“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 2007-8 revision
Russ Arjal, M.D.
Geoff Jensen, M.D.
Stevany Peters, M.D.
Hanna Kraus, M.D.
Matt Quallick, M.D.
# TABLE OF CONTENTS

## ESOPHAGUS
- Gastroesophageal Reflux Disease (GERD) 5
  - Endoscopic grading of GERD 5
  - Indications for endoscopy in patients with GERD 5
  - Barrett’s esophagus 5
- Esophageal Varices 7
  - Factors that favor increased risk of bleeding 7
  - Endoscopic screening for varices 7
  - Octreotide in acute variceal hemorrhage 7
  - Prophylaxis of variceal bleeding – EVL vs. beta blockers 7
  - Instructions for use of the Sengstaken-Blakemore tube 7

## STOMACH AND DUODENUM
- Peptic Ulcer Disease 11
  - Predictors of risk of re-bleeding from a peptic ulcer 11
  - IV and soluble proton pump inhibitors 11
  - Erythromycin for emptying the stomach before endoscopy 11
  - *Helicobacter pylori* 12
  - Indications for checking serum gastrin 13
- Gastric Polyps 13
  - Relation to malignancy 13
  - Management of adenomatous gastric polyps 13

## SMALL INTESTINE AND COLON
- Irritable Bowel Syndrome 14
  - Rome III criteria 14
  - Recommended laboratory investigations in suspected IBS 14
  - Drugs that may be useful in the treatment of IBS 14
  - Dietary modifications 16
  - Alarm signals 16
- Celiac Sprue 16
  - Sensitivity and specificity of serologic tests in celiac sprue 17
  - Disorders associated with celiac sprue 17
  - Causes of intestinal villous atrophy that may resemble celiac sprue 17
  - Considerations in failure to respond to a gluten-free diet or to deteriorate when on a gluten-free diet 18
- Diarrhea and Gas 18
  - Pathogenetic mechanisms of diarrhea 18
  - Stool osmolality in distinguishing osmotic from secretory diarrheas 19
  - Acute diarrhea 19
Chronic diarrhea 20

Common colonic gas-producing foods 20
Fecal leukocytes in intestinal infections 21
Travelers’ diarrhea 21

Chronic Inflammatory Bowel Diseases 21
Treatment overview for Crohn’s disease 21
Azathioprine regimens in the treatment of Crohn’s disease 22
Managing azathioprine therapy with TPMT testing 22
5-aminosalicylic acid drugs and site of activity 22
Treatment overview for ulcerative colitis 24
Cyclosporine in severe ulcerative colitis 24
Budesonide 24
Inflammatory bowel disease drugs in pregnancy 24

C. difficile-induced Colitis-Treatment 25

Anal fissures 26
Characteristics 26
Treatment 26

Ogilvie’s Syndrome 27
Contributing factors 27
Neostigmine protocol 27

Colonic Neoplasms 27
Indications for colonoscopy and appropriate intervals 27
Amsterdam criteria for HNPCC 28
Classification of colonic cancer 29
Dukes’ classification 29
American Joint Committee on Cancer (TNM classification) 29

Blood in Stool 30

HEPATOBILIARY 30

Acute fulminant liver failure 30
Kings College criteria 30
Liver transplantation 30
Transplant workup/laboratory tests 31

Hepatitis (HBV) 31
Hepatitis B serologies 31
Recommended treatment strategies (AASLD) 31

Hepatitis C (HCV) 32
Considerations before treating HCV 32
Frequency of viral load checks in patients undergoing treatment 32
Starting doses of HCV medications 32
Drug adjustments based on laboratory abnormalities 33
Use of G-CSF in patients receiving HCV treatment 33
Use of epoetin (Epogen) in patients receiving HCV treatment 34

Cirrhosis and Complications 34
Child-Turcotte-Pugh scoring system 34
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification of ascites by serum-ascites albumin gradient</td>
<td>35</td>
</tr>
<tr>
<td>Ascitic fluid in cirrhosis</td>
<td>335</td>
</tr>
<tr>
<td>Albumin infusion accompanying paracentesis in the management of ascites</td>
<td>35</td>
</tr>
<tr>
<td>TIPS: contraindications</td>
<td>35</td>
</tr>
<tr>
<td>Hepatic encephalopathy—Common precipitating factors</td>
<td>36</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>37</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>37</td>
</tr>
<tr>
<td>Discriminant function for use of corticosteroids in alcoholic hepatitis</td>
<td>38</td>
</tr>
<tr>
<td>Management of hepatocellular carcinoma</td>
<td>38</td>
</tr>
<tr>
<td>Alcohol Content of Beverages</td>
<td>39</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>39</td>
</tr>
<tr>
<td>Wilson’s Disease</td>
<td>40</td>
</tr>
<tr>
<td>Drug-induced Liver Disease</td>
<td>41</td>
</tr>
<tr>
<td>A clinicopathologic classification of drug-induced liver disease</td>
<td>41</td>
</tr>
<tr>
<td>Treatment of acetaminophen toxicity</td>
<td>41</td>
</tr>
<tr>
<td>Methotrexate (MTX) liver injury</td>
<td>42</td>
</tr>
<tr>
<td>Herbal remedies that have been implicated in hepatotoxicity</td>
<td>42</td>
</tr>
<tr>
<td>Pyogenic and Amebic Liver Abscess: Clinical Distinctions</td>
<td>43</td>
</tr>
</tbody>
</table>

**PANCREAS**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Pancreatitis</td>
<td>43</td>
</tr>
<tr>
<td>Ranson’s criteria</td>
<td>43</td>
</tr>
<tr>
<td>CT criteria for severity of acute pancreatitis</td>
<td>44</td>
</tr>
<tr>
<td>Drugs That May Cause Pancreatitis</td>
<td>44</td>
</tr>
<tr>
<td>Sphincter of Oddi Dysfunction</td>
<td>45</td>
</tr>
<tr>
<td>Cystic Lesions of the Pancreas</td>
<td>47</td>
</tr>
</tbody>
</table>

**GENERAL**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines for the Evaluation and Treatment of Osteoporosis/Osteomalacia in Gastrointestinal and Hepatobiliary Diseases</td>
<td>45</td>
</tr>
</tbody>
</table>
ESOPHAGUS

Gastroesophageal Reflux Disease (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 are 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.

- 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
  
  - “Chronic” GERD (> 5 yrs) or onset after age 50 at risk for Barrett’s Esophagus, so called “Screening for Barrett’s”
  
  - Prior to consideration of surgical anti-reflux procedure
  
  - When diagnosis of GERD is in doubt, i.e., failure to respond to maximal medical therapy

- Barrett’s esophagus

  - **Definitions**

    - Inlet patch Barrett’s: proximal esophageal patch of mucosa, usually located below criocopharyngeus muscle.

