CHAPTER 5

Digestive Diseases

L. Michael Snyder and Michael J. Mitchell

Disease States Associated with Abdominal Pain (Acute and Chronic) 143

Disease States Associated with Abdominal Pain 145

Disorders of the Esophagus 145
- Mallory-Weiss Syndrome 145
- Perforation of the Esophagus, Spontaneous 146
- Plummer-Vinson Syndrome 146

Disorders of the Stomach 146
- Gastritis, Chronic 146
- Carcinoma of the Stomach 147

Disorders of the Pancreas 147
- Carcinoma of the Pancreas 147
- Cystic Fibrosis of the Pancreas 148
- Macroamylasemia in Vivo Artifact 149
- Pancreatitis 149
- Pseudocyst of the Pancreas 154
- Dyspepsia and Peptic Ulcer Disease 155

Ascites 157

Disorders of the Peritoneum Associated with Ascites 159
- Chronic Liver Disease 159
- Infected Ascitic Fluid 160
- Secondary Peritonitis 160
- Continuous Ambulatory Peritoneal Dialysis 160
- Pancreatic Disease 161
- Malignant Ascites 161
- Ascites in Fetus or Neonate 161
- Peritonitis, Acute 162

Diarrhea 163

Diarrhea, Acute 167
- Osmotic Diarrhea 167
- Secretory (Abnormal Electrolyte Transport) Diarrhea 167

Exudative Diarrhea (Inflammatory Causes) 168
- Motility Disturbances 168
- Infectious Gastrointestinal Diseases 168

Diarrhea, Chronic 173

Other Gastrointestinal Conditions Associated with Chronic Diarrhea 174
- Diverticulosis, Colon 174
- Enterocolitis, Necrotizing, in Infancy 174
- Inflammatory Bowel Disease 174
- Regional Enteritis (Crohn Disease) 174
- Ulcerative Colitis, Chronic Non-specific 175
- Malabsorption 176
- Carbohydrate Absorption Indices 177
- Celiac Disease (Gluten-Sensitive Enteropathy, Nontropical Sprue, Idiopathic Steatorrhea) 178
- Enteropathy, Protein Losing 180
- Colitis, Collagenous 181
- Colitis, Pseudomembranous 181
- Gallstone Ileus 181
- Gastroenteritis, Eosinophilic 181

Gastrointestinal Bleeding 182
- Upper Gastrointestinal Bleeding (Adult) 182
- Gastrointestinal Bleeding, Small Intestine 184
- Lower Gastrointestinal Bleeding (Adult), Acute 186

Hepatomegaly 188
- Fatty Liver 191
- Neoplasms of the Liver: Hepatocellular Carcinoma (Hepatoma) 193

Jaundice (See Hepatomegaly) 193
- Hyperbilirubinemia 196
Diseases Associated with Jaundice 198
Conjugated Hyperbilirubinemia/ Hepatocellular Jaundice 198
Infectious Disease: Viral Hepatitis 201
Vascular and Ischemic Disorders of the Liver 218

Biliary Extrahepatic Obstruction, Complete 220
Diseases of the Gallbladder and Biliary Tree (Intrahepatic or Extrahepatic) (See Abdominal Pain) 220
Cancer of the Gallbladder and Bile Ducts 220
Cholangitis, Acute 221
Cholangitis, Primary Sclerosing 221
Choledocholithiasis 223
Atresia, Extrahepatic Biliary, Congenital 223
Other Considerations 223
Intrahepatic Obstruction Cholestasis 224
Cirrhosis, Primary Biliary (Cholangiolitic Cirrhosis, Hanot
Hypertrophic Cirrhosis, Chronic Nonsuppurative Destructive Cholangitis, Etc.) 224
Congenital Conjugated Hyperbilirubinemia 226
Rotor Syndrome 226

Causes of Unconjugated Hyperbilirubinemia 228
Unconjugated Bilirubinemia 228
Physiologic Jaundice 228
Nonphysiologic Jaundice 229

Hereditary and/or Congenital Causes of Unconjugated Hyperbilirubinemia 229
Crigler-Najjar Syndrome (Hereditary Glucuronyl-Transferase Deficiency) 229
Gilbert Disease 229
Neonatal Jaundice: Breast Milk Jaundice 230
Lucey-Driscoll Syndrome (Neonatal Transient Familial Hyperbilirubinemia) 230
Wilson Disease 230
Trauma 231

This chapter focuses on several common GI clinical presentations: abdominal pain (acute and chronic); ascites; diarrhea (acute and chronic); GI bleeding upper and lower; hepatomegaly; jaundice and associated diseases, including hepatitis. When appropriate, the discussion includes radiologic and endoscopic procedures as part of the diagnostic evaluation.

DISEASE STATES ASSOCIATED WITH ABDOMINAL PAIN (ACUTE AND CHRONIC)

Definition
Acute abdomen is defined as an episode of severe abdominal pain that lasts several hours or longer and requires medical attention. The acute abdomen usually, but not necessarily, has a surgical cause. However, the term “acute abdomen” should not be equated with a need for emergency surgery. The history and physical examination remain the most important aspects of diagnosis. The key feature in the evaluation of patients with acute abdomen is early diagnosis.

Differential Diagnosis
- The differential diagnosis of an acute abdomen is most appropriately considered by its anatomic location (Table 5-1).
- Common gynecologic causes of lower quadrant pain include mittelschmerz, ovarian cyst, endometriosis, fibroids, ovarian torsion, pelvic inflammatory disease, ovarian tumor, ectopic pregnancy, infection of the uterus, threatened abortion, and round ligament pain secondary to pregnancy.
Medical conditions that may present as acute abdomen are many. Common examples include lower lobe pneumonias, acute myocardial infarction (MI), DKA, acute hepatitis, porphyria, adrenal hemorrhage, and musculoskeletal problems. Appendicitis is a clinical diagnosis. The triad of right lower quadrant pain, anorexia, and leukocytosis is the most sensitive diagnostic tool. Nausea and vomiting usually follow the onset of pain. The patient may have a low-grade fever and mild leukocytosis. Fevers with higher temperatures or increased WBC counts suggest perforation.

### Table 5–1. Differential Diagnosis of the Acute Abdomen

<table>
<thead>
<tr>
<th>Right Upper Quadrant Pain</th>
<th>Right Lower Quadrant Pain</th>
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<tbody>
<tr>
<td>Cholecystitis</td>
<td>Appendicitis</td>
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<tr>
<td>Choledocholithiasia</td>
<td>Ruptured ovarian cyst</td>
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<tr>
<td>Cholangitis</td>
<td>Meckel diverticulitis</td>
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<td>Hepatitis</td>
<td>Cecal diverticulitis</td>
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<tr>
<td>Liver tumors</td>
<td>Cholecystitis</td>
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<tr>
<td>Hepatic abscess</td>
<td>Perforated colon</td>
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<tr>
<td>Appendicitis</td>
<td>Colon cancer</td>
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<tr>
<td>Peptic ulcer disease (PUD)</td>
<td>Urinary tract infection</td>
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<tr>
<td>Perforated ulcer</td>
<td>Small bowel obstruction</td>
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<tr>
<td>Pancreatitis</td>
<td>Inflammatory bowel disease (IBD)</td>
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<tr>
<td>Gastritis</td>
<td>Nephrolithias</td>
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<td>Pyelonephritis</td>
<td>Pyelonephritis</td>
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<tr>
<td>Nephrolithias</td>
<td>Ectopic pregnancy</td>
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<tr>
<td>Pneumonia</td>
<td>Bowel incarceration</td>
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<td></td>
<td>Pelvic inflammatory disease (PID)</td>
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<table>
<thead>
<tr>
<th>Left Upper Quadrant Pain</th>
<th>Lower Left Quadrant Pain</th>
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<tbody>
<tr>
<td>PUD</td>
<td>Diverticulitis</td>
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<tr>
<td>Perforated ulcer</td>
<td>Sigmoid volvulus</td>
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<tr>
<td>Gastritis</td>
<td>Perforated colon</td>
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<tr>
<td>Splenic disease (e.g., infarct, abscess, or rupture)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Urinary tract infection</td>
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<tr>
<td>Dissecting aortic aneurysm</td>
<td>Small bowel obstruction</td>
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<tr>
<td>Pyelonephritis</td>
<td>IBD</td>
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<tr>
<td>Nephrolithias</td>
<td>Nephrolithias</td>
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<tr>
<td>Hiatal hernia</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Boerhaave syndrome (i.e., rupture of the esophagus)</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>Incarceration</td>
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<tr>
<td>Diverticulitis</td>
<td>PID</td>
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<tr>
<td>Bowel obstruction</td>
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<table>
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<tr>
<th>Midepigastric Pain</th>
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<tr>
<td>PUD</td>
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<tr>
<td>Perforated ulcer</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Abdominal aortic aneurysm</td>
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<tr>
<td>Esophageal varices</td>
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<tr>
<td>Hiatal hernia</td>
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<tr>
<td>Boerhaave syndrome (i.e., rupture of the esophagus)</td>
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<tr>
<td>Mallory-Weiss tear</td>
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</table>
Thirty percent of patients with appendicitis have an elevated WBC count, whereas 95% have a left shift.

The intensity of pain is somewhat in proportion to the degree of irritation to the parietal peritoneum. Therefore, a retrocecal appendix (which is the most common location) may cause only a dull ache, given the lack of contact with the parietal peritoneum.

**Laboratory Findings**

Laboratory studies are undertaken to support a clinical hypothesis. The evaluation generally includes a CBC, liver chemistries, amylase and lipase, coagulation profile, urinalysis, and urine pregnancy test.

- Lactic acid level should be obtained for patients with suspected ischemic bowel. An elevated level is associated with tissue hypoperfusion.
- Beta-hCG levels must be obtained for all women of childbearing age to exclude the possibility of ectopic pregnancy.

**Radiographic studies:**

- Chest radiograph should be obtained on all patients with acute abdomen to rule out free air. Pneumonia may present as an acute abdomen.
- Abdominal radiograph is most effective in detecting either bowel obstruction or pneumoperitoneum. An upright and supine view is necessary.
  - Appendicolith can be seen in 15% of patients with appendicitis, whereas renal stones may also be visualized up to 85% of the time.
  - Other radiographic findings of acute appendicitis include right lower quadrant ileus, loss of psoas shadow, deformity of the cecal outline, free air, and soft tissue density.
- Abdominal ultrasound is the study of choice in patients with possible acute cholecystitis or ovarian cyst. A sonographic Murphy sign is more sensitive than a clinical Murphy sign for acute cholecystitis. An inflamed appendix can be visualized with compression ultrasound (sensitivity ranges from 80 to 90%).
- CT can also be used to diagnose appendicitis in patients whose clinical symptoms are ambiguous.
  - Air in the appendix or a normal-appearing contrast-filled appendix virtually rules out the diagnosis of appendicitis.
  - CT will provide an alternate diagnosis in 15% of patients when assessing for appendicitis.
- Arteriography is the test of choice for patients with suspected mesenteric ischemia.

