
  - SAAG <1.1

- **Portal Hypertensive**
  - Protein
  - AFP <2.5
  - AFP ≥2.5
  - DDx: Pre-sinusoidal—Portal Thrombosis, Schistosomiasis, Sinusoidal—Cirrhosis, Acute Hepatitis, Nodular hyperplasia, Cong. Hepatic Fibrosis, Sarcoidosis, Liver Mass, Post-Sinusoidal—Budd-Chiari, Veno-occlusive

- **Non-Portal Hypertensive**
  - Protein
  - DDx: Right Heart Failure, Budd-Chiari, Veno-occlusive Sarcoidosis

- **Hepatopetal**
  - DDx: Pre-sinusoidal—Portal Thrombosis, Schistosomiasis, Sinusoidal—Cirrhosis, Acute Hepatitis, Nodular hyperplasia, Cong. Hepatic Fibrosis, Sarcoidosis, Liver Mass, Post-Sinusoidal—Budd-Chiari, Veno-occlusive

- **Cardiac**
  - DDx: Right Heart Failure, Budd-Chiari, Veno-occlusive Sarcoidosis

- **SBP**
  - >250 PMN Cx +
  - <250 PMN Cx -

- **Culture (-) Neutrocytic ascites**
  - Cx Polymicrobial LDH >225 Glu <50

- **Non-Neutrocytic Bacterio-Ascites**
  - Cx Polymicrobial LDH >225 Glu <50

- **Secondary Peritonitis**
  - Eval Abscess, Cancer
  - Repeat paracentesis 48-72 hours

**TIPS contraindications**

**Absolute contraindications**
- Renal Failure; creatinine >2
- Bilirubin >3
- Complete portal vein thrombosis
- Severe pulmonary hypertension
- Multiple hepatic cysts
- Congestive heart failure
- Sepsis or uncontrolled infection
- Unrelieved biliary obstruction

**Relative contraindications**
- INR >1.5
- Platelets <100 k
- Partial portal vein thrombosis
- Moderate pulmonary hypertension
- Liver cancer
- Hepatic encephalopathy, poorly controlled
- Hepatic vein occlusion obstruction
- Not a transplant candidate

**Alcoholic Hepatitis**

(Lucey MR, et al "Alcoholic Hepatitis (Review Article)" NEJM 2009; 360.)

**Criteria for treatment**

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Components</th>
<th>Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maddrey’s Discriminant Function</td>
<td>Bili, PTT</td>
<td>≥32 = 35-50% 1m mortality; &lt;32 = &lt;10% 1m mortality</td>
<td>Oldest, Easy to use clinically; Non-linear, poor predictor; All scores &gt;33 show same mortality</td>
</tr>
<tr>
<td>Glasgow Score on steroid.Tx</td>
<td>Age, BUN, PTT, WBC</td>
<td>≥9 = 62% 6m mortality; &lt;9 =</td>
<td>Predicts response to steroids in those with MDF ≥32</td>
</tr>
<tr>
<td>MELD</td>
<td>Bili, INR, Cr</td>
<td>≥22 = 20% 90d mortality</td>
<td>Linear (better fit) model</td>
</tr>
</tbody>
</table>
### Treatment options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>40mg PO QD x28d</td>
<td>Contraindications: infection, bleeding</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40mg PO QD x28d</td>
<td>Theoretically less toxic</td>
</tr>
<tr>
<td>Pentoxiphylline</td>
<td>400mg PO TID x1m</td>
<td>Benefit is renal protection, ok in infection</td>
</tr>
</tbody>
</table>

Nutrition: adequate Micronutrient (B vitamins) and Protein-Calorie intake may be important. Abstain from ETOH: Minimal benefit from tx for those with continued use.

*No data on combination therapy. †Milk Thistle, Vitamin E, PPC, SAMe show mixed results.