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

    - 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>Selected patients, individualize care</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>Yearly and biopsy</td>
<td>Repeat endoscopy yearly until no dysplasia</td>
<td>If 2 pathologists concur, yearly endoscopy; if disagreement, surveillance every 3 years</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, repeat endoscopy to exclude cancer; if focal (&lt;5 glands in a single biopsy), every 3 months; if multifocal, ablation or surgical resection</td>
<td>Confirm histology; repeat endoscopy to exclude cancer; consider patient status, expertise of surgeons and gastroenterologists, focality of dysplasia; consider intensive surveillance, 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.
**Esophageal Varices**

- **Factors that favor increased risk of bleeding**
  - 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.

  **Who should not be screened?**
  Patients who are unlikely to benefit from prophylactic therapies designed to prevent the first variceal hemorrhage, those with short life expectancy, and those with previous UGI hemorrhage (they should have already undergone endoscopy).

- **Octreotide in acute variceal hemorrhage**
  50 µg IV bolus followed by 50-100 µg/hr continuous infusion for 72 hr

- **Prophylaxis of variceal bleeding – EVL vs. non-selective beta blockers - evidence**

  **Primary prophylaxis**
  - RCTs and meta analyses have shown that prophylactic EVL is more effective than beta-blockers in preventing the first variceal bleeding from moderate-to-large esophageal varices (RRR 44%) but offers no survival advantage.
  - Combination treatment: Not well studied. In the largest RCT, combination treatment was not more effective than EVL alone in preventing bleeding or death, but it may have helped prevent the development of recurrent varices.

  **Secondary prophylaxis**
  - Beta-blockers: Meta-analyses suggest that the risk of bleeding is decreased by 40%, the risk of death by 20%.
  - EVL vs beta blockers: Probably equally efficacious, but results of studies have been mixed.
  - Combination treatment: May be superior to EVL alone. In one study, EVL plus nadolol and sucralfate, lowered re-bleeding from 47% to 23% compared to EVL alone (trend towards decreased mortality in the combined-treatment group). In a second study, EVL plus nadolol reduced re-bleeding from 38% to 14% compared to EVL alone (no difference in mortality).
• Instructions for use of the Sengstaken-Blakemore tube

Insertion and maintenance of the tube

- 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.

- 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.

- 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.)

- Deflate the balloons.

- Lubricate the balloons well.

- 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.

- 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).

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

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

- 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.**

- 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.
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.
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

  - **VAMC**
    *Pantoprazole (Protonix)* For active bleeding.
    80 mg IV bolus followed by 8mg/hour gtt.

  - **DHMC**
    *Esomeprazole (Nexium)*. Must document that GI service has been notified or will be. Before endoscopy: two doses of 40 or 80 mg permitted
    After endoscopy: may be used for bleeding duodenal or gastric ulcer at 8mg/hr gtt. Endoscopy report must state this recommendation.

  - **UCHSC**
    *Esomeprazole (Nexium)* IV and PO. See above. No restrictions.

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

  - Some advocate giving 250 mg in 50 mL NS over 5 min, then endoscope after 20 min.
  - 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 been 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*

**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>

**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

For Treatment Failures—Three possibilities
1. Quadruple Therapy (14 days)
   - PPI BID
   - Bismuth subsalicylate (Pepto-Bismol) 2 tabs QID
   - Metronidazole 500 mg TID
   - Tetracycline 500 mg TID

2. Sequential Therapy
   - PPI BID plus
   - Amoxicillin 1 g BID for 5 days
   - followed by
   - PPI BID
   - Clarithromycin 500 mg BID
   - Tinidazole 500 mg BID

3. “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)

* Gastroenterology 2007; 133: 985-1001

**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 (Patient must be off PPI for at least 1 wk, or appreciate that an elevated value obtained while patient is taking maybe falsely elevated.)**
  - 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
  - * Gastric pH or gastric biopsies should be performed to exclude atrophic gastritis

**Gastric Polyps (Approximately 1% patients will have)**

- **Relation to malignancy**

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk of Malignancy</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic*</td>
<td>Variable, 0.6-4.5%</td>
<td>75%</td>
</tr>
<tr>
<td>Adenomatous*</td>
<td>As high as 75%, depending on size, especially if &gt;2 cm</td>
<td>6-10%</td>
</tr>
<tr>
<td>Fundic gland*</td>
<td>Rare</td>
<td>10-20%</td>
</tr>
<tr>
<td>Hamartomas</td>
<td>None</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Carcinoid</td>
<td></td>
<td>1-2%</td>
</tr>
</tbody>
</table>

*increased prevalence in familial adenomatous polyposis
• Management of adenomatous gastric polyps

Excise entirely, by multiple forceps biopsies if <5 mm, by snare polypectomy if >5 mm. Biopsy the surrounding mucosa for metaplasia. Endoscopic surveillance: at 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 eval for colon polyps. Biopsy for *H. pylori* and treat if positive (eradication can promote resolution of hyperplastic polyps).

SMALL INTESTINE AND COLON

Irritable Bowel Syndrome

**Definition:** Group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation.

**Prevalance:** It may affect as many as 1 in 5 US adults, woman >men, typically 30-50yrs old. Symptoms often exacerbated by psychosocial stress.

Three general patterns exist: diarrhea-predominant, constipation-predominant and mixed.

• **Rome III Criteria 2006 (Manning criteria seldom used)**

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:

- improvement with defecation
- onset associated with a change in the frequency of stool
- onset associated with change in the form (appearance) of stool

Symptoms that cumulatively support the diagnosis of IBS:

- abnormal stool frequency (>3/day or <3/wk)
- abnormal stool form (lumpy/hard or loose/watery)
- abnormal stool passage (straining, urgency, feeling of incomplete evacuation)
- passage of mucus
- bloating or feeling of abdominal distention

Symptom onset must occur at least 6months prior to diagnosis.