**DISEASE STATES ASSOCIATED WITH ABDOMINAL PAIN**

**DISORDERS OF THE ESOPHAGUS**

**MALLORY-WEISS SYNDROME**

**Definition**

Mallory-Weiss syndrome is characterized by spontaneous cardioesophageal laceration, usually caused by excessive retching. Laboratory findings are due to hemorrhage from cardioesophageal laceration.
PERFORATION OF THE ESOPHAGUS, SPONTANEOUS

In spontaneous perforation, gastric contents are found in thoracocentesis fluid.

PLUMMER-VINSON SYNDROME

Definition
Plummer-Vinson syndrome is an iron deficiency anemia associated with dysphagia, atrophic gastritis, glossitis, and so on. It carries an increased risk of cancer of the esophagus and hypopharynx.

DISORDERS OF THE STOMACH

GASTRITIS, CHRONIC

- A diagnosis of chronic gastritis depends on biopsy of gastric mucosa.

Atrophic (Type A Gastritis, Autoimmune Type)
- Gastric antrum is spared.
- Parietal cell antibodies and intrinsic factor antibodies help identify those patients prone to pernicious anemia (PA).
- Characteristics include the following:
  ▼ Achlorhydria
  ▼ Vitamin B₁₂–deficient megaloblastosis
  ▼ Hypergastrinemia (due to hyperplasia of gastrin-producing cells)
  ▼ Gastric carcinoids
  ▼ Low serum pepsinogen I concentrations
- Laboratory findings may be due to other accompanying autoimmune diseases (e.g., Hashimoto thyroiditis, Addison disease, Graves disease, myasthenia gravis, hypoparathyroidism, type 1 DM).

Nonatrophic (Type B Gastritis)
- Gastric antrum is involved.
- Anemia caused by iron deficiency, and malabsorption may occur.
- Helicobacter pylori infection is detectable in approximately 80% of patients with peptic ulcer and chronic gastritis. Diagnosis is by biopsy, culture, direct Gram staining, urease breath test, and serologic tests.
- Hypogastrinemia is caused by destruction of gastrin-producing cells in the antrum.
- Chronic antral gastritis is consistently present in patients with benign gastric ulcer.
- Gastric acid studies are of limited value. Severe hypochlorhydria or achlorhydria after maximal stimulation usually denotes mucosal atrophy.

Other Causes
- Infections (other bacteria [syphilis], viral [e.g., CMV], parasitic [e.g., anisakiasis], fungal)
- Chemical (e.g., NSAIDs, bile reflux, other drugs)
- Lymphocytic gastritis
Disease States Associated with Abdominal Pain

- Eosinophilic gastroenteritis
- Noninfectious granulomatous (e.g., sarcoidosis, Crohn disease)
- Ménétrier disease
- Radiation

CARCINOMA OF THE STOMACH

- **Laboratory Findings**
  
  Carcinoma of the stomach should always be searched for by periodic prophylactic screening in high-risk patients, especially those with PA, gastric atrophy, or gastric polyps.
  
  **Cytology:** Exfoliative cytology positive in 80% of patients; false-positive result in <2%.
  
  **Tumor markers:** Increased serum CEA (>5 ng/dL) in 40–50% of patients with metastases and 10–20% of patients with surgically resectable disease. May be useful for postoperative monitoring for recurrence or to estimate metastatic tumor burden. Increased serum AFP and CA 19-9 in 30% of patients, usually incurable. Markers are not useful for early detection.
  
  **Gastric analysis:** Normal in 25% of patients. Hypochlorhydria in 25% of patients. Achlorhydria following histamine or betazole in 50% of patients.
  
  **Core laboratory:** Anemia due to chronic blood loss. Occult blood in stool.

DISORDERS OF THE PANCREAS

CARCINOMA OF THE PANCREAS

- **Laboratory Findings**

  **Imaging studies:** Most useful tests are ultrasound or CT scanning followed by ERCP (at which time fluid is also obtained for cytologic and pancreatic function studies). This combination will correctly diagnose or rule out cancer of the pancreas in ≥90% of cases. ERCP with brush cytology has S/S = ≤25%/≤100%. Radioisotope scanning of the pancreas may be done (75Se) for lesions >2 cm.

  **Histology:** Ultrasound-guided needle biopsy has reported sensitivity of 80–90%; false positives are rare.

  **Tumor markers:** Serum markers for tumor (CA 19-9, CEA, and so on) are often normal. In carcinoma of the pancreas, CA 19-9 has S/S = 70%/87%, PPV = 59%, and NPV = 92%; there is no difference in sensitivity between local disease and metastatic disease. Often normal in early stages, they are not useful for screening. Increased values may help differentiate benign disease from cancer. Declines to normal in 3–6 months if cancer is completely removed so may be useful for prognosis and follow-up. Detects tumor recurrence 2–20 weeks before clinical evidence. Not specific for pancreas because high levels may also occur in other GI cancers, especially those affecting the colon and bile duct. CEA level in bile (obtained by percutaneous transhepatic drainage) was reported increased in 76% of a small group of cases.

  **Testosterone:** Dihydrotestosterone ratio <5 (normal approximately 10) in >70% of men with pancreatic cancer (due to increased conversion by tumor); less sensitive but more specific than CA 19-9 and present in higher proportion of stage I tumors.
Serum amylase and lipase: May be slightly increased in early stages (<10% of cases); with later destruction of the pancreas, they are normal or decreased. They may increase following secretin–pancreozymin stimulation before destruction is extensive; therefore, the increase is less marked with a diabetic glucose tolerance curve. Serum amylase response is less reliable. See Serum Glycoprotein 2.

Glucose tolerance: Curve is of the diabetic type, with overt diabetes in 20% of patients with pancreatic cancer. Flat blood sugar curve with IV tolbutamide tolerance test indicates destruction of islet cell tissue. Unstable, insulin-sensitive diabetes that develops in an older man should arouse suspicion of carcinoma of the pancreas.

Serum LAP: Increased (>300 U) in 60% of patients with carcinoma of the pancreas due to liver metastases or biliary tract obstruction. It may also be increased in chronic liver disease.

Other: Triolein-131I test demonstrates pancreatic duct obstruction with absence of lipase in the intestine, causing flat blood curves and increased stool excretion.

HEAD (SEE JAUNDICE)

- The abnormal pancreatic function tests and increased tumor markers that occur with carcinoma of the body of the pancreas may be evident.

Laboratory Findings

Core laboratory: Serum bilirubin is increased (12–25 mg/dL), mostly conjugated (increase persistent and nonfluctuating). Serum ALP is increased. Both urine and stool urobilinogen are absent. Increased serum cholesterol (usually >300 mg/dL) with esters not decreased. Other liver function tests are usually normal. See Serum Glycoprotein 2.

Hematology: Increased prothrombin time (PT); normal after IV vitamin K administration.

Other: Secretin–cholecystokinin stimulation evidences duct obstruction when duodenal intubation shows decreased volume of duodenal contents (<10 mL/10-minute collection period) with usually normal bicarbonate and enzyme levels in duodenal contents. Acinar destruction (as in pancreatitis) shows normal volume (20–30 mL/10-minute collection period), but bicarbonate and enzyme levels may be decreased. Abnormal volume, bicarbonate, or both are found in 60–80% of patients with pancreatitis or cancer. In carcinoma, the test result depends on the relative extent and combination of acinar destruction and of duct obstruction.

Histology: Cytologic examination of duodenal contents shows malignant cells in 40% of patients. Malignant cells may be found in up to 80% of patients with periampullary cancer.

CYSTIC FIBROSIS OF THE PANCREAS

Core laboratory: Hypochloremic metabolic alkalosis and hypokalemia. Serum protein electrophoresis shows increasing IgG and IgA with progressive pulmonary disease; IgM and IgD are not appreciably increased. Serum albumin is often decreased (because of hemodilution due to cor pulmonale; may be found before cardiac involvement is clinically apparent). Serum chloride, sodium, potassium, calcium, and phosphorus are normal unless complications occur (e.g., chronic pulmonary
disease with accumulation of CO$_2$; massive salt loss due to sweating may cause hyponatremia). Urine electrolytes are normal. Excessive loss of electrolytes in sweat and stool. Impaired glucose intolerance in approximately 40% of patients with glycosuria, and hyperglycemia in 8% precedes DM. Protein–calorie malnutrition, hypoproteinemia; fat malabsorption with vitamin deficiency. Stool and duodenal fluid show lack of trypsin digestion of x-ray film gelatin; useful screening test up to age 4; decreased chymotrypsin production.

**Saliva findings:** Submaxillary saliva is more turbid, with increased calcium, total protein, amylase, chloride, and sodium but not potassium. These changes are not generally found in parotid saliva.

**Other findings:** Overt liver disease, including cirrhosis, fatty liver, bile duct strictures, and cholelithiasis, in ≤5% of cases. Meconium ileus during early infancy. Chronic or acute and recurrent pancreatitis. Pancreatic insufficiency frequency by age 1 >90%; in adults >95%. Increased incidence of GI tract cancers. GU tract abnormalities with aspermia in 98% due to obstructive changes in the vas deferens and epididymis are confirmed by testicular biopsy.

### MACROAMYLASEMIA IN VIVO ARTIFACT

- **Definition**
  Complex of amylase with IgA, IgG, or other high molecular weight plasma proteins that cannot filter through the glomerulus due to its large size associated with no specific symptoms or disease states.

- **Laboratory Findings**
  **Core laboratory:** Serum lipase is normal; normal pancreatic-to-salivary amylase ratio. Urine amylase normal or low. Serum amylase persistently increased (often 1–4× normal) without apparent cause. Amylase–creatinine clearance ratio <1% with normal renal function is very useful for this diagnosis; should make the clinician suspect this diagnosis. Macroamylase is identified in serum by special gel filtration or ultracentrifugation technique.

- **Limitations**
  - Macroamylase may be found in approximately 1% of randomly selected patients and 2.5% of persons with increased serum amylase level. Same findings may also occur in patients with normal molecular weight hyperamylasemia in which excess amylase is principally salivary gland isoamylase types 2 and 3.