### Etoh content of alcoholic beverages

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiskey</td>
<td>80 proof</td>
</tr>
<tr>
<td>Beer</td>
<td>4% 12 oz x 6</td>
</tr>
<tr>
<td>Wine</td>
<td>12% 750 ml</td>
</tr>
<tr>
<td>Wine, fortified</td>
<td>20% 750 ml</td>
</tr>
</tbody>
</table>

Moderate alcohol consumption: Men: <40 gm/day, Women: <20 gm/day

Heavy alcohol consumption: Men: >80 gm/day, Women: >20 gm/day

Approximately 20% of men drinking >12 beers/day develop cirrhosis in 10 years.

### NAFLD and NASH

#### Etiology of NAFLD/NASH (no associated findings in as much as 15%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes/Metabolic syndrome</td>
<td>~70-80%. Unclear if related to glucose control</td>
</tr>
<tr>
<td>Isolated Hyperlipidemia</td>
<td>Hypertriglyceridemia &gt; LDL &gt;&gt; others</td>
</tr>
<tr>
<td>Obesity (without above)</td>
<td>Weight loss (in all causes) may be best treatment</td>
</tr>
<tr>
<td>Jejunal Bypass/Resection</td>
<td>Continues despite weight loss</td>
</tr>
<tr>
<td>TPN</td>
<td>Related to both lipoid component and rate</td>
</tr>
<tr>
<td>Rapid weight loss</td>
<td>Transient</td>
</tr>
<tr>
<td>Bacterial Overgrowth</td>
<td></td>
</tr>
<tr>
<td>Weber-Christian Disease</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>HAART, Amiodarone, Diltiazem, glucocorticoids, (valproate, tetracycline—microvesicular steatosis)</td>
</tr>
</tbody>
</table>

#### Treatments

1. Weight loss and exercise
2. Vitamin E 800 iu PO QD
3. Pioglitazone 30mg PO QD (improved ALT but not histology)
4. Metformin 500mg PO BID (improved ALT but not histology)
Hemochromatosis

- **Diagnostic tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin &gt;500</td>
<td>Acute phage reactant. Normal occasionally (but Trans Sat high)</td>
</tr>
<tr>
<td>TIBC &gt;85%</td>
<td>Fasting! 30-50% with viral, ETOH, NASH have abnormal TIBC</td>
</tr>
<tr>
<td>Transferrin Saturation &gt;45%</td>
<td>(Iron/TIBC) x 100. More specific than other labs.</td>
</tr>
<tr>
<td>Hepatic Iron Index &gt;2.0</td>
<td>Does not distinguish from secondary iron overload</td>
</tr>
<tr>
<td>HFE gene testing</td>
<td>C282Y and H63D in 87%</td>
</tr>
</tbody>
</table>

- **Management and phlebotomy protocols**

1. Rationale for treatment: The major causes of death in HH are decompensated cirrhosis, hepatocellular carcinoma, diabetes mellitus and cardiomyopathy. Survival is normal in HH patients in whom treatment is initiated before the development of cirrhosis or diabetes.

   a. unit phlebotomy = 250 mg iron
   b. Do weekly phlebotomy until Hct <35%.
   c. Attain ferritin <50 ng/ml; transferrin saturation <50%.
   d. Then proceed with maintenance phlebotomy (usually 1 unit every 2-3 months) to maintain a serum ferritin concentration at 50 ng/ml or less
   e. Recommend limited intake of ethanol and iron or vitamin C supplements

- **Family screening**

1. Test serum iron, transferrin saturation and serum ferritin in all first-degree relatives of proband as an initial screening method. Confirm abnormal lab tests with genetic testing for C282Y mutation.
2. Perform liver biopsy for stainable and biochemical iron on anyone who has abnormal tests.

Wilson’s Disease


- **Diagnostic criteria**
Management and therapeutic options

- D-Penicillamine start 250mg PO QD increased to 1000-2000 mg QD, with B6 25 mg QD
- Trientine 500mg PO BID (not with food or iron)
- Zinc acetate 50mg PO TID additive by decreasing intestinal absorption

Autoimmune Hepatitis

- Diagnostic criteria
### Indications for treatment

- **Liver histology**
  Interface hepatitis of moderate or severe activity with or without lobular hepatitis or central portal bridging necrosis, but without biliary lesions or well defined granulomas or other prominent changes suggestive of a different etiology.