• **Recommended laboratory investigations in patients suspected of having IBS**

All patients

CBC, erythrocyte sedimentation rate, FOBT
If diarrhea is persistent or severe
--Malabsorption screen (fecal fat, serum B12, red cell folate, plasma ferritin, serologic tests for celiac sprue), 24hr stool volume and fat, laxative screen
--Stool cultures, *Clostridium difficile* toxin, ova and parasites
--Colonoscopy w/ biopsy for microscopic colitis, EGD w/ small bowel biopsy for celiac disease
--Lactose tolerance test
--TSH

Severely constipated patients and those with severe rectal urgency or fecal incontinence
--Colonoscopy (if >50)
--Colonic transit study using Sitz mark technique
--Anorectal function tests, e.g., manometry or motility w/ balloon expulsion
--Endoanal ultrasonography
--Defecography (to evaluate for enterocele or rectocele)
--Look for responsible medications (opiates, calcium-channel blockers, anticholenergics)

Pain –Predominant symptoms
--abdominal films
--amylase, liver tests if suspect pancreatic/biliary disease.
--CT (low yield if no alarm symptoms)

**Drugs that may be useful in the treatment of IBS**

Antispasmodics (not convincing evidence supporting their efficacy yet per the AGA but often used first-line)

Anticholenergics:
- Dicyclomine hydrochloride (Bentyl) 10-20 mg tid before meals
- Hyoscyamine butylbromide (Donnatal) 10-20 mg qid

Combination antispasmodics/sedatives:
- Clindium bromide and chlordiazepoxide

Smooth muscle relaxants:
- Alverine or mebeverine (not available in US)

Antidiarrheal agents
- Loperamide hydrochloride (Imodium) 2-8 mg/day in divided doses
- Diphenoxylate hydrochloride (Lomotil) 2-6 pills/day
- Cholestyramine 1-3 packets/day, 30 min a.c.
Antidepressants: TCAs have more supportive evidence than SSRIs and are shown to improve abdominal pain. TCAs often cause constipation so are best suited for diarrhea-predominant IBS. SSRIs ok for either type.

Imipramine hydrochloride (Tofranil) 10-100 mg/day
Amitryptyline hydrochloride (Elavil) 1-75 mg/day

In constipation-predominant IBS in women
Tegaserod (Zelnorm) (type 4 serotonin receptor) Off the market 3/07
Polyethylene glycol (Miralax)

Probiotics
Lactobacilli and bifidobacteria have both been studied.

Antibiotics
Rifaximin 400mg tid x 10days

Laxatives
Osmotic laxitives (mag citrate or sodium phosphate)
Hyperosmotic laxative (polyethylene glycol)
***Avoid regular use of stimulant laxitives.

Selective type 3 Serotonin Receptor Antagonists
Alosetron (Lotronex) 0.5-1.0 mg bid
***Only approved for woman w/ severe diarrhea-predominant IBS. SE include severe constipation and ischemic colitis (1 in 700).

- **Dietary Modification: (not proven to reduce IBS symptoms)**
  --Eliminate foods that can exacerbate symptoms, e.g., coffee, chocolate and sugar substitutes. 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.

- **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.

**Celiac Sprue**

- **Prevalence:** 1 per 120-300 people in North America.

- **Clinical Presentation:** Typically presents with episodic diarrhea, flatulence, and weight loss. Diarrhea is present in only 50%. Fe-deficient anemia is the most
common presentation. Abdominal pain and bloating are common. Lab abnormalities also may include macrocytic anemia (folate deficiency), coagulopathy (vitamin K deficiency), hypocalcemia or elevated alkaline phosphatase (vitamin D def) and hypertransaminasemia. Enteropathy often results in lactose intolerance. Half of all cases present atypically or silently.

- **Diagnosis:** Serum tests and small bowel biopsy (recommend 6-8 biopsies from the 2<sup>nd</sup>-3<sup>rd</sup> portion of the duodenum).

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

<table>
<thead>
<tr>
<th>Serum tests</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA endomysial antibodies**</td>
<td>85-98%</td>
<td>97-100%</td>
</tr>
<tr>
<td>IgA tissue transglutaminase antibodies**</td>
<td>90-98%</td>
<td>94-97%</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  
**not elevated in serum IgA deficiencies

- **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)
  - Peptic duodenitis (including Zollinger-Ellison syndrome)
  - Crohn’s disease
  - Small intestinal bacterial overgrowth
Eosinophilic enteritis
Radiation or cytotoxic chemotherapy
Tropical sprue
Severe malnutrition
Diffuse small intestinal lymphoma
Graft versus host disease
Hypogammaglobulinemia
Alpha chain disease

**Treatment**
-- Gluten free diet- 70% of patients have symptomatic improvement within 2wks. Adherence decreases the risk of disease associated cancers (especially T-cell lymphoma).
-- Avoid dairy products for 3-6 mo as patients often have secondary lactose intolerance.
-- Rarely IV corticosteroids are needed for critically ill patients with acute celiac crisis.

**Considerations in failure to respond to a gluten-free diet or to deteriorate when on a gluten-free diet**
-- Non-adherence to the gluten-free diet
-- Development of small intestinal lymphoma
-- Refractory sprue (treat with corticosteroids, imuran/cyclosporin and/or TPN
-- Collagenous sprue or collagenous colitis
-- Unsuspected concurrent disease such as pancreatic insufficiency
-- Development of diffuse intestinal ulceration (ulcerative jejunoileitis)

**Diarrhea and Gas**

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

**Four main pathophysiologic mechanisms** (often overlap):
- **Osmotic Diarrhea:** Excessive ingestion of poorly absorbable osmotically active solutes, e.g., carbohydrate malabsorption, certain laxatives (magnesium, sodium phosphate or PEG)
- **Secretory Diarrhea:** Excessive intestinal secretion or inadequate ion absorption, e.g., infections, stimulant laxatives, intestinal resection, bile acid malabsorption, fatty acid malabsorption, small intestinal diseases such as celiac sprue or lymphoma.
- **Intestinal Dysmotility:** IBS, diabetes, scleroderma, hyperthyroidism, fecal impaction with incontinence.
o **Inflammatory Diarrhea**: May have passage of blood, mucus or protein in the stool, e.g., IBD, ischemic colitis, infection.