### PANCREATITIS

#### PANCREATITIS, ACUTE

- **Laboratory Findings**
  **Lipase:** Serum lipase increases within 3–6 hours with peak at 24 hours and usually returns to normal over a period of 8–14 days; is superior to amylase; increases to a greater extent and may remain elevated for up to 14 days after amylase returns to normal. In patients with signs of acute pancreatitis, pancreatitis is highly likely (clinical specificity = 85%) when lipase ≥5× upper reference limit (URL); if values...
change significantly with time, and if amylase and lipase changes are concordant. (Lipase should always be determined whenever amylase is determined.) Urinary lipase is not clinically useful. It has been suggested that a lipase:amylase ratio >3 (and especially >5) indicates alcoholic rather than nonalcoholic pancreatitis. If lipase ≥5× URL, acute pancreatitis or organ rejection is highly likely but unlikely if <3× URL (Figure 5-1).

*Amylase:* Increase begins in 3–6 hours, rises rapidly within 8 hours in 75% of patients, reaches maximum in 20–30 hours, and may persist for 48–72 hours; >95% sensitivity during the first 12–24 hours. The increase may be ≤40× normal, but the height of the increase and rate of fall do not correlate with the severity of the disease, prognosis, or rate of resolution. In patients with signs of acute pancreatitis, amylase >3× ULN or >600 Somogyi units/dL is very suggestive of acute pancreatitis. An increase >7–10 days suggests an associated cancer of the pancreas or pseudocyst, pancreatic ascites, or nonpancreatic etiology. Similar high values may occur in obstruction of the pancreatic duct; they tend to fall after several days; ≤19% of patients with acute pancreatitis (especially when seen more than 2 days after onset of symptoms) may have normal values, especially with an alcoholic etiology and longer duration of symptoms, even when dying of acute pancreatitis. May also be normal in relapsing chronic pancreatitis and patients with hypertriglyceridemia (technical interference with test). Frequently normal in acute alcoholic pancreatitis. Acute abdomen due to GI infarction or perforation rather than acute pancreatitis is suggested by only moderate increase in serum amylase and lipase (<3× URL), evidence of bacteremia. Of patients with acute alcoholic intoxication, 10–40% have elevated serum amylase (about half are salivary type); they often present with abdominal pain, but increased serum amylase is usually <3× URL.

**Figure 5–1** Algorithm for increased serum amylase and lipase. ULN, upper limit of normal.
Levels >2.5× URL indicate metastatic tumor rather than pancreatitis. Serum pancreatic isoamylase can distinguish elevations due to salivary amylase that may account for 25% of all elevated values. (In healthy persons, 40% of total serum amylase is pancreatic type and 60% is salivary type.) Only slight increase in serum amylase and lipase values suggests a different diagnosis than acute pancreatitis. Many drugs increase both amylase and lipase in serum.

Increased urinary amylase tends to reflect serum changes by a time lag of 6–10 hours, but sometimes, increased urine levels are higher and of longer duration than serum levels. The 24-hour level may be normal even when some of the 1-hour specimens show increased values. Amylase levels in hourly samples of urine may be useful. Ratio of amylase clearance to creatinine clearance is increased (>5%) and avoids the problem of timed urine specimens; also increased in any condition that decreases tubular reabsorption of amylase (e.g., severe burns, DKA, chronic renal insufficiency, multiple myeloma, acute duodenal perforation). Considered not specific and now discouraged by some but still recommended by others.

Calcium: Serum level is decreased in severe cases 1–9 days after onset (due to binding to soaps in fat necrosis). The decrease usually occurs after amylase and lipase levels have become normal. Tetany may occur. (Rule out hyperparathyroidism if serum calcium is high or fails to fall in hyperamylasemia of acute pancreatitis.)

Bilirubin: Serum levels may be increased when pancreatitis is of biliary tract origin but is usually normal in alcoholic pancreatitis. Serum ALP, ALT, and AST may increase and parallel serum bilirubin rather than amylase, lipase, or calcium levels. Marked amylase increase (e.g., >2,000 U/L) also favors biliary tract origin. Fluctuation >50% in 24 hours of serum bilirubin, ALP, ALT, and AST suggests intermittent biliary obstruction.

Trypsin: Serum level is increased. High sensitivity makes a normal value useful for excluding acute pancreatitis. But low specificity (increased in large proportion of patients with hepatobiliary, bowel, and other diseases and renal insufficiency; increased in 13% of patients with chronic pancreatitis, 50% with pancreatic carcinoma) and RIA technology limit utility.

CRP: Level peaks 3 days after onset of pain; at 48 hours, sensitivity = 65–100%, PPV = 37–77%. Level of 150 mg/L distinguishes mild from severe disease.

Laboratory criteria for severe disease or predictor of mortality:

- \( \text{PaO}_2 < 60 \ \mu\text{mol/L} \)
- Creatinine >2 mg/dL after rehydration
- Blood glucose >250 mg/dL
- Hemoconcentration (Hct >47% or failure to decrease in 24 hours after admission), but Hct may be decreased in severe hemorrhagic pancreatitis
- GI bleed >500 mL/24 hours
- Presence, volume, and color of peritoneal fluid
- Methemalbumin may be increased in serum and ascitic fluid (AF) in hemorrhagic (severe) but not edematous (mild) pancreatitis; may distinguish these two conditions but not useful in diagnosis of acute pancreatitis.
- WBC is slightly to moderately increased (10,000–20,000/μL).
- Glycosuria appears in 25% of patients.
- Hypokalemia, metabolic alkalosis, or lactic acidosis may occur.
Laboratory findings due to predisposing conditions (may be multiple):

- Alcohol abuse accounts for approximately 36% of cases.
- Biliary tract disease accounts for 17% of cases.
- Idiopathic accounts for >36% of cases.
- Infections (especially viral such as mumps and coxsackievirus, CMV, and AIDS).
- Trauma and postoperative factors account for >8% of cases.
- Drugs (e.g., steroids, thiazides, azathioprine, estrogens, sulfonamides; children taking valproic acid) account for >5% of cases.
- Hypertriglyceridemia (hyperlipidemia—types V, I, IV) accounts for 7% of cases.
- Hypercalcemia from any cause.
- Tumors (pancreas, ampulla).
- Anatomic abnormalities of the ampullary region causing obstruction (e.g., annular pancreas, Crohn disease, duodenal diverticulum).
- Hereditary.
- Renal failure; renal transplantation.
- Miscellaneous (e.g., collagen vascular disease, pregnancy, ischemia, scorpion bites, parasites obstructing the pancreatic duct [Ascaris, fluke], Reye syndrome, fulminant hepatitis, severe hypotension, cholesterol embolization).

Laboratory findings due to complications:

- Pseudocysts of the pancreas.
- Pancreatic infection or abscess diagnosed by increased WBC count, Gram staining, and culture of aspirate.
- Polyserositis (peritoneal, pleural, pericardial, synovial surfaces). Ascites may develop cloudy or bloody or “prune juice” fluid, 0.5–2.0 L in volume, containing increased amylase with a level higher than that of serum amylase. No bile is evident (unlike in perforated ulcer). Gram stain shows no bacteria (unlike infarct of the intestine). Protein >3 g/dL and marked increase in amylase.
- Adult respiratory distress syndrome (with pleural effusion, alveolar exudate, or both) may occur in approximately 40% of patients; arterial hypoxemia is present.
- DIC.
- Hypovolemic shock.
- Others.

Prognostic Laboratory Findings

- On admission
  - WBC >16,000/μL
  - Blood glucose >200 mg/dL
  - Serum LD >350 U/L
  - Serum AST >250 U/L
  - Age >55 years
- Within 48 hours
  - >10% decrease in Hct
  - Serum calcium <8.0 mg/dL
  - Increase in BUN >5 mg/dL
  - Arterial pO2 <60 mm Hg
  - Metabolic acidosis with base deficit >4 mEq/L
Mortality
1%, if 3 signs are positive
15%, if 3 to 4 signs are positive
40%, if 5 to 6 signs are positive
100%, if ≥7 signs are positive

Degree of amylase elevation has no prognostic significance.

CT scan, MRI, and ultrasound are useful for confirming diagnosis or identifying causes or other conditions.

Suggested Readings

PANCREATITIS, CHRONIC

See also Malabsorption.

Laboratory Findings
Laboratory findings are often normal.

Imaging studies: CT, ultrasound, and ERCP are most accurate for diagnosing and staging chronic pancreatitis. Radioactive scanning of the pancreas (selenium) yields variable findings in different clinics.

Cholecystokinin–secretin test: Measures the effect of IV administration of cholecystokinin and secretin on volume, bicarbonate concentration, and amylase output of duodenal contents and increase in serum lipase and amylase. This is the most sensitive and reliable test (gold standard) for chronic pancreatitis especially in the early stages. However, it is technically difficult and is often not performed accurately; gastric contamination must be avoided. Some abnormality occurs in >85% of patients with chronic pancreatitis. Amylase output is the most frequent abnormality. When all three are abnormal, there is a greater frequency of abnormality in the tests listed below.

Normal duodenal contents:
▼ Volume: 95–235 mL/hour
▼ Bicarbonate concentration: 74–121 mEq/L
▼ Amylase output: 87,000–276,000 mg

Serum amylase and lipase increase after administration of cholecystokinin and secretin in approximately 20% of patients with chronic pancreatitis. They are more often abnormal when duodenal contents are normal. Normally serum lipase and amylase do not rise above normal limits.

Fasting serum amylase and lipase are increased in 10% of patients with chronic pancreatitis.

Serum pancreolauryl test: Fluorescein dilaurate with breakfast is acted on by a pancreas-specific cholesterol ester hydrolase–releasing fluorescein, which is absorbed from gut and measured in serum; preceded by administration of secretin and followed by metoclopramide. Reported S/S = 82%/91%.

Glucose tolerance test (GTT): In 65% of patients with chronic pancreatitis and frank diabetes in >10% of patients with chronic relapsing pancreatitis. When GTT
is normal in the presence of steatorrhea, the cause should be sought elsewhere than in the pancreas.

Laboratory findings due to malabsorption: Occurs when >90% of exocrine function is lost.
- Bentiromide test is usually abnormal with moderate to severe pancreatic insufficiency but often normal in early cases.
- Schilling test may show mild malabsorption of vitamin B₁₂ (no longer performed).
- Xylose tolerance test and small bowel biopsy are not usually done but are normal.
- Chemical determination of fecal fat demonstrates steatorrhea. It is more sensitive than tests using triolein-¹³¹I.
- Triolein-¹³¹I is abnormal in one third of patients with chronic pancreatitis.
- Starch tolerance test is abnormal in 25% of patients with chronic pancreatitis.