- **Serum biochemistry**
  Any abnormality in serum aminotransferases, especially if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of alpha antitrypsin, copper and ceruloplasmin.

- **Serum immunoglobulins**
  Total serum globulin or γ globulin or IgG concentrations greater than 1.5 times the upper normal limit.

- **Serum autoantibodies**
  Seropositivity for ANA, SMA, or anti LKM 1 antibodies at titers greater than 1:80. Lower titers (particularly of anti LKM 1) may be significant in children. Seronegativity for AMA.

- **Viral markers**
  Seronegativity for markers of current infection with hepatitis A, B, and C viruses.

- **Other etiological factors**
  Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.

---

### Table 3. Revised Original Scoring System of the International Autoimmune Hepatitis Group

<table>
<thead>
<tr>
<th>Feature</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver histology</td>
<td>Interface hepatitis of moderate or severe activity with or without lobular hepatitis or central portal bridging necrosis, but without biliary lesions or well defined granulomas or other prominent changes suggestive of a different etiology.</td>
<td>Same as for “definite”</td>
</tr>
<tr>
<td>Serum biochemistry</td>
<td>Any abnormality in serum aminotransferases, especially if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of alpha antitrypsin, copper and ceruloplasmin.</td>
<td>Same as for “definite” but patients with abnormal serum concentrations of copper or ceruloplasmin may be included, provided that Wilson disease has been excluded by appropriate investigations.</td>
</tr>
<tr>
<td>Serum immunoglobulins</td>
<td>Total serum globulin or γ globulin or IgG concentrations greater than 1.5 times the upper normal limit.</td>
<td>Any elevation of serum globulin or γ globulin or IgG concentrations above the upper normal limit.</td>
</tr>
<tr>
<td>Serum autoantibodies</td>
<td>Seropositivity for ANA, SMA, or anti LKM 1 antibodies at titers greater than 1:80. Lower titers (particularly of anti LKM 1) may be significant in children. Seronegativity for AMA.</td>
<td>Same as for “definite” but at titers of 1:40 or greater. Patients who are seronegative for these antibodies but who are seropositive for other antibodies specified in the text may be included.</td>
</tr>
<tr>
<td>Viral markers</td>
<td>Seronegativity for markers of current infection with hepatitis A, B, and C viruses.</td>
<td>Same as for “definite”.</td>
</tr>
<tr>
<td>Other etiological factors</td>
<td>Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.</td>
<td>Alcohol consumption less than 50 g/day and no recent use of known hepatotoxic drugs. Patients who have consumed larger amounts of alcohol or who have recently taken potentially hepatotoxic drugs may be included, if there is clear evidence of continuing liver damage after abstinence from alcohol or withdrawal of the drug.</td>
</tr>
</tbody>
</table>

---

- Indications for treatment
Liver Disease in Pregnancy

- Physiologic changes in LFTs during pregnancy
  - Bilirubin: Unchanged
  - AST, ALT: AST increased <2 fold, ALT unchanged
  - INR: Unchanged
  - Fibrinogen: Increases >50%
  - Ceruloplasmin: Increased
  - Iron Studies: Ferritin increased, TIBC decreased
  - Lipids: Increased
  - Leukocytes: Increased

- Liver disorders stratified by gestational age

  Coincidental liver disease worsened by pregnancy (e.g. Hep B, Hep A/E, HSV)
  Chronic liver diseases complicated by pregnancy (e.g. autoimmune, Wilson, Hepatitis C)
  Chronic disease worsened by pregnancy (e.g. IBD, Lupus, thyroiditis, etc)
  Gallstones (increased risk during pregnancy)
  Budd-Chiari
  Cholestasis of Pregnancy →
  Hyperemesis Gravidarum →
  Preeclampsia →
  HELLP Syndrome →
  Acute Fatty Liver of Pregnancy →