- **Stool osmolality in distinguishing osmotic from secretory diarrheas**
  
  o Fecal \((Na^+ + K^+) \times 2 = \text{approximate stool osmolality (mOsm/Kg)}\)
  
  o 290 mOsm/Kg – calculated stool osmolality = fecal osmotic gap
  
  o Gap < 50 usually is due to a secretory diarrhea, > 125 usually to an osmotic diarrhea.
  
  o If stool osmolality is <290mOsm/kg than the stool has been diluted (by urine/water etc…)

- **Acute Diarrhea (<3wks)**
  
  o Often due to viruses, bacteria, food poisoning, or drugs. Evaluation only needed if patient has clinical toxicity, is immunocompromised, has bloody stools or worsening symptoms over 7days.

  o **Major causes:**

  Non inflammatory:
  
  - Viral disease (Rotavirus, Norwalk virus, Cytomegalovirus, Herpes simplex virus)
  
  - Bacterial toxin-mediated disease (Nontyphoidal Salmonella, S. aureus, Bacillus cereus, Clostridium perfringens, Listeria monocytogenes)
  
  - Protozoal disease (Giardia lamblia, Cryptosporidium)
  
  - Medication-induced diarrhea (Mg antacids, Antibiotics, Laxatives, colchicine, lactulose, metformin)
  
  - Irritable bowel syndrome
  
  - Dietary intolerance
    
    - Disaccharidase deficiency (e.g., lactase)
    
    - Fructose intolerance (e.g., non-diet soft drinks)
    
    - Altered diet (osmotic agent)

  Inflammatory diarrhea:
  
  - Invasive Bacterial disease (Shigella, Salmonella, Campylobacter, Yersina, Vibrio, C. Difficile, Enteroinvasive E. Coli)
  
  - Toxin-mediated (Enterohemorrhagic E. Coli O157)
  
  - Protozoal disease (Entamoeba histolytica, Strongyloides stercoralis)
  
  - Mesenteric ischemia
  
  - Radiation colitis
  
  - Inflammatory bowel disease
• **Chronic Diarrhea (>4 wks)**
  - Often due to IBS, IBD, malabsorption or parasitic infection. Also consider laxative abuse, cancer, alcohol, endocrine abnormalities, neuroendocrine tumors, food allergy and medications.

  - **Initial Evaluation of Chronic Diarrhea:**
    - Send stool specimen for fecal leukocytes, occult blood, sudan stain, O and P, electrolytes, and pH (<5.3 suggests carbohydrate malabsorption), laxative screen.
    - Consider 72-hr collection for stool weight and quantitative fat. Normal daily stool fat is <7g/day on 100g/day diet.
    - CBC, ESR, TSH
    - Review the medication list
    - 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.
    - Consider an empiric trial of metronidazole for treatment of possible small bowel bacterial overgrowth or giardiasis.

  - **Selected Chronic Diarrhea States:**
    - **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).
    - **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.
    - **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.
    - 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.

• **Common colonic gas-producing foods**
<table>
<thead>
<tr>
<th>Food</th>
<th>Malabsorbed Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products (milk, ice cream, cottage</td>
<td>Lactose</td>
</tr>
<tr>
<td>cheese, yogurt)</td>
<td></td>
</tr>
<tr>
<td>Soft drinks (not “diet” drinks), honey</td>
<td>Fructose</td>
</tr>
<tr>
<td>Legumes (baked beans, soy beans)</td>
<td>Melitose, stachyose</td>
</tr>
<tr>
<td>Dietetic candies and chewing gum</td>
<td>Mannitol, sorbitol, xylitol</td>
</tr>
</tbody>
</table>

- **Fecal leukocytes in intestinal infections**

  Present: *Shigella, Campylobacter, Enteroinvasive/Enterohemorrhagic E. coli*
  Variable: *Salmonella, Yersinia, V. parahaemolyticus, C. difficile, Aeromonas*
  Absent: *V. cholerae, Enterotoxigenic/Enteropathogenic E. coli, Rotavirus, Norwalk virus, Giardia lamblia, Entamoeba histolytica, Staphylococcus aureus, Clostridium perfringens, Bacillus cereus*

- **Travelers’ diarrhea**
  - Up to 50% of travelers to developing countries affected within first 2 weeks. 10-20% of travelers have onset of diarrhea after returning home.
  - Travelers’ diarrhea may be an important etiologic feature in the development of IBS.
  - Common etiologies include: *Shegella, Salmonela, Yersinia, E. coli, S. aureus, Bacillus cereus, C. difficile, Listeria, Rotavirus, Norwalk virus, Giardia and Entamoeba histolytica*.

  - **Prophylaxis**
    - Rifaximin, 200 mg PO BID, taken with meals as soon as traveler gets to destination; stop upon return.
    - Bismuth subsalicylate (2 tabs with meals and q hs [8tabs daily])
    - Ciprofloxacin, 500mg; norfloxacin, 400mg; or ofloxacin, 300mg PO QD

  - **Treatment of dysentery**
    - Loperamide or bismuth subsalicylate plus
      - azithromycin, 500 mg PO QD, or
      - fluoroquinolone (ciprofloxacin, 500 PO BID, levofloxacin 500 mg PO QD, or norfloxacin 400 mg PO BID), or
      - rifaximin 200 mg PO TID, for 3-5 days

- **Chronic Inflammatory Bowel Diseases**

  - **Treatment Overview for Crohn’s Disease:**
    - For mild to moderate disease start with a 5-ASA drug (which one depends on the site of the disease). If no/inadequate response consider trial of antibiotics
before proceeding to steroids. Start with prednisone 40-60 mg/day x 2wks then taper slowly (5 mg/wk). If unable to taper off consider transitioning to budesonide. If still unable to wean off steroids start immunomodulator therapy (such as azathioprine and/or infliximab). Methotrexate is rarely used today in adults (usually for those unresponsive to azathioprine of the present of anti-TNF antibodies).

- For severe disease consider hospitalization for initiation of IV steroids, bowel rest and TPN if needed. If still unresponsive consider IV cyclosporine or Remicade (limited data).
- Perianal disease- start with a trial of metronidazole (500 mg tid x 2-4 wks) or ciprofloxacin (500 mg bid). Often, long term therapy is needed.
- Fistulas- Start with both infliximab and azathioprine (good data). Surgery often needed.
- **Step-up approach** The early use of highly effective but potentially more toxic treatment strategies early in the course.
- **Step-down approach** A sequential treatment strategy beginning with less toxic and often less effective treatments as first line.

- **Azathioprine regimens in the treatment of Crohn’s disease**

  *(per J. Levine)*

  Start at 100 mg/day after checking CBC/liver panel  
  Follow WBC every two weeks and liver panel every month, and increase dose by 50 mg/day increments as long as WBC is ≥4000 (rarely using as much as 400 mg/day to induce remission).

  *(per J. W. Singleton)*

  Start at 2.0-2.5 mg/kg/day (John feels there is no evidence that starting at a lower dose has less toxicity).

  Check CBC and LFTs before starting the drug, then:  
  Check CBC weekly for one month, then monthly for the first year and quarterly thereafter.  
  Check LFTs after 1-2 months, then quarterly thereafter  
  *Try to avoid the WBC going below 4000

  If 6-mercaptopurine (6-MP) is used, start at 1.0-1.5 mg/kg/day

- **Managing azathioprine therapy with TPMT testing**

  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-methyl-mercaptopurine ribonucleotides. (6-MMPN). Patients who have low or absent TPMT can shunt 6-MP to high 6-TGN levels, which 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.