Laboratory findings due to chronic pancreatitis and pancreatic exocrine insufficiency:
- Alcohol in 60–70%
- Idiopathic in 30–40%
- Obstruction of pancreatic duct (e.g., trauma, pseudocyst, pancreas divisum, cancer, or obstruction of duct or ampulla)
- Others occasionally (e.g., CF, primary hyperparathyroidism, heredity, malnutrition, miscellaneous [Z-E syndrome, Shwachman syndrome, alpha₁-antitrypsin deficiency, trypsinogen deficiency, enterokinase deficiency, hemochromatosis, parenteral hyperalimentation])

PSEUDOCYST OF THE PANCREAS

- Imaging studies: Detected by ultrasound or CT scan.
  - Core laboratory: Serum conjugated bilirubin is increased (>2 mg/dL) in 10% of patients. Serum ALP is increased in 10% of patients. Fasting blood sugar is increased in <10% of patients.
  - Secretin–pancreozymin stimulation: Duodenal contents usually show decreased bicarbonate content (<70 mEq/L) but normal volume and normal content of amylase, lipase, and trypsin.
  - Pancreatic cyst fluid findings: High fluid viscosity and CEA indicate mucinous differentiation and exclude pseudocyst, serous cystadenoma, other non-mucinous cysts, or cystic tumors. Pancreatic enzymes, leukocyte esterase, and NB/70K are increased in pseudocyst fluid. Increased CA 72-4, CA 15-3, and tissue polypeptide antigen are markers of malignancy; if all are low, pseudocyst or serous cystadenoma is most likely. CA 125 is increased in serous cystadenoma.
  - Other: Laboratory findings due to conditions preceding acute pancreatitis are noted (e.g., alcoholism, trauma, duodenal ulcer, cholelithiasis), infection, perforation, and hemorrhage by erosion of blood vessel or into a viscus.
DYSPEPSIA AND PEPTIC ULCER DISEASE

Definition

- Dyspepsia encompasses any or all of a great variety of upper abdominal symptoms, including upper abdominal pain or discomfort, nausea, bloating, heartburn, early satiety, regurgitation, and belching.
- Nonulcerative dyspepsia is defined as persistent or recurrent abdominal pain or discomfort centered in the upper abdomen without definite structural or biochemical explanation. By definition, nonulcerative dyspepsia is a diagnosis of exclusion. Possible mechanisms include dysmotility of the stomach or small intestine, heightened visceral sensitivity, altered intestinal or gastric reflexes, and psychological distress.
- Peptic ulcer disease (PUD)
  - Epigastric abdominal pain is the most common symptom. Pain is nonradiating and is described as a “gnawing” or “hunger pain.” Pain occurs 1–2 hours postprandially and is relieved characteristically by food or antacids.
  - Nocturnal pain is more specific for PUD and is due to the physiologic increase in acid secretion, which occurs in the early morning hours.
  - Asymptomatic:
    - Patients with PUD induced by NSAIDs are frequently asymptomatic.
    - As many as 60% of patients who develop bleeding as a complication of PUD are also asymptomatic.
- Dyspepsia is typically a chronic relapsing condition. Between 65% and 86% of patients with dyspepsia will experience dyspeptic symptoms, at least intermittently, 2 to 3 years after the initial presentation. Long duration of symptoms and intermittent symptoms can also occur in PUD and esophagitis; therefore, these characteristics are not reassuring as to the absence of pathology.
- Gastroesophageal reflux disease (GERD) and dyspepsia have similar symptoms. Gastroesophageal reflux is a normal physiologic process that occurs daily in all individuals. GERD (expressed clinically as heartburn).
- *Helicobacter pylori* infection is clearly implicated in the etiology of recurrent PUD, yet its role in nonulcerative dyspepsia remains unclear. Between 30% and 60% of patients with nonulcerative dyspepsia have *H. pylori*. However, the background prevalence in the general population is also high.

Recommended Tests

- Laboratory investigation may not be necessary in young patients (<45 years of age) who have a normal examination and no indicators for organic disease. The etiology of dyspepsia is presented in Table 5-2.
- In older patients at increased risk, the minimal laboratory workup should include a CBC, electrolytes, calcium, and liver chemistries.
- Thyroid tests, hCG, amylase, and stool studies should be ordered if specific features of the history or examination are suggestive.
- Additional studies
  - Upper endoscopy (i.e., esophagastroduodenoscopy [EGD]): In the majority of cases, this is the study of first choice when further evaluation of dyspepsia is required, including the ability to obtain biopsies. As many as two thirds of endoscopies are completely normal in younger patients.
Nonulcerative dyspepsia occurs in up to 60% of cases, but the diagnosis requires the exclusion of other diagnostic entities.

**TABLE 5–2. Differential Diagnosis of Dyspepsia**

<table>
<thead>
<tr>
<th>Structural Disease Involving the Stomach or Esophagus</th>
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<tbody>
<tr>
<td>Peptic ulcer disease (15–25% of cases)</td>
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<tr>
<td>Reflux esophagitis (5–15% of cases)</td>
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<tr>
<td>Gastric or esophageal cancer (&lt;2% of cases)</td>
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<tr>
<td>Infiltrative disease</td>
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<tr>
<td>Eosinophilic gastritis</td>
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<tr>
<td>Crohn disease</td>
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<tr>
<td>Sarcoidosis</td>
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</tbody>
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<table>
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<tr>
<th>Other gastrointestinal-related diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
</tr>
<tr>
<td>Chronic pancreatitis or pancreatic cancer</td>
</tr>
<tr>
<td>Celiac disease</td>
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<tr>
<td>Lactose intolerance</td>
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<tr>
<td>Hepatoma</td>
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<tr>
<th>Medications</th>
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<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Theophylline</td>
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<tr>
<td>Erythromycin</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td>Caffeine</td>
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<tr>
<td>Nicotine</td>
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<table>
<thead>
<tr>
<th>Other possible causes</th>
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</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Intestinal angina</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Nonulcerative dyspepsia*</td>
</tr>
</tbody>
</table>

*Nonulcerative dyspepsia occurs in up to 60% of cases, but the diagnosis requires the exclusion of other diagnostic entities.

(i.e., <45 years of age). Therefore, it is best applied to older patients and to younger patients with classic symptoms.

▼ **Upper GI radiography:** This test is less accurate than upper endoscopy and cannot provide tissue diagnosis. It is best reserved for situations where endoscopy expertise is unavailable, for patients who refuse endoscopy or have low pretest probability of disease, and in situations where endoscopy might be considered unsafe.

■ **Helicobacter pylori testing**

■ **Gastric emptying studies:** Gastric scintigraphy and gastroduodenal manometry studies generally do not influence medical management and are reserved for patients with normal laboratory tests and a normal EGD, yet who continue to have frequent or protracted vomiting suggestive of a motility disorder. Even in these cases, empiric treatment with prokinetic agents should probably be tried first. Disorders of the gallbladder (see Biliary Extrahepatic Obstruction, Complete).
Suggested Readings

ASCITES

Definition
- Ascites is a collection of free fluid in the peritoneal cavity.
- Etiology
  - Chronic liver disease (infectious hepatitis and alcoholism) causes 80% of cases of ascites (see Hepatomegaly, Jaundice).
  - Multiple causes, including cirrhosis, peritoneal carcinomatosis, or tuberculous peritonitis, account for 3–5% of cases.
  - Carcinomatosis causes <10% of cases of ascites.
  - Heart failure is responsible for <3–5% of cases, and nephritic syndrome is a rare cause of ascites.
  - Cryptogenic cirrhosis may account for up to 10% of cases.

Classification
- Ascites is currently classified as high gradient or low gradient, depending on the serum ascites albumin gradient (SAAG). Calculation of SAAG involves the difference (not the ratio) between serum values and AF values.
  - High-gradient ascites results from portal hypertension, whether on the basis of cirrhosis or noncirrhosis. Nephrotic syndrome is an exception and will usually cause low-gradient ascites due to marked hypoalbuminemia.
  - Low-gradient ascites usually occurs as the result of cardiac failure, malignant carcinomatosis of the peritoneum, infections (such as TB), perforation of the bowel, connective tissues diseases, SLE, and chemical inflammation as in pancreatitis.

Laboratory Findings (Figure 5-2)
- Culture: Bedside inoculation of AF in blood culture bottles has increased the positive bacterial yield to interpreted in concert with the cell count. A Gram stain should also be done.
  - Imaging studies: Ultrasonography is useful for detecting the presence of ascites as well as for determining the etiology. It may reveal evidence of chronic liver disease, malignancy, hepatomegaly, and pancreatic disorder.
  - Ascites fluid findings: AF examination is the principle diagnostic tool. Using abdominal paracentesis to obtain and study the fluid is crucial to making a diagnosis.
  - Transparent to pale fluid: Is seen in cases of portal hypertension. Neutrophilia in excess of 1,000/mL results in opalescence. A concentration of RBCs in excess of 10,000/mL gives a faint pink tinge, and cell counts >20,000/mL.
color it red. A traumatic tap is evident by a streak of blood rather than homogeneously red fluid and the tendency to clot. Hepatocellular carcinoma and, rarely, metastatic disease; can cause a bloody tap. TB is only a rare cause of hemorrhagic ascites.

**Chylous or milky ascites:** Has a higher triglyceride concentration than serum and >200 mg/dL. It is rarely seen and is usually an indication of cirrhosis rather than lymphoma or TB as was previously thought. The triglycerides are >1,000 mg/dL in truly milky ascites. Dark-brown ascites may be seen in significant hyperbilirubinemia, biliary perforation (when ascitic bilirubin is higher than serum bilirubin), pancreatitis, and, rarely, in malignant melanoma.

**Bloody ascites fluid:** Once a traumatic tap has been ruled out, 50% of cases are due to hepatocellular carcinoma. TB rarely causes bloody fluid.

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**Figure 5–2** Algorithm for the workup of patients with ascites. AILD, alcohol-induced liver disease; CEA, carcinoembryonic antigen; NASH, nonalcoholic steatohepatitis; TB, tuberculosis; TNC, total neutrophil count.
Ascites

- **Staining**: Gram staining has low yield. Even with centrifugation, it has 10% sensitivity in spontaneous bacterial peritonitis. AFB smear for TB have very low sensitivity. In an appropriate clinical setting of low-grade fever, malaise, and weight loss, a high cell count with lymphocytic predominance and low SAAG is suggestive of TB ascites.

- **Protein concentration** of AF categorized ascites into exudative (ascitic protein >2.5 g/dL) or transudative (ascitic protein <2.5 g/dL). The significance of this has never been evaluated adequately and objectively.

- **Cell count and differential**: In uncomplicated cirrhosis, the total WBC count is <500 cells/μL with <250 neutrophils/μL. After diuresis, the total cell count may go up, but the neutrophil count remains below 250 cells/μL. In spontaneous bacterial peritonitis, the total WBC count and neutrophil count are usually, but not always, raised. In TB and carcinomatosis, the cell count rises but with a predominance of lymphocytes. In traumatic taps, for every 250 RBCs, one neutrophil is subtracted from the total WBC count.