  First Trimester   Second Trimester   Third Trimester   Post-Partum

Drug-Induced Liver Disease

- A clinicopathologic classification of drug-induced liver disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic adaptation</td>
<td>Phenytoin, warfarin</td>
</tr>
<tr>
<td>Dose-dependent hepatotoxicity</td>
<td>Rifampicin, flavaspidic acid</td>
</tr>
<tr>
<td>Other cytopathic, acute steatosis</td>
<td>Valproic acid, nicotinic acid, amodiaquine</td>
</tr>
</tbody>
</table>
Acute hepatitis | Isoniazid, nitrofurantoin, halothane, sulfonamides, phenytoin, disulfiram, ketoconazole, troglitazone
Chronic hepatitis | Nitrofurantoin, diclofenac, trazadone
Granulomatous hepatitis | Allopurinol, carbamazepine, quinidine, quinine
Cholestasis without hepatitis | Oral contraceptives, androgens
Cholestatic hepatitis | Chlorproamazine, tricyclic antidepressants, erythromycins, amoxicillin/clavulanic acid
Steatohepatitis | Perhexiline, amiodarone
Veno-occlusive disease | In bone marrow transplantation: 6-thioguanine, busulfan, azathioprine, mitomycin, pyrrolizidine alkaloid

- **Treatment of acetaminophen toxicity**

**N-acetylcysteine**: Oral or by NG tube: 140 mg/kg followed by 17 maintenance doses of 70 mg/kg every 4 hr. NAC can also be given IV with equal or superior efficacy:

In patients with INR <2.0, use 20 hr IV protocol: 150 mg/kg loading dose over 15 minutes, followed by 50 mg/kg infused over 4 hours, with the final 100 mg/kg infused over the remaining 16 hours. In patients with INR >2.0, administer the 20 hour IV protocol (150 mg/kg loading dose over 15 minutes, followed by 50 mg/kg infused over 4 hours, followed by 100 mg/kg infused over the next 16 hours) followed by a continuous IV NAC infusion at 6.25 mg/kg per hour until INR is <2.0

**Note**: Although NAC may be effective up to 24 hr after the ingestion of acetaminophen, it is most effective if given within 8 hr, so don’t miss this window! NAC is safe, so if in doubt, give it.

Below is the **Rumack-Matthews nomogram** for predicting liver injury from acetaminophen and directing therapy.
- **Alternative therapies implicated in hepatotoxicity**

<table>
<thead>
<tr>
<th>Common names</th>
<th>Hepatic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaparral</td>
<td>Acute and subacute hepatitis</td>
</tr>
<tr>
<td>Chinese herbs</td>
<td>Unconjugated hyperbilirubinemia</td>
</tr>
<tr>
<td>Comfrey</td>
<td>Veno-occlusive disease</td>
</tr>
<tr>
<td>Germander</td>
<td>Reversible acute hepatitis</td>
</tr>
<tr>
<td>Gordolobo</td>
<td>Potential for veno-occlusive disease</td>
</tr>
<tr>
<td>Ma huang</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Mistletoe</td>
<td>Hepatitis with piecemeal necrosis</td>
</tr>
<tr>
<td>Senna</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Skullcap</td>
<td>Hepatitis with centrolobular and bridging necrosis</td>
</tr>
<tr>
<td>Valerian (garden heliotrope)</td>
<td>Hepatitis with piecemeal necrosis, chronic aggressive hepatitis with fibrosis</td>
</tr>
</tbody>
</table>
Evaluation of Liver Mass
(Rockey DC et al "AASLD Position Paper: Liver Biopsy," Hepatology, March 2009)