- **Pre-treatment TPMT genotyping:**
  If low, avoid thiopurines
  If intermediate, use lower dose azathioprine, expecting full therapeutic response
  If normal, give full initial dose azathioprine.
  If high, higher dose azathioprine may be need to get a therapeutic response. (Metabolite testing does not replace lab monitoring for toxicity!)

- **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.

<table>
<thead>
<tr>
<th>TPMT genotype</th>
<th>% Patients</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous (normal/increased)</td>
<td>89%</td>
<td>Decreased risk, ?increase dose</td>
</tr>
<tr>
<td>Heterozygous (intermediate)</td>
<td>11%</td>
<td>At risk, ?decrease dose</td>
</tr>
<tr>
<td>Homozygous (low/none)</td>
<td>0.3%</td>
<td>High risk, no treatment</td>
</tr>
</tbody>
</table>

  **Step 2:** Metabolite testing (during treatment)
  Can help guide dosing, check patient’s compliance, avoid overdosing.

  6-TGN desired range: 230-400
  Lower level suggests underdosing or nonadherence, or preferential metabolism via an alternative pathway.
  Higher level may prompt concern for leukopenia.

  6-MMPN desired range:<5700 may prompt concern for hepatotoxicity.

- **5-aminosalicylic acid drugs and site of activity**

<table>
<thead>
<tr>
<th>5-ASA</th>
<th>Release</th>
<th>Site of Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol</td>
<td>pH &gt; 7.0</td>
<td>Terminal ileum and colon</td>
</tr>
<tr>
<td>Pentasa</td>
<td>pH &gt; 6.0</td>
<td>Small bowel and colon</td>
</tr>
<tr>
<td>Olsalazine (Dipentum)</td>
<td>Bacteria</td>
<td>Colon (ileum with bacterial overgrowth)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Bacteria</td>
<td>Colon (ileum with bacterial overgrowth)</td>
</tr>
</tbody>
</table>
• **Treatment overview for UC:**
  - Often depends on the severity and site of the colitis.
    - Proctitis- limited to the rectum seen in 30% patients. Start with 5-ASA suppository q hs until patient is in remission. If reoccurs leave on maintenance. For more severe disease add a steroid foam.
    - 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.
    - Pancolitis- For mild/moderate disease again start with 5-ASA po drug. Add prednisone for inadequate response or severe disease. For steroid refractory disease consider azathioprine or infliximab.
    - Severe colitis: Start with bowel rest, TPN and IV steroids. Add broad spectrum antibiotics if no response or 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**
  - Start at 2-2.5 mg/kg/day IV, continue for 10-14 days (target blood level 250-300).
  - When patient’s condition is stable, convert to oral; conversion is usually double the IV dose.

• **Budesonide**
  - Effective in active ileal or right colonic Crohn’s disease (all is released by mid-transverse colon).
  - 9 mg po q a.m. is about equal to 40 mg prednisone.
  - Can be used to help taper prednisone

• **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 maintaining remission.</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</td>
</tr>
</tbody>
</table>
Cyclosporine  
C Weight-based IV  
data.  
Justified in active disease  
refractory to other oral or 
topical agents. Can cause  
small-for-gestational-age  
births.

Metronidazole  
B 250-500 mg tid  
Seems safe, but use is limited  
to 2d and 3d trimesters because  
of potential mutagenicity in the  
first trimester.

Methotrexate  
X  
Contraindicated owing to  
teratogenicity.

C. difficile-induced Colitis-Treatment

- **Specific treatment**  
  Antimicrobial agents (if symptoms are severe or persistent). Vancomycin and  
  metronidazole are equally effective. Vancomycin is preferred in pregnant patients.  
  - **Oral agents:** (preferred)  
    Vancomycin 125 mg PO qid x 10-14 days  
    Metronidazole 500 mg PO tid x 10-14 days  
  - **Parenteral agent:** (to be used only until oral agents are tolerated)  
    Metronidazole 500 mg IV q8h  
  - **Other:**  
    Rifaximin is a non-absorbed antibiotic that achieves high concentrations in the gut lumen. Data are emerging  
    regarding its use in C. difficile colitis (see below)

- **Alternative treatments**  
  - 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)  
  - Alter fecal flora: Lactinex (Lactobacillus): 1-g packet PO qid x 7-14 days  
  - IV gamma globulin

- **Treatment of recurrences**  
  - Initial recurrence: Occurs in 10-25% of patients  
    Confirm diagnosis with stool toxin assay  
    Withhold antibiotics if symptoms are mild  
    14-day course of metronidazole 500 mg tid or  
    vancomycin 250 qid
Second recurrence: *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

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)

Some authors recommend *Rifaximin* 400 mg po TID x 2 weeks, then 200 mg po TID x 2 weeks for recurrences

### Anal Fissures

- **Characteristics**
  - Majority are caused by trauma to the anal canal (such as passage of hard stool). Less common causes: Crohn’s disease, TB, leukemia
  - A midline sentinel skin tag is often associated.
  - 90% are mid-posterior; 10% anterior
  - Any not anterior or posterior may be Crohn’s disease

- **Treatment**
  - *Fiber, stool softeners:*
    - Nitroglycerin (increases blood flow and reduces pressure at the internal anal sphincter)
      - At DHMC: order NitroBid ointment, diluted to 0.2% in Vaseline
      - At DVAMC: in computer, find nitroglycerin ointment, 0.2% in petrolatum
      - At UCHSC: order 0.2% nitroglycerin ointment. Dispensed in 30-g tubes.

  - **Note:** be sure to specify 0.2%, not 2%.

  - *Nifedipine*
0.2% gel bid or 20 mg po bid

2-5% lidocaine ointment or hydrocortisone can be used pre-BMs; Sitz baths can be used after BMs.

Other: Botulinum toxin (injection into anal sphincter)

Last Resort: Surgery: lateral sphincterotomy. Successful but may result in fecal incontinence.

Ogilvie’s Syndrome (acute colonic pseudobstruction)

- Contributing factors
  Recent surgery, general anesthesia
  Chronic obstructive pulmonary disease
  Underlying neurological disease
  Medications (antidepressants, antipsychotics, opiates)
  Diabetes
  Congestive heart failure
  Uremia
  Infection
  Hip fracture
  Electrolyte abnormalities
  Severe medical illness

- Neostigmine protocol

  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.