**Core laboratory**: The serum and AF glucose concentrations are nearly the same in uncomplicated portal hypertension (large numbers of WBCs, bacteria, or tumor cells consume glucose and may lead to diminished levels). Amylase values may be about 3–5 times higher than the serum values. LD levels rise because of release of LD from the neutrophils. The rise occurs in cases of secondary peritonitis, TB, and pancreatitis.

**Cytology**: Has limitations in the diagnosis of malignant ascites and has been replaced largely laparoscopic examination of the peritoneum along with biopsy and culture.

- **Limitations**
  - Errors may occur if serum albumin is very low or when serum and ascitic samples are not obtained within a short space of time from each other.
  - A high globulin level in serum may also give a false result.

**DISORDERS OF THE PERITONEUM ASSOCIATED WITH ASCITES**

**CHRONIC LIVER DISEASE (SEE P. 198)**

- This disease differs from ascites caused by malignancy.

- **Laboratory Findings**
  - **Albumin**: Almost always ≥1.1 g/dL in cirrhosis (most common cause), alcoholic hepatitis, massive liver metastases, fulminant hepatic failure, portal vein thrombosis, Budd-Chiari syndrome, cardiac ascites, fatty liver, acute fatty liver of pregnancy, myxedema, mixed (e.g., cirrhosis with peritoneal TB). May be falsely low if serum albumin <1.1 g/dL or the patient in shock. May be falsely high with chylous ascites (lipid interferes with albumin assay). Albumin levels <1.1 g/dL in >90% of cases of peritoneal carcinomatosis (most common cause), TB, pancreatic or biliary ascites, nephrotic syndrome, bowel infarction or obstruction, and serositis in patients without cirrhosis.
Ascites fluid findings: AF total protein >2.5 mg/dL in cancer is only 56% accurate because of high protein content in 12–19% of these ascites as well as changes caused by albumin infusion and diuretic therapies. AF/serum albumin ratio <0.5 in cirrhosis (>90% accuracy). AF/serum ratio of LD (>0.6) or protein (>0.5) is not more accurate (approximately 56%) than only total protein for diagnosis of exudate. AF cholesterol <55 mg/dL in cirrhosis (94% accuracy). Albumin gradient (serum albumin minus AF albumin) reflects portal pressure. Total WBC count is usually <300/µL (50% of cases) and PMN <25% (50% of cases).

Core laboratory: Liver function tests are abnormal.

Other: Cirrhosis findings are similar with or without hepatocellular carcinoma. Cardiac ascites is associated with a blood–AF albumin gradient >1.1 g/dL, but malignant AF shows blood–AF albumin gradient <1.1 g/dL in 93% of cases.

INFECTED ASCITIC FLUID

Laboratory Findings

Culture: AF in blood culture bottles has 85% sensitivity. Ascites fluid findings:

- WBC count >250/µL: sensitivity = 85%, specificity = 93%, and neutrophils >50% are presumptive of bacterial peritonitis.
- pH <7.35 and arterial–AF pH difference >0.10; both these findings are virtually diagnostic of bacterial peritonitis and the absence of the above findings virtually excludes bacterial peritonitis.
- Lactate >25 mg/dL and arterial–AF difference >20 mg/dL are often present. LD is markedly increased. Phosphate, potassium, and gamma-glutamyltransferase may also be increased. Glucose is unreliable for diagnosis. Total protein <1.0 g/dL indicates high risk for SBP.
- Gram stain shows few bacteria in spontaneous bacterial peritonitis (SBP) but many when caused by intestinal perforation. Culture sensitivity = 50% for SBP and approximately 80% for secondary peritonitis. TB acid-fast stain sensitivity = 20–30% and TB culture sensitivity = 50–70%.

SECONDARY PERITONITIS

- This condition shows polymicrobial infection, total protein >1.0 g/dL, AF/LD greater than serum upper limit of normal, and glucose <50 mg/dL compared with spontaneous bacterial peritonitis (SBP).
- Prevalence of SBP 15%; due to Escherichia coli approximately 50%, Klebsiella, and other gram-negative bacteria; gram-positive bacteria approximately 25% (especially streptococci).

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Monitor dialysate for the following:

- Infection: Peritonitis is defined as WBC count >100/µL, usually with >50% PMNs (normal is <50 WBC/µL, usually mononuclear cells), or positive
Gram stain or culture (most prevalent: coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus* sp.; multiple organisms, especially mixed aerobes and anaerobes occur with bowel perforation). Successful therapy causes fall in WBC count within first 2 days and a return to <100/μL in 4–5 days; differential returns to predominance of monocytes in 4–7 days with increased eosinophils in 10% of cases. Patients check outflow bags for turbidity. Turbid dialysate can occur occasionally without peritonitis during the first few months of placing catheter (due to catheter hypersensitivity) with WBC count 100–8,000/μL, 10–95% eosinophils, sometimes increased PMNs, and negative cultures. Occasional RBCs may be seen during menstruation or with ovulation at midcycle. Because of low WBC decision level, *manual hemocytometer count rather than an automated instrument must be used.*

- **Metabolic change**: Assay dialysate for creatinine and glucose; calculate ultrafiltrate volume by weighing dialysate fluid after 4-hour dwell time and subtracting it from preinfusion weight using specific gravity of 1.0.

### PANCREATIC DISEASE

- AF amylase level greater than serum amylase level is specific for pancreatic disease, but both levels are normal in 10% of cases.
- Methemalbumin in serum or AF and total protein >4.5 g/dL indicate poor prognosis.

### MALIGNANT ASCITES

- Increased fluid cholesterol (>45 mg/dL) and fibronectin (>10 mg/dL) have S/S 90%/82%.
- Positive cytology has S/S 70%/100%.
- Increased AF CEA (>2.5 mg/dL) has S/S 45%/100%.

### ASCITES IN FETUS OR NEONATE

- **Causes**
  - Nonimmune (occurs in 1 in 3,000 pregnancies)
    - Cardiovascular abnormalities causing CHF (e.g., structural, arrhythmias) (40% of cases)
    - Chromosomal (e.g., Turner and Down syndromes are most common; trisomy 13, 15, 16, and 18) (10–15% of cases)
    - Hematologic disorders (any severe anemia) (10% of cases)
    - Inherited (e.g., α-thalassemia, hemoglobinopathies, G6PD deficiency)
    - Acquired (e.g., fetal–maternal hemorrhage, twin-to-twin transfusion, congenital infection [parvovirus B19], methemoglobinemia)
    - Congenital defects of the chest and abdomen.
    - Structural (e.g., diaphragmatic hernia, jejunal atresia, volvulus, intestinal malrotation)
Peritonitis caused by GI tract perforation, congenital infection (e.g., syphilis, TORCH [toxoplasmosis, other agents, rubella, CMV, and herpes simplex], hepatitis), meconium peritonitis

- Lymphatic duct obstruction
- Biliary atresia
- Nonstructural (e.g., congenital nephrotic syndrome, cirrhosis, cholestasis, hepatic necrosis, GI tract obstruction)
- Lower GU tract obstruction (e.g., posterior urethral valves, urethral atresia, and ureterocele) is most common cause
- Inherited skeletal dysplasias (enlarged liver causing extramedullary hematopoiesis)
- Fetal tumors, most often teratomas and neuroblastomas
- Vascular placental abnormalities
- Genetic metabolic disorders (e.g., Hurler syndrome, Gaucher disease, Niemann-Pick disease, $G_{M1}$ gangliosidosis type I, I-cell disease, $\beta$-glucuronidase deficiency)
- Immune (maternal antibodies reacting to fetal antigens [e.g., Rh, C, E, Kell])

**PERITONITIS, ACUTE**

- See Figures 5-3 and 5-4.

**PRIMARY PERITONITIS**

*Ascites fluid findings:* Gram stain of direct smear and culture of peritoneal fluid usually shows streptococci in children. In adults, it is caused by *E. coli* (40–60%) or *S. pneumoniae* (15%), other gram-negative bacilli, and enterococci; usually one organism. May be caused by *Mycobacterium tuberculosis*. Marked increase in WBC ($\leq 50,000/\mu L$) and PMN (80–90%).

*Peritoneal lavage fluid findings:* Shows WBC count $>200/\mu L$ in 99% of cases.

*Other:* Laboratory findings due to nephrotic syndrome and post–necrotic cirrhosis and occasionally bacteremia in children and cirrhosis with ascites in adults.

**SECONDARY PERITONITIS**

Occurs and recurs very frequently in continuous ambulatory peritoneal dialysis.

Laboratory findings due perforation of hollow viscus (e.g., appendicitis, perforated ulcer).

*Dialysate findings:* Turbid (indicates $>300$ WBC/µL); Gram stain, culture, and leukocytosis may be absent. Caused by gram-positive bacteria in approximately 70%, enteric gram-negative bacilli and *P. aeruginosa* in 20–30%, others in 10–20%, and sterile in 10–20%. If more than one pathogen is found, rule out perforated viscus. Usually more than one organism is found.

**Suggested Readings**


Diarrhea

Definition

Diarrhea is defined as >200 g of stool or an increase in the frequency or fluidity of normal stools. It may be acute or chronic, and it is considered chronic when it lasts at least 4 weeks.
Diarrhea can result from any of the following mechanisms.

1. Osmosis: Molecules not normally present in the intestinal lumen increase the osmolality of chime, drawing water into the lumen (i.e., lactose).
2. Secretion: Substances can cause intestinal cells to secrete sodium and water (i.e., cholera toxin).
3. Inflammation results in denuding of the intestinal lining, which in turn disrupts normal absorption, thereby allowing compounds from the lining to leak into the lumen resulting in an increased osmosis.
4. Motility: Hypermotility leads to an increased stool volume. Hypomotility can lead to bacterial overgrowth, which causes diarrhea through several different mechanisms.
5. Anal sphincter dysfunction causes fecal incontinence, which can be interpreted by the patient as diarrhea.

**Differential Diagnosis**

1. Laxative abuse accounts for approximately 15% of all chronic causes. It should be suspected in patients with a mental health disorder.
2. Sorbitol can cause diarrhea. In one study, approximately 17% of people had diarrhea following the ingestion of 4–5 minutes containing sorbitol.
3. Both bile salts and fatty acids cause secretion of chloride followed by water into the colon. Excess bile salts also lead to a mild degree of fat malabsorption.
Diarrhea 165

4. Bacterial overgrowth can occur secondary to diabetes, blind loop syndrome, amyloidosis, diverticulitis, and scleroderma, among other causes.