Radiographic findings of certain liver masses

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Radiographic Appearance*</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple cyst</td>
<td>Thin walled with homogenous low-density interior on CT imaging</td>
<td>Very common, often incidental</td>
</tr>
<tr>
<td>Hemangioma†</td>
<td>Vascular enhancement is often prominent (periphery of the lesion may be prominent) on contrasted CT imaging</td>
<td>The commonest benign hepatic neoplasm</td>
</tr>
<tr>
<td>FNH</td>
<td>Contrast-enhanced CT reveals intense arterial phase enhancement and the lesion becomes inhomogeneous to liver and difficult to detect in portal venous phase. A central scar typically shows little enhancement in the arterial phase</td>
<td>Commonest in young women</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Well-circumscribed, hyperechoic mass on ultrasound. Contrast-enhanced CT shows transient intense enhancement in the arterial phase, followed by rapid washout of contrast in portal venous phase</td>
<td>Commonest in young women (associated with oral contraceptives); may be difficult to distinguish from hepatocellular carcinoma</td>
</tr>
<tr>
<td>Focal fat</td>
<td>Nonspherical shape, absence of mass effect, and a low density on contrast enhanced CT</td>
<td>Almost always occurs in the setting of cirrhosis</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>On contrast-enhanced CT, tumor enhances in arterial phase and becomes hypervascular in portal venous phase</td>
<td>Almost always occurs in the setting of biliary disease</td>
</tr>
<tr>
<td>carcinoma</td>
<td>Solid appearing, with no vascular enhancement</td>
<td>Clinical scenario often consistent with a primary tumor at another site</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Solid appearing, with variable but typically minimal vascular enhancement</td>
<td>Classic clinical scenario includes fever</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Solid appearing, with variable but typically minimal vascular enhancement</td>
<td>Patients are usually from an area in which the disease is endemic</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>Air suggests anaerobic bacteria. Amoebic cysts often have a hypodense, water density</td>
<td></td>
</tr>
<tr>
<td>Hydatid cysts</td>
<td>May have daughter cysts within a thick-walled main cavity</td>
<td></td>
</tr>
</tbody>
</table>

*Features may be variable for many lesions.
†Some other hypervascular tumors include neuroendocrine/islet cell tumor, carcinoid, renal cell carcinoma, and melanoma.

Algorithm for evaluation of liver mass
**Pyogenic and Amebic Liver Abscess**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pyogenic</th>
<th>Amebic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Often multiple</td>
<td>Usually single</td>
</tr>
<tr>
<td>Location</td>
<td>Either lobe</td>
<td>Usually right hepatic lobe,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>near the diaphragm</td>
</tr>
<tr>
<td>Presentation</td>
<td>Subacute</td>
<td>Acute</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Mild, if present</td>
<td>Moderate, if present</td>
</tr>
<tr>
<td>Source</td>
<td>Biliary tract dz,</td>
<td>Colonic infection with <em>Entamoeba</em></td>
</tr>
<tr>
<td></td>
<td>cryptogenic</td>
<td><em>histolytica</em></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>US or CT +/-</td>
<td>US or CT and serology</td>
</tr>
<tr>
<td></td>
<td>aspiration</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>IV antibiotics +/- drainage</td>
<td>Metronidazole, 750 mg tid for 5 d, orally or IV, followed by iodoquinol, 650 mg orally tid for 20 d; diloxanide furoate, 500 mg orally tid for 10 d; or paromomycin 25-35 mg/kg orally in three divided doses for 7 d.</td>
</tr>
</tbody>
</table>

---

**GENERAL**

**Guidelines for the Evaluation and Treatment of Osteoporosis/Osteomalacia in Gastrointestinal and Hepatobiliary Diseases**

**CROHN’S DISEASE AND ULCERATIVE COLITIS**

- Osteomalacia and **vitamin D** deficiency are not common in IBD (including Crohn's disease) and are unlikely to be important causes of most cases of diminished bone mineral density in IBD. IBD has only a modest effect on BMD.
- Crohn's disease and ulcerative colitis carry comparable risks for osteoporosis and fracture.
- Males and females share a comparable risk for fracture.
- Corticosteroid use is the variable most strongly associated with osteoporosis. However, it is difficult to distinguish corticosteroid use from disease activity in terms of causal impact on bone density, because the two are closely linked.