Colonic Neoplasms

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
</tr>
<tr>
<td>Average risk</td>
<td>10 y (begin at age 50y)</td>
</tr>
<tr>
<td>Single first-degree relative (FDR) with cancer (or adenomas) at age ≥60y</td>
<td>10 y (begin at age 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>
</tbody>
</table>
HNPCC (begin age 20-25y) 1-2 y

**Postadenoma resection**

- 1-2 tubular adenomas of <1 cm 5-10 y
- 3-10 adenomas or adenoma with villous features ≥ 1 cm or with high-grade dysplasia 3 y
- >10 adenomas <3 y
- Flat adenomas removed in piecemeal fashion Consider follow-up in 2-6 months

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

**Ulcerative Colitis, Crohn’s surveillance after 8 y of pancolitis or 15 y of left-sided colitis**

- Pancolitis:
  - > 8 years: 1-2 years
  - >15 years: yearly
- Left sided disease:
  - >8 years: 2 years
  - >15 years: yearly.

- **Amsterdam criteria for hereditary nonpolyposis colorectal cancer (HNPCC)**
  - (3) At least three relatives with colorectal cancer (one must be a first-degree relative of other two)
  - (2) Colorectal cancer involving at least two generations
  - (1) One or more colorectal cancer cases before age 50 years
  - FAP has been excluded
    (The Amsterdam II criteria allow for any HNPCC-related cancer (endometrial, ovarian, gastric, hepatobiliary, small bowel cancer, or transitional cell carcinoma of the renal pelvis or ureter) to replace colonic cancer in the original criteria.)

- **Bethesda Criteria** (for identification of patients with colorectal tumors who should undergo testing for microsatellite instability)
  - Individuals with cancer in families that meet the Amsterdam criteria
  - 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)
  - 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)
  - Individuals with CRC or endometrial CA diagnosed at age <45
  - Individuals with right-sided CRC with an undifferentiated pattern on histopathology diagnosed at age <45
  - Individuals with signet-ring type CRC diagnosed at age <45
  - Individuals with adenomas diagnosed at age <40 years
• Classification of colonic cancer
  
  o Dukes’ classification (Astler-Coller modification)
    
    A   limited to the mucosa
    B1  confined to the muscularis propria
    B2  through the muscularis propria, into or through serosa
    C1  same as B1 plus regional nodal metastases
    C2  Same as B2 plus regional nodal metastases
    D   distant metastases

    Five-year survival
    A   90%
    B1  80%
    B2  60%
    C   40%
    D   5%

  o American Joint Committee on Cancer (TNM Classification)
    
    Stage 0
    Carcinoma in situ intraepithelial or invasion of lamina propria (Tis N0 M0)

    Stage I
    Tumor invades submucosa (T1 N0 M0) Dukes’ A
    Tumor invades muscularis propria (T2 N0 M0)

    Stage II
    Tumor invades through the muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues (T3 N0 M0) Dukes’ B
    Tumor perforates the visceral peritoneum or directly invades other organs or structures and/ or perforates visceral peritoneum (T4 N0 M0)

    Stage III
    Any degree of bowel wall perforation with regional lymph node metastasis
    N1 Metastasis in 1 to 3 regional lymph nodes
    N2 Metastasis in 4 or more regional lymph nodes
    Any T N1 M0, Dukes’ C
    Any T N2 M0

    Stage IV
    Any invasion of bowel wall with or without lymph node metastasis, but with evidence of distant metastasis
Blood in Stool
- Melena: 150-200 ml blood in single bleed will cause it
- FOBT (+): 20 ml/d will cause it
- 100 ml/d may have normal-appearing stools
- 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

HEPATOBILIARY

Acute Liver Failure
- **Kings college criteria**
  - Acetaminophen toxicity
    - 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.*
  - Other causes of fulminant hepatic failure
    - 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.*

Liver Transplantation
- **Transplant work-up labs**
  - ANA
  - HIV
  - Anti-mitochondrial Ab
  - HSV type-specific Ab
  - Anti-smooth muscle Ab
  - CMV IgG
  - Ceruloplasmin
  - EBV IgM and IgG
  - Iron, TIBC, Ferritin
  - TSH
  - Alpha-1 anti-trypsin level and phenotype
  - AFP
  - Hepatitis B SAg and SAb, core IgM and IgG Ab
  - RPR
  - Hepatitis C Ab
  - Toxin Screen
  - Hepatitis A IgM and IgG
  - Urine Analysis
- **Other tests to consider**

  Abdominal US with Doppler studies of hepatic vasculature  
  EGD, colonoscopy (certain populations)  
  EKG and Dobutamine Stress Echo  
  Chest X-Ray  
  Pulmonary Function Tests  
  Pap smear and mammogram

**Hepatitis B (HBV)**

- **Hepatitis B serologies**

  **Anti-HB core IgM**: early indicator of acute infection with HBV. Sole marker of acute HBV infection during the window period between the disappearance of HBsAg and the appearance of anti-HBs

  **HBeAg**: Indicates high degree of replication and infectivity. Order only when evaluating patient with chronic HBV. If negative in presence of ongoing HBsAg and HBV DNA, indicates pre-core or core promoter mutation.

  **Anti-HBeAb**: presence associated with resolution of active infection, but often signifies virus is integrated into host DNA, especially if host remains HBsAg-positive.

  **Anti-HBsAb**: typically indicates immunity (clinical recovery of HBV infection or prior immunization). Anti-HBs may not be detectable until several weeks to months after immunogenicity.

  **HBsAg**: indicates either acute or chronic infection with HBV. Persistence of HBsAg for more than six months implies chronic infection.

  **YMDD Mutation**: Check in patients treated with nucleoside analogues who have a bump in HBV DNA.

- **Recommended Treatment Strategies: AASLD**

<table>
<thead>
<tr>
<th>HBeAg Status</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Recommended Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>&lt;10^5 copies/ml</td>
<td>≤2x ULN</td>
<td>Monitor, treatment generally not recommended</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;10^5 copies/ml</td>
<td>≤2x ULN</td>
<td>Monitor, consider biopsy, treat if significant disease</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;10^5 copies/ml</td>
<td>&gt;2x ULN</td>
<td>Biopsy, treat</td>
</tr>
<tr>
<td>Negative</td>
<td>≤10^6 copies/ml</td>
<td>≤1x ULN</td>
<td>Monitor, treatment generally not recommended</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;10^5 ≤ 10^6 copies/ml</td>
<td>1-2x ULN</td>
<td>Monitor, consider biopsy, treat if significant disease</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;10^6 copies/ml</td>
<td>&gt;2x ULN</td>
<td>Biopsy, treat</td>
</tr>
<tr>
<td>Positive or Negative</td>
<td>Detectable</td>
<td>Cirrhosis</td>
<td>Compensated, ≥10^4 copies/ml: NA Compensated, ≤10^4 copies/ml: NA vs observe Decompensated: Combo NA + OLT</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Positive or Negative</td>
<td>Undetectable</td>
<td>Cirrhosis</td>
<td>Compensated: observe Decompensated: OLT</td>
</tr>
</tbody>
</table>

*1 IU/ml = 5 copies/ml

- **Considerations in Choosing Initial Hepatitis B Therapy**
  - **Nucleoside Analog first:** Cirrhosis, particularly with decompensation
  - **PEG-IFN first:**
    - Younger age (HBsAg clearance, better tolerability)
    - Genotype A and B > C >> D
    - Lower levels of virus (<910^5 copies/mL)
  - **Either PEG IFN or Nucleoside Analog :**
    - High ALT: Avoidance of IFN side effects, high rate of HBeAg seroconversion with NA vs potential for cure with PEG-IFN.