5. Irritable bowel syndrome classically presents with diarrhea alternating with constipation, but it can also occur in a diarrhea-predominant form.

6. Gastric surgery syndrome results in a decreased contact time with the luminal surface and decreased digestive juices mixing with the chyme.

7. Hyperthyroidism usually has increased frequency and amount of diarrhea but not fluidity. Diarrhea is present in approximately 25% of hyperthyroid cases.

8. Inflammatory bowel disease (IBD):
   ▼ Ulcerative colitis is a relapsing and remitting disease that leads to acute inflammation of the colorectal mucosa. The rectum is involved in 55% of cases. In severe cases, bloody diarrhea often leads to weight loss, anemia, and electrolyte imbalance.
   ▼ Crohn disease is a chronic relapsing disorder characterized by transmural, asymmetric, and segmental inflammation. It typically involves the ileum, colon, or perianal region; right lower quadrant pain associated with bloody diarrhea is present in 80% of patients.

9. Neoplasia:
   ▼ Villous adenoma produces prostaglandins, which stimulate chloride and water secretion from the colon.
   ▼ Serotonin from carcinoid cells stimulates gut motility and increases intestinal secretion.
   ▼ Tumor-associated calcitonin stimulates gut motility.
   ▼ Gastrinoma leads to increased gastric acid, which directly causes fluid secretion.

10. Infection:
    ▼ Refer to p. 624, Foodborne Infectious Illnesses, and see other sections on specific agents that cause diarrheal disease.

Laboratory Findings

Endoscopy: Lower endoscopy may help. One series has a 20% yield in identifying a pathologic diagnosis. In non–HIV-infected patients, the role of sigmoidoscopy versus colonoscopy is unclear. When clinically suspected, even if no gross abnormalities are noted, consider doing blind biopsies looking for lymphocytic and collagenous colitis. The yield of biopsy with no gross abnormalities ranges from 6% to 42%. Upper endoscopy is useful for making the diagnosis of sprue, Whipple disease, and other small bowel infiltrative processes.

Radiology: An upper GI series with small bowel follow-through is most commonly used when evaluating for Crohn disease. Enteroclysis is superior, with 100% sensitivity and 98% specificity for small bowel involvement with Crohn disease.

Recommended laboratory tests of stool:

- Fecal leukocytes.
- Stool for osmolality gap: The osmolality gap is calculated by the following formula: 2 (stool Na + K). The accuracy is fair in distinguishing between osmotic (if gap is 50) and secretory (if gap is >50) diarrhea.
- Stool for pH: For carbohydrate intolerance (e.g., lactose or sorbitol), one small study found the pH <5.6. For bile acid–induced diarrhea, the pH is usually over 6.8.
Stool for fecal fat: This test is used to detect steatorrhea on the basis of malabsorption.

- Qualitative: Sensitivity is 97–100%, but the specificity varies from 56% to 86%.
- Quantitative: Based upon a 72-hour collection, the patient should be on a 75- to 100-g fat diet. A nutritional consult is advised to maximize compliance.
- Test(s) for infectious agents (e.g., stool culture, O&P examination, rotavirus detection) based on clinical presentation.

Other recommended tests:

- Nutrition indices: CBC, albumin, and potassium (sensitivity of hypokalemia is 100% for pancreatic cholera or [VIPoma]) are routine studies in the evaluation of chronic diarrhea.
- Hormonal studies: TSH, fasting serum gastrin level, calcitonin level, and 24-hour urine collection for 5-hydroxy indole acetic acid (5-HIAA) are recommended.
- D-xylose testing: This tests for small bowel malabsorption syndromes (e.g., sprue, Crohn disease, amyloidosis). Twenty-five grams of D-xylose are administered. A 5-hour urine collection and a 1-hour serum sample are obtained. A decreased amount of D-xylose in the urine and serum indicates small bowel malabsorption. The sensitivity of the test is decreased in the following situations: creatinine clearance of <30 mg/dL, portal hypertension, ascites, delayed gastric emptying, fiber supplements, glucose load, aspirin, and glipizide.
- Bentiromide test (to test for pancreatic exocrine insufficiency): N-benzyol-l-tyrosyl para-aminobenzoic acid (NBT PABA) is administered orally. The molecule is cleaved by chymotrypsin; PABA is absorbed and then measured in a 6-hour urine collection. PABA alone is a somewhat inaccurate measure, so additional markers have been used to increase the accuracy.
- Serum immune markers: Several serum immune markers performed by ELISA have been found to be valuable for the diagnosis, stratification, and management of IBD (see Celiac Disease):
  - Deoxyribonuclease (DNAses)-sensitive perinuclear antineutrophil cytoplasmic antibody (P-ANCA) is positive in 60–80% of adults with ulcerative colitis (UC) and in 83% of children with UC. P-ANCA is positive in 10% of patients with Crohn disease.
  - Anti-Saccharomyces cerevisiae antibody (ASCA) is present in 70% of patients with Crohn disease.
  - Pancreatic antibody may be positive in 30–40% of patients with Crohn disease.
  - Outer membrane porin from *E. coli* (OmpC) antibody: An immunoglobulin A (IgA) response to OmpC is seen in 55% of patients with Crohn disease.
  - Lactoferrin, stool: A sensitive and specific marker for detecting inflammation or from irritable bowel syndrome (IBS) once infectious causes of inflammation and colorectal cancer are ruled out.
  - Calprotectin for screening of patients with diarrhea to help distinguish between active IBD and IBS.
OSMOTIC DIARRHEA

Definition
Defined as diarrhea with a <3-week (upper limit 6–8 weeks) duration. Increased osmotically active solutes in the bowel; diarrhea usually stops during fasting.

Causes
- Exogenous
  - Laxatives (e.g., magnesium sulfate, milk of magnesia, sodium sulfate [Glauber salt], sodium phosphate, polyethylene glycol/saline)
  - Drugs (e.g., lactulose, colchicine, cholestyramine, neomycin, para-aminosalicylic acid [PAS])
  - Foods (e.g., mannitol, sorbitol [in diet candy, chewing gum, soda])
- Endogenous
  - Congenital malabsorption
    - Specific (e.g., lactase deficiency, fructose malabsorption)
    - General (e.g., abetalipoproteinemia and hypobetalipoproteinemia, congenital lymphangiectasia, cystic fibrosis)
  - Acquired malabsorption
    - Specific (e.g., pancreatic disease, celiac sprue, parasitic infestation, rotavirus enteritis, metabolic disorders [thyrotoxicosis, adrenal insufficiency], jejunoileal bypass, bacterial overgrowth, short-bowel syndrome, inflammatory disease [e.g., mastocytosis, eosinophilic enteritis])

SECRETORY (ABNORMAL ELECTROLYTE TRANSPORT) DIARRHEA

Definition
Diarrhea caused by increased water and chloride secretion; normal water and sodium absorption may be inhibited.

Due to
- Exogenous
  - Drugs
    - Laxatives (e.g., aloe, anthraquinones, bisacodyl, castor oil, dioctyl sodium sulfosuccinate, phenolphthalein, senna)
    - Diuretics (e.g., furosemide, thiazides), asthma (theophylline), thyroid drugs
    - Cholinergic drugs (cholinesterase inhibitors, quinidine, clozapine, ACE inhibitors)
  - Toxins (e.g., arsenic, mushrooms, organophosphates, alcohol)
  - Infectious agents (For a discussion of infectious causes of diarrhea, see the Infectious Gastrointestinal Diseases section in this chapter and Chapter 13)
- Endogenous
  - Hormones (serotonin, calcitonin, VIP)
  - Gastric hypersecretion (Z-E syndrome, systemic mastocytosis, short-bowel syndrome)
Bile salts (e.g., disease or resection of the terminal ileum)
- Fatty acids (e.g., disease of small intestine mucosa, pancreatic insufficiency)
- Congenital (e.g., congenital chloride diarrhea, congenital sodium diarrhea)

Laboratory Findings
Stool findings: Watery stool, volume >1 L/day, blood and pus are absent, stool osmolality close to plasma osmolality with no anion gap.

Exudative Diarrhea (Inflammatory Causes)
Due to infection, injury, ischemia, vasculitis, abscess, and/or idiopathic.
Laboratory findings: Stool contains blood and pus.

Motility Disturbances
Due to
- Decreased small intestinal motility (e.g., hypothyroidism, DM, amyloidosis, scleroderma)
- Increased small intestinal motility (e.g., hyperthyroidism, carcinoid syndrome)
- Increased colonic motility (e.g., irritable bowel syndrome)

Infectious Gastrointestinal Diseases
Definition
Ingestion of viable pathogenic microorganisms or toxins is responsible for a wide variety of gastrointestinal complaints. Ingestion of toxic nonbiologic agents, such as heavy metals, may also cause gastrointestinal symptoms, as discussed above. Disease is usually manifested by GI tract signs and symptoms but may be manifested by systemic or localized illness without significant GI symptoms (e.g., enteric fever, botulism). Fecal–oral transmission of infectious agents is commonly mediated by contamination of food but may be mediated by contaminated environmental sources. A foodborne illness is any illness related to food ingestion. Foodborne illnesses and other transmissible enteric diseases are of interest to public health authorities, and many are subjected to mandated reporting because of the possibility of widespread dissemination. Department of Public Health epidemiologists often coordinate clinical and laboratory investigations.
A foodborne illness may be restricted to a single individual or a small group, or may represent a large outbreak with many patients linked to a common source of infection. In the United States, enteric viruses cause most infectious diarrhea cases; common bacterial pathogens associated with gastroenteritis are Salmonella spp., Campylobacter spp., E. coli (STEC) O157 and Shigella spp.

Who Should Be Suspected?
Patients with foodborne illness usually present with a variety of symptoms including nausea, vomiting, abdominal pain, diarrhea, and anorexia. Certain foodborne illnesses, however, may be associated with minimal GI symptoms but have prominent systemic or localized symptoms.
Diarrhea illness may be noninflammatory or inflammatory. Noninflammatory diarrhea is usually caused by disease of the small intestine resulting in hypersecretion or decreased absorption. There is usually abrupt onset and resolution after a brief duration of illness. Systemic symptoms are usually absent or mild. Dehydration may be a complication, especially in the young or elderly.

Inflammatory diarrhea is characterized by mucosal invasion or cytotoxic damage by the pathogen. The large intestine is most commonly affected. The mucosal invasion typically results in bloody stools with many fecal leukocytes. Systemic symptoms are typical, including fever, abdominal pain and tenderness, nausea and vomiting, headache, and malaise.