**Recommendations for BMD testing**

- Indications for DXA scanning in IBD: prolonged corticosteroid use (>3 consecutive months or recurrent courses), low-trauma fracture, postmenopausal female or male age > 50.
- Repeat DXA: Consider repeating DXA in 1 year in patients receiving prolonged corticosteroids. Repeat DXA in two years in patients with osteopenia, 3-5 years in patients with normal bone density.
CELIAC DISEASE

- Risk of osteoporosis and osteoporosis-related fractures are more common in patients with celiac disease (untreated > treated) than the general population.
- **Vitamin D** deficiency is common in celiac disease.
- Patients with celiac disease, even without symptoms, increase their BMD after initiating a gluten-free diet.
- The high prevalence of osteoporosis among patients with celiac disease, including asymptomatic subjects, provides a rationale for instituting gluten-free diet therapy for those who do not have overt malabsorption.

**Recommendations for BMD testing**
- Obtain DXA in adults with newly diagnosed celiac disease 1 year after initiation of a gluten-free diet, to allow for stabilization of bone density.
- Guidelines for repeat DXA same as for IBD.
- 25-OH vitD, calcium, and possibly intact PTH should be measured in patients with newly diagnosed celiac disease.

POSTGASTRECTOMY STATES

- Postgastrectomy patients typically have a number of risk factors for osteoporosis, and bone disease may not necessarily be a sequel of the surgery per se. Nonetheless, postgastrectomy patients are at risk for bone disease.
- Postgastrectomy states are associated with an increased risk of fracture and thus should be evaluated for possible underlying bone disease.
- There is no difference in risk for postgastrectomy bone disease between a Billroth I procedure and a Billroth II procedure or a partial or total gastrectomy.

**Recommendations for BMD testing**
- Patients who are at least 10 years postgastrectomy (especially postmenopausal females, males age >50 years, and patients with low-trauma fractures), should undergo DXA testing.
- 25-(OH) vitamin D level, calcium, alkaline phosphatase, and intact PTH recommended.
- Guidelines for repeat DXA same as for IBD.

**Therapy for all the above**

- Patients with osteoporosis (or low-trauma fractures) should be evaluated for other causes of low bone density. Basic evaluation includes: CBC, LFTs, phosphorous, calcium, creatinine, HCO₃, 25-(OH) vitamin D level, protein electrophoresis, TSH, and testosterone level in men, 24 hour urine collection for calcium (and creatinine).
- All patients, regardless of BMD, should receive education on the importance of lifestyle changes (e.g., engaging in regular weight-bearing exercise, quitting smoking, avoiding excessive alcohol intake).
- Patients with osteoporosis or at high risk for osteoporosis should receive oral calcium carbonate or citrate (1,000-1,500 mg/day) and vitamin D (400-800 IU/day).
- **Testosterone** should be used to treat hypogonadism in men.
Bisphosphonates should be given to patients with osteoporosis. Consider bisphosphonates for the prevention of fracture in individuals unable to withdraw from steroids after 3 months regardless of BMD.

**CHRONIC LIVER DISEASE**

- On average, there is a mild BMD deficit in chronic liver disease, but considerable patient heterogeneity exists.
- Vertebral and nonvertebral fracture rates are increased in chronic liver disease, especially in postmenopausal women.
- Patients with primary biliary cirrhosis are at increased risk for osteoporosis due to predominant female sex and older age, but cholestatic disease per se does not differ significantly from noncholestatic disorders in terms of osteoporosis and fracture risk.
- Bone loss after OLT follows a biphasic course, with the greatest decrease during the first 3 to 6 months and then spontaneous stabilization or even improvement.

**Recommendations for BMD testing**

- Patients who have experienced a fragility fracture, who are postmenopausal, and who require long-term treatment with corticosteroids (>3 months) should undergo BMD testing. BMD should also be assessed when the diagnosis of primary biliary cirrhosis is first made, in patients with cirrhosis, and before liver transplantation.
- Patients with a normal initial BMD result should be retested after 2 to 3 years to exclude significant bone loss. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy.
- 25-hydroxyvitamin D, calcium, phosphate, +/- iPTH recommended.

**Therapy**

- Lifestyle changes, calcium + vitamin D, testosterone replacement, bisphosphonates as above.
**Figure 1.** A management approach for osteoporosis in gastrointestinal diseases.

*complete blood count, serum calcium, alkaline phosphate, creatinine, 25-OH-vitamin D, protein electrophoresis, testosterone [males]*