**Hepatitis C (HCV)**

- **Considerations before treating HCV**
  - **Laboratory:** HCV genotype, HCV viral load, HAV IgG, HBsAb, HBsAg, LFTs, CBC, alpha fetoprotein, serum iron, TIBC, ferritin, ANA, TSH, chem 7 and HIV
  - **Radiology studies:** Abdominal ultrasound
  - **Other considerations:**
    - Liver biopsy (definitely in genotypes 1 and 4; consider in genotypes 2 and 3, especially if concern for the possibility of cirrhosis)
    - Mental health clearance if there is a history of depression
    - Substance abuse clearance if there is concern for recent substance abuse
    - For women, pregnancy test and documentation of contraception if pre-menopausal
    - Vaccination for HAV and HBV if naïve
    - Documentation of recommendation of spousal testing if spouse hasn’t been checked

- **Frequency of viral load checks in patients undergoing treatment**
  - pre-treatment
  - 4 weeks, 12 weeks, 24 weeks and end of treatment
  - 6 months post-treatment

- **Starting doses of HCV medications**
  - Interferon alfa-2a (Intron-A): 3 MU SQ TIW
  - Peginterferon alfa-2b (Peg-Intron): 1.5 µg/kg/wk
- Peninterferon alfa-2a (Pegasys): 180 µg/wk
- Ribavirin: 1000 or 1200 mg/kg/d (wt <75kg or >75kg respectively) in genotype 1 and 4’s. 800mg/d in genotype 2 and 3’s.

**Drug adjustments based on laboratory abnormalities**

- 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.
- 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.
- 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.
- 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 G-CSF in patients receiving HCV treatment**

- Consider using it if patients have cirrhosis or are post-liver transplant and require reduction in their interferon dose at any point.
- 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.
- 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.
- 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.
- Contraindications to G-CSF treatment:
  - Acute myelocytic leukemia
  - Allergy to E. coli-derived proteins
  - Vasculitis
  - Cardiovascular disease
  - Autoimmune disease
  - Sepsis
- Potential adverse reactions to G-CSF:
  - Skin rash
  - Vasculitis
  - Bone pain
  - Myalgias
  - Headache
  - Thrombocytopenia
Nausea, vomiting, abdominal pain
Leukocytosis
Injection-site redness
Exacerbation of psoriasis.

- Less frequent adverse reactions:
  - Allergic reaction
  - Severe anaphylaxis
  - Splenomegaly
  - Transient hypotension.

**Use of epoetin (Epogen) in patients receiving HCV treatment**

- 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.

- All patients should have iron stores, vitamin B-12, and folic acid evaluated.

- 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.

- 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.

- 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 and Complications**

- **Child-Turcotte-Pugh scoring system**

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>0</td>
<td>Mild (or controlled by diuretics)</td>
<td>At least moderate despite diuretic treatment</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>
Grade A = score 5-6 = 1 year survival 100%
Grade B = score 7-9 = 1 year survival 80%
Grade C = score 10-15 = 1 year survival 45%

- **Classification of ascites by serum-ascites albumin gradient (SAAG)**

<table>
<thead>
<tr>
<th>High gradient (&gt;1.1 g/dl)</th>
<th>Low gradient (&lt;1.1 g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Tuberculous peritonitis</td>
</tr>
<tr>
<td>Cardiac ascites</td>
<td>Pancreatic ascites</td>
</tr>
<tr>
<td>“Mixed” ascites</td>
<td>Bowel obstruction or infarct</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>Biliary ascites</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Postoperative lymphatic leak</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>Serositis (connective tissue diseases)</td>
</tr>
<tr>
<td>Myxedema</td>
<td></td>
</tr>
<tr>
<td>Fatty liver of pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

- **Ascitic fluid in cirrhosis**

Uncomplicated ascites: <250 PMNs/mm³

Spontaneous bacterial peritonitis (SBP): >250 PMNs/mm³ and positive culture (usually for a single organism)

Culture-negative neutrocytic ascites: >250 PMNs/mm³ with negative culture

Monomicrobial non-neutrocytic bacterascites: <250 PMNs/mm³ with positive culture for one organism (usually represents colonization phase of ascitic fluid infection).

Polymicrobial non-neutrocytic bacterascites: <250 PMNs/mm³ with positive culture for more than one organism (usually caused by needle puncture of the gut during paracentesis).

Traumatic tap: subtract 1 PMN for 250 RBCs. Subtract 1 WBC for 750 RBCs.

- **Albumin infusion accompanying paracentesis in the management of ascites**

Although the use of albumin in large-volume paracentesis is controversial, if it is used the AASLD guidelines may be useful: albumin is unnecessary if the volume to be removed is <5 liters; if >5 liters is to be removed give 50 g (25% solution).

- **TIPS: contraindications**
  - Absolute contraindications
  - Renal failure: Serum creatinine >2 mg/dL
Liver failure: Serum bilirubin >3 mg/dL
Portal vein thrombosis with cavernous transformation
Severe pulmonary hypertension
Multiple hepatic cysts
Congestive heart failure
Uncontrolled systemic infection or sepsis
Unrelieved biliary obstruction

Relative contraindications
INR >1.5
Platelets < 100K
Portal vein thrombosis without cavernous transformation
Moderate pulmonary hypertension
Liver cancer
Hepatic encephalopathy poorly controlled by medical therapy
Obstruction of all hepatic veins
Patient not a liver transplant candidate

- **Hepatic encephalopathy**
  - **Grades of HE**
    1. Changes in behavior with minimal change in level of consciousness.
    2. Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior.
    3. Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli.
    4. Comatose, unresponsive to pain, decorticate or decerebrate posturing.