When evaluating a patient with a likely foodborne illness, a number of issues should be pursued:

- What is the interval between likely exposure and onset of symptoms?
- What is the duration of clinical symptoms in affected patients?
- What are the prominent signs and symptoms of disease?
- Does any of the patient’s recent contacts have similar illness?
- Has the patient eaten any unusual food? Eaten at any function with mass-produced meals? Eaten any raw or incompletely cooked or pasteurized food?
- Has there been new contact with animals: domesticated, farm, or wild?
- Has the patient had recent travel to regions where foodborne illness is endemic?
- Does the patient, or does a close contact, attend or reside in a day care center, long-term care facility, or other facility at which transmission of an agent may be facilitated?

The following lists provide common agents based on disease presentation. In addition to the clinical presentation, epidemiologic risk should be considered when determining diagnostic and therapeutic strategies. Additional information is provided for a number of agents in *Chapter 11. Infectious Diseases.*

- Gastroenteritis with vomiting as the prominent symptom. Suspect:
  - Anisakiasis
  - Enteric viruses (e.g., rotavirus, norovirus, enteric adenovirus)
  - Preformed toxin ingestion (*S. aureus, B. cereus*)
- Noninflammatory diarrhea (watery without marked fecal WBCs or RBCs). Suspect:
  - *Clostridium perfringens*
  - *Cryptosporidium* species
  - *Cyclospora cayetanensis*
  - Enteric virus (astrovirus, norovirus or other calicivirus, adenovirus, rotavirus)
  - Enterotoxigenic *E. coli*
  - *Giardia lamblia*
  - *Vibrio cholerae*
- Inflammatory diarrhea as the prominent symptom (grossly bloody stool, pus or increased fecal WBCs, fever, and systemic signs and symptoms). Suspect
  - *Campylobacter* species
  - *Entamoeba histolytica*
- Enterotoxigenic Escherichia coli, enteroinvasive, or enterohemorrhagic
- Salmonella species
- Shigella species
- Noncholera Vibrio species
- Yersinia enterocolitica

Persistent diarrhea as the prominent symptom (2 weeks or longer). Suspect
- Cryptosporidium parvum
- Cyclospora cayetanensis
- Entamoeba histolytica
- Giardia lamblia

 Neurologic manifestation as the prominent symptom (paraesthesia, respiratory depression, cranial nerve palsy, respiratory difficulty). Suspect
- Clostridium botulinum toxin
- Guillain-Barré syndrome (after Campylobacter jejuni gastroenteritis)
- Intoxication/poisoning (scombroid fish poisoning, ciguatera fish poisoning, Tetraodon [fish] poisoning, shellfish poisoning)
- Mushroom poisoning
- Organophosphate/insecticide poisoning
- Thallium poisoning

Systemic signs and symptoms as the predominant presentation, with minimal GI symptoms. Suspect
- Brucella species
- Entamoeba histolytica liver abscess
- HAV and HEV
- Listeria monocytogenes
- Salmonella typhi or paratyphi
- Toxoplasma gondii
- Trichinella spiralis
- Vibrio vulnificus

Diagnosis and Reporting
Most cases of diarrheal illness are mild and self-limited, and testing to establish a specific cause is rarely necessary. Diagnostic testing is recommended for patients with profuse, watery diarrhea, passage of stools with blood or mucus, persistent diarrhea (>48 hours), immunocompromised patients, and patients with severe gastrointestinal or systemic symptoms (like severe abdominal pain, fever, or hypovolemia). Testing to establish a specific diagnosis is also recommended for patients at risk for complications of gastrointestinal infections, like patients with inflammatory bowel disease, patients involved in any investigation of a possible outbreak of diarrheal illness, and patients who may be at increased risk for transmitting infection to others, like food handlers.

Because of the diverse etiology and variety of tests required to make a specific diagnosis, consultation with infectious disease experts and clinical microbiologists may improve diagnostic strategies. For many agents of foodborne diseases, reporting to the local department of public health is required; public health officials may be able to provide important information concerning ongoing outbreaks or diagnostic support.
Diagnostic testing: The type of testing will depend on the agent suspected, clinical presentation, source of specimen submitted for testing and other factors. Diagnostic techniques for microbial pathogens are discussed in other sections of this book.

- **Bacteria:** Bacterial pathogens may be isolated by culture of stool, vomitus, or other patient specimen. Stool culture is most commonly submitted. Consider submitting stool for culture in patients with
  - Immunocompromise or increased risk for complication of bacterial gastroenteritis
  - Inflammatory bowel disease, to distinguish between infection and flare
  - Severe illness, including severe vomiting or diarrhea, abdominal pain, hypovolemia, or prolonged duration
  - Signs of inflammation, like blood, mucus, or leukocytes in stool; fever; or sepsis; involvement of organ systems outside the gastrointestinal tract

Fecal culture requires use of selective, differential media optimized for isolation of specific pathogens. The pathogens routinely tested may vary from laboratory to laboratory. *Campylobacter, Salmonella,* and *Shigella* spp. are typically isolated by routine stool cultures. Antigen assays are also available for sensitive and specific direct detection of *Campylobacter* in stool specimens. Special cultures may have to be requested if another pathogen is suspected on clinical or epidemiologic grounds (e.g., *E. coli* O157:H7, other Shiga-toxigenic enteric GNB, *Vibrio* spp., *Aeromonas* spp., *Listeria monocytogenes*). Bacterial pathogens are present in high concentrations during acute symptomatic infection. Therefore, submission of a single specimen is usually sensitive for detection of bacterial causes of diarrhea; repeat cultures may be necessary for detection of *Shigella* or asymptomatic carriage of an enteric pathogen.

After isolation, additional testing may be required to detect specific pathogenic mechanisms (e.g., enteropathogenic *E. coli*, Shiga toxin production) or for epidemiologic studies (e.g., serotype analysis of *Salmonella* isolates). Culture of blood, CSF, and other specimens are recommended for patients with signs of systemic illness or localized infection outside the gastrointestinal tract.

In hospitalized patients with onset of symptoms more than 48 hours after admission, testing for *Clostridium difficile* is recommended; routine stool culture or O&P evaluation is unlikely to yield clinically significant results. Several different assays may be used to detect toxigenic *C. difficile*, including toxin A and B EIA, specific glutamate dehydrogenase, cytotoxicity, isolation by anaerobic bacterial culture and PCR.

Evaluation of food or environmental specimens for enteric pathogens is typically performed by a Public Health Laboratory, or other specialized reference laboratory, and is usually performed only as part of a formal epidemiologic investigation.

- **Enteric viruses:** Viral gastroenteritis is most commonly mild and self-limited with few systemic symptoms and may be effectively treated symptomatically without establishing a specific diagnosis. Four viral pathogens are responsible for most cases of viral gastroenteritis in the United States: norovirus, rotavirus, enteric adenoviruses, and astroviruses.
  - Viruses may be detected in stool by electron microscopic techniques, but this testing is not available for routine evaluation of patient specimens.
Viral culture is also of limited utility because of long turnaround time as well as the limited availability of the specialized viral cultures required for enteric viruses that may be isolated in culture. Some clinical laboratories may provide viral culture testing to rule out enteric adenoviruses (serotypes 40 and 41).

Antigen detection testing is available for several enteric viruses and provides reliable detection of rotavirus and enteric adenovirus in stool specimens.

Molecular diagnostic tests now play an important role in the detection of enteric virus infection because of their high sensitivity and specificity, as well as short turnaround time for most assays. Many Public Health and Reference Laboratories offer testing for relevant viruses, and an increasing number of approved assays are becoming commercially available.

Parasites: O&P testing is not cost-effective for routine testing of patients with gastrointestinal complaints but should be considered in patients with persistent diarrhea. Specific epidemiologic risks, like travel to regions with a high endemic rate of enteric parasitic infections, exposure to infants in day care centers, diarrhea in men who have sex with men, patients with HIV infection, and patients who develop diarrhea during a waterborne or other regional outbreak of diarrhea caused by parasitic pathogens. Sensitive and specific stool antigen testing is available for Cryptosporidium, Giardia, and E. histolytica. Antigen testing may serve as cost-effective initial testing for patients who require testing to rule out parasitic infection. Because ova and parasites may be shed intermittently, three specimens for O&P testing should be submitted, separated by at least 24 hours, over 3–6 days, if needed.

Serology: Detection of specific IgM and IgG is used for diagnosis of acute hepatitis A virus infection. Serology plays a minor role in the diagnosis of acute infection by other enteric pathogens. However, patient seroconversion may provide important diagnostic information during the convalescent phase, especially for epidemiologic investigations regarding the cause or scope of a potential epidemic of gastrointestinal disease.

Toxins: Clinical laboratories do not routinely offer testing for detection of specific toxins, like botulinum toxin, in food or patient specimens. Testing for toxins is typically performed by a Public Health Laboratory, or other specialized reference laboratory, and is usually performed only as part of a formal epidemiologic investigation.

Conclusion
It is important for health care providers to

- Consider the possibility of foodborne illness in evaluating a patient’s illness.
- Realize that many, but not all, foodborne illnesses present with prominent GI tract illness. Patients may present with predominant systemic, neurologic, or other signs and symptoms.
- Understand the testing required for likely pathogens. When specific diagnosis is required, ensure that appropriate specimens and cultures, or other tests, are submitted for testing.
Obtain a clinical history that may provide clues regarding the source of the illness as well as assessing the possibility of a larger outbreak.

Report suspect cases to public health officials, as appropriate. Be aware that a patient may be a part of a larger outbreak in the community.

Instruct patients about how to prevent further transmission of illness to contacts.

Suggested Readings

DIARRHEA, CHRONIC

Definition
Chronic diarrhea is diarrhea that lasts for more than 4 weeks.

Causes
- Infectious agents (For a discussion of infectious causes of diarrhea, see the Infectious Gastrointestinal Diseases section in this chapter and Chapter 11)
- IBD (e.g., Crohn disease, UC, collagenous colitis)
- Carbohydrate malabsorption (e.g., lactase or sucrase deficiency)
- Foods (e.g., ethanol, caffeine, sweeteners such as sorbitol, fructose)
- Drugs (e.g., antibiotics, antihypertensive, antiarrhythmic, antineoplastic, colchicine, cholestyramine; see previous section on acute diarrhea.)
- Laxative abuse, factitious
- Endocrine (e.g., DM, adrenal insufficiency, hyperthyroidism, hypothyroidism)
- Hormone-producing tumors (e.g., gastrinoma, VIPoma, villous adenoma, medullary thyroid carcinoma, pheochromocytoma, ganglioneuroma, carcinoid tumor, mastocytosis, somatostatinoma, ectopic hormone production by lung or pancreas carcinoma)
- Injury caused by radiation, ischemia, and so on
- Infiltrations (e.g., scleroderma, amyloidosis, lymphoma)
- Colon carcinoma
- Previous surgery (e.g., gastrectomy, vagotomy, intestinal resection)
- Immune system disorders (e.g., systemic mastocytosis, eosinophilic gastroenteritis)
Intraluminal maldigestion (bile duct obstruction, pancreatic exocrine insufficiency)
Celiac sprue
Whipple disease
Abetalipoproteinemia
Dermatitis herpetiformis
Intestinal lymphangiectasia
Allergy
Idiopathic

OTHER GASTROINTESTINAL CONDITIONS ASSOCIATED WITH CHRONIC DIARRHEA

DIVERTICULOSIS, COLON

- **Laboratory Findings**
  Core laboratory: Hypochromic microcytic anemia, increased WBCs. Increased ESR. Positive occult blood.