- **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>

- **Treatment**
  Correct underlying precipitating factor.
  Lactulose 30-45 ml PO TID, titrate to 2-3 stools daily
    (Can also be given as a 300 cc retention enema q 4-6 h)
  Neomycin 1000-3000 mg PO q 6h (watch for nephrotoxicity) or
  Rifaximin 400 mg PO TID
• Spontaneous Bacterial Peritonitis (SBP)

  o Treatment (AASLD Guidelines)

  Ascitic fluid PMN counts > 250 cells/mm\(^3\): 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/mm\(^3\) 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/mm\(^3\) 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)

  o Prophylaxis (AASLD Guidelines)

  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.

• Hepatorenal syndrome

  o 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.
Criteria for hepatorenal syndrome

**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.

**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

- **Discriminant function for use of corticosteroids in alcoholic hepatitis**

  **Note:** Discriminant function is only valid in the absence of a background of advanced liver disease.

  \[4.6 \times (\text{patient’s prothrombin time - control prothrombin time}) + \text{serum bilirubin}\]

  *Patients who have a score of 32 or higher may benefit from receiving corticosteroids (prednisolone 40mg qd x 4weeks followed by 2 week taper)*

- **Management of HCC – AASLD guidelines**
Alcohol Content of Beverages

Whiskey  qt  80 proof  300 g
Beer  (4%) 12 oz x 6  75 g
Wine  (12%) 750 ml  90 g
Wine, fortified  (20%) 750 ml  150 g

Men: Women
Moderate alcohol consumption: <40 gm/day <20 gm/day
Heavy alcohol consumption: >80gm/day >20gm/day

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

Hemochromatosis

- Representative iron measurements

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hereditary Hemochromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron, µg/dl</td>
<td>50-150</td>
<td>180-300</td>
</tr>
<tr>
<td>Transferrin, mg/dl</td>
<td>250-370</td>
<td>200-300</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>20-50</td>
<td>80-100</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Serum ferritin, ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20-300</td>
<td>500-6000</td>
</tr>
<tr>
<td>Women</td>
<td>15-250</td>
<td>500-6000</td>
</tr>
</tbody>
</table>

Hepatic iron index >2: homozygous hereditary hemochromatosis
Hepatic iron index <2: heterozygotes, normal persons, alcoholic liver disease

- **Treatment**
  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.

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

- **Family screening**
  - 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.
  - Perform liver biopsy for stainable and biochemical iron on any one who has abnormal tests.

**Wilson’s Disease:** Autosomal recessive defect in cellular copper transport. An impairment in biliary excretion leads to accumulation of copper in the liver.

- **Diagnosis**
  - Serum ceruloplasmin*
  - Urinary copper**
  - Hepatic copper
  - Hepatic histology
  - Slit-lamp examination for Kayser-Fleischer rings

*Order first but remember that 15% of Wilson’s disease patients have levels within the lower limits of normal.
**If urinary copper levels are elevated do liver biopsy for copper stain and quantitative copper determination.
• **Characteristic laboratory features**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Wilson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum copper, µg/dL</td>
<td>80-140</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Urine copper, µg/24 h</td>
<td>&lt;40</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Serum ceruloplasmin, mg/dl</td>
<td>20-40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Hepatic copper concentration, µg/g dry weight</td>
<td>15-50</td>
<td>250-3000</td>
</tr>
</tbody>
</table>

**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>
<tr>
<td>Acute hepatitis</td>
<td>Isoniazid, nitrofurantoin, halothane, sulfonamides, phenytoin, disulfiram, ketoconazole, troglitazone</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Nitrofurantoin, diclofenac, trazadone</td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>Allopurinol, carbamazepine, quinidine, quinine</td>
</tr>
<tr>
<td>Cholestasis without hepatitis</td>
<td>Oral contraceptives, androgens</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>Chlorproamazine, tricyclic antidepressants, erythromycins, amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>Perhexiline, amiodarone</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>In bone marrow transplantation: 6-thioguanine, busulfan, azathioprine, mitomycin, pyrrolizidine alkaloid</td>
</tr>
</tbody>
</table>

• **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.

![Rumack-Matthews nomogram](image)

- **Methotrexate (MTX) liver injury. Monitoring for the development of chronic hepatitis and cirrhosis**

  For all MTX candidates
  - Check laboratory values, advise alcohol abstinence
  - If LFTs are abnormal or liver disease is present, do pre-treatment liver biopsy
  - Check LFTs and albumin q 6-8 weeks; if abnormal do liver biopsy
  - Liver biopsies are advised every 2 or 3 years (or every 1.5 gm of cumulative dose).

  For psoriasis patients
  - Do biopsies on the basis of cumulative dose (q 1.5-2.0 g)
  - Have a low threshold for doing early liver biopsy (after 2-4 months of MTX therapy)

- **Herbal remedies that have been 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>

**Pyogenic and Amebic Liver Abscess: Clinical Distinctions**

<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, 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, cryptogenic</td>
<td>Colonic infection with <em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>US or CT +/- aspiration</td>
<td>US or CT and serology</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>

**PANCREAS**

**Acute Pancreatitis**

- **Ranson’s criteria**

  **On Admission:**
  - Age > 55
  - WBC > 16,000/mm³
  - Glucose > 200 mg/dL
  - LDH > 350 IU/L
AST > 250 IU/L

**Within 48 hours:**
- Hematocrit decrease > 10%
- BUN rise > 5 mg/dL
- Calcium < 8 mg/dL
- Arterial pO\(_2\) < 60 mm Hg
- Base deficit > 4 mEq/L
- Fluid deficit > 6 L

**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%.

**Drugs That May Cause Pancreatitis**

- **Definite association**
  - 6-mercaptopurine
  - Azathioprine
  - Sulfonamides (sulfasalazine, Bactrim)
  - Pentamidine
  - Tetracycline
Valproic acid
Furosemide
Estrogens
Aldomet
Octreotide
Thiazide diuretics
IV lipid infusions
L-aspariginase

Probable association
Didanosine
Oral 5-aminosalicylic acid (olsalazine [Dipentum] and mesalamine [Asacol])
Metronidazole
Nitrofurantoin
Corticosteroids
Chlorthalidone
Ethacrynic acid
Phenformin
Non-steroidal inflammatory drugs
Methyldopa

Angiotensin-converting enzyme inhibitors
Cimetidine
Salicylates
Acetaminophen

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 W&gt;M</td>
<td>Macrocystic</td>
<td>Mucinous</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>F</td>
<td>Middle Age W&gt;M</td>
<td>Macrocystic</td>
<td>Malignant, mucinous</td>
<td>High</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td>Mixe 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 W&gt;M</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>Mixe d</td>
<td>Middle Age W=M</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 W&gt;M</td>
<td>Mixed solid and cystic</td>
<td>Endocrine-like</td>
<td>Low</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, HCO$_3^-$, 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.