ENTEROCOLITIS, NECROTIZING, IN INFANCY

- **Definition**
  Syndrome of acute intestinal necrosis of unknown cause. It is especially associated with prematurity and exchange transfusions.

- **Laboratory Findings**
  There may be oliguria, neutropenia, and anemia. Persistent metabolic acidosis, severe hyponatremia, and DIC are a common triad in infants. Bloody stools feature no characteristic organisms; significant organisms are often found by frequent repeated cultures of blood, urine, and stool.

INFLAMMATORY BOWEL DISEASE

- **Definition**
  IBD refers to a chronic relapsing spectrum of disorders of unknown cause with destructive mucosal immune reaction in a genetically susceptible host. It is caused by an aberrant immune response and loss of tolerance to normal intestinal flora, leading to chronic inflammation of the gut.

REGIONAL ENTERITIS (CROHN DISEASE)

- **Definition**
  Systemic inflammatory disease with predominantly GI tract involvement. There are no pathognomonic findings for Crohn disease or to distinguish it from ulcerative colitis.
Diarrhea

- **Laboratory Findings**
  
  **Histology:** Endoscopic biopsy may show granulomas in >60% of cases of Crohn disease but in only 6% of cases of UC.
  
  **Serology:** Atypical perinuclear-staining antineutrophil cytoplasmic antibodies (P-ANCA) are found in <15% of cases of Crohn disease but in ≤70% of ulcerative colitis patients. Anti-S. cerevisiae (baker’s or brewers’ yeast) antibodies (ASCA) are found in approximately 60% of Crohn disease cases but in only approximately 10% of cases in ulcerative colitis.
  
  Lactoferrin and calprotectin high sensitivity and specificity distinguishing between IBD and noninflammatory IBS.
  
  **Hematology:** Increased WBC, ESR, CRP, and other acute-phase reactants correlate with disease activity. Mild increase of WBC indicates activity, but a marked increase suggests suppuration (e.g., abscess). ESR tends to be higher in disease of the colon than of the ileum. Anemia due to iron deficiency or vitamin B₁₂ or folate deficiency or chronic disease.
  
  **Core laboratory:** Decreased serum albumin, increased γ-globulins. Hyperchloremic metabolic acidosis, dehydration, decreased sodium, potassium, magnesium. Mild liver function test changes due to pericholangitis (especially increased serum ALP). Laboratory changes due to complications or sequelae (e.g., malabsorption, perforation and fistula formation, abscess formation, arthritis, sclerosing cholangitis, iritis, uveitis).

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**ULCERATIVE COLITIS, CHRONIC NONSPECIFIC**

- **Definition**
  
  There are no pathognomonic findings for this disease, nor are there findings that distinguish it from Crohn disease.

- **Laboratory Findings**
  
  **Serology:** P-ANCA are found in 70% of ulcerative colitis patients but only occasionally in cases of Crohn disease. Stools are negative for usual enteric pathogens and parasites.
  
  **Hematology:** With diarrhea and fever, hemoglobin <7.5 g/dL, increased neutrophil count, and ESR >30 mm/hour indicate severe disease.
  
  **Core laboratory:** Serum ALP often increased slightly. Other liver function tests are usually normal. Stools are positive for blood.

- **Other Considerations**
  
  - Laboratory changes due to complications or sequelae (e.g., hemorrhage, carcinoma, electrolyte disorders, toxic megacolon with perforation).
  
  - The lower sensitivity of combined serologic tests only modestly influences pretest and posttest probability in IBD but is very useful in distinguishing Crohn disease from UC. Serial measurements are not useful and do not correlate with disease activity; titers are stable over time.

- **Suggested Reading**
  
MALABSORPTION

Definition
Malabsorption is defective nutrient absorption by the small intestine.

Causes
- Inadequate mixing of food with bile salts and lipase (e.g., pyloroplasty, subtotal or total gastrectomy, gastrojejunostomy)
- Inadequate lipolysis due to lack of lipase (e.g., CF of the pancreas, chronic pancreatitis, cancer of the pancreas or ampulla of Vater, pancreatic fistula, vagotomy)
- Inadequate emulsification of fat due to lack of bile salts (e.g., obstructive jaundice, severe liver disease, bacterial overgrowth of the small intestine, disorders of the terminal ileum)
- Primary absorptive defect in the small bowel
- Inadequate absorptive surface due to extensive mucosal disease (e.g., regional enteritis, tumors, amyloid disease, scleroderma, irradiation)
- Biochemical dysfunction of mucosal cells (e.g., celiac sprue syndrome, severe starvation, or administration of drugs such as neomycin sulfate, colchicine, or PAS)
- Obstruction of mesenteric lymphatics (e.g., by lymphoma, carcinoma, intestinal TB)
- Inadequate length of normal absorptive surface (e.g., surgical resection, fistula, shunt)
- Miscellaneous (e.g., “blind loops” of the intestine and diverticula, Z-E syndrome, agammaglobulinemia, endocrine and metabolic disorders)
- Infection (e.g., acute enteritis, tropical sprue, Whipple disease [Tropheryma whippeli]; in common variable hypogammaglobulinemia, 50–55% of patients have chronic diarrhea and malabsorption caused by a specific pathogen such as G. lamblia or overgrowth of bacteria in the small bowel.)

Laboratory Findings
Core laboratory: Serum cholesterol may be decreased. Decreased serum carotene, albumin, and iron; increased stool weight (>300 g/24 hours) and stool fat (>7 g/24 hours).

Hematology: PT may be prolonged because of malabsorption of vitamin K. Increased ESR.

Anemia is caused by deficiency of iron, folic acid, vitamin B₁₂, or various combinations, depending on their decreased absorption.

Other: Normal D-xylene test, low serum trypsinogen, and pancreatic calcification on radiograph of the abdomen establish diagnosis of chronic pancreatitis. If calcification is absent (as occurs in 70–80% of cases), abnormal contents of pancreatic secretion after secretin–cholecystokinin stimulation or abnormal bentiromide tests establish diagnosis of chronic pancreatitis.

Recommended Tests
Fat absorption indices (steatorrhea): Direct qualitative stool examination. ≥2 random stool samples are collected on diet of >80 g of fat daily.
Serum trypsinogen: <10 ng/mL in 75–85% of patients with severe chronic pancreatitis (those with steatorrhea) and 15–20% of those with mild to moderate disease; occasionally low in cancer of the pancreas; normal (10–75 ng/mL) in nonpancreatic causes of malabsorption.

Carotene tolerance test: Measure serum carotene following daily oral loading of carotene for 3–7 days. Low values for serum carotene levels are usually associated with steatorrhea. Increase of serum carotene by >35 μg/dL indicates previously low dietary intake of carotene and/or fat. Patients with sprue in remission with normal fecal fat excretion may still show low carotene absorption.

Vitamin A tolerance test (for screening steatorrhea): Measure plasma vitamin A level 5 hours after ingestion. Normal rise is 9× fasting level. Flat curve in liver disease. Not useful after gastrectomy. With vitamin A as ester of long-chain fatty acid, flat curve occurs in both pancreatic disease and intestinal mucosal abnormalities; when water-soluble forms of vitamin A are used, the curve becomes normal in patients with pancreatic disease but remains flat in intestinal mucosal abnormalities. An abnormal result indicates a defect in small bowel mucosal absorption function (e.g., sprue, Whipple disease, regional enteritis, TB enteritis, collagen diseases involving the small bowel, extensive resection). Abnormal pancreatic function does not affect the test.

CARBOHYDRATE ABSORPTION INDICES

- Disaccharide malabsorption
  - Causes
    - Primary malabsorption (congenital or acquired) because of absence of specific disaccharidase in brush border of small intestine mucosa
    - Isolated lactase deficiency (also called milk allergy, milk intolerance, congenital familial lactose intolerance, lactase deficiency) (is most common of these defects; occurs in approximately 10% of whites and 60% of blacks; infantile type shows diarrhea, vomiting, failure to thrive, malabsorption, and so on; often appears first in adults; become asymptomatic when lactase is removed from diet)
  - Sucrose–isomaltose malabsorption (inherited recessive defect)
    - Oral sucrose tolerance curve is flat, but glucose plus fructose tolerance test is normal. Occasionally, there is an associated malabsorption with increased stool fat and abnormal D-xylose tolerance test, although intestinal biopsy is normal.
    - Hydrogen breath test after sucrose challenge.
    - Intestinal biopsy with measurement of disaccharidase activities.
    - Sucrose-free diet causes cessation of diarrhea.
  - Glucose–galactose malabsorption (inherited autosomal recessive defect that affects the kidney and intestine)
    - Oral glucose or galactose tolerance curve is flat, but IV tolerance curves are normal.
    - Glucosuria is common. Fructose tolerance test is normal.
  - Secondary malabsorption
    - Resection of >50% of the colon disaccharidase activity. Lactose is most marked, but there may also be sucrose. Oral disaccharide tolerance
Diffuse intestinal disease—especially celiac disease in which activity of all disaccharidases may be decreased, with later increase as intestine becomes normal on gluten-free diet; also cystic fibrosis of the pancreas, severe malnutrition, UC, severe *Giardia* infestation, blind loop syndrome, \( \beta \)-lipoprotein deficiency, effect of drugs (e.g., colchicine, neomycin, birth control pills). Oral tolerance tests (especially lactose) are frequently abnormal, with later return to normal with gluten-free diet. Tolerance tests with monosaccharides may also be abnormal because of defect in absorption as well as digestion.

Small intestinal bacterial overgrowth (see Figure 5-4)
- Quantitative aerobic and anaerobic culture of aspirate of small bowel content showing \( >10^5 \) cfu/mL of anaerobic organisms is considered diagnostic. The utility of culture is limited, however, because it requires invasive collection; there may be sampling error due to limited regions of involvement within the small bowel, and culture techniques and interpretation are not standardized.
- \(^{14}\)C-d-xylose breath test has good specificity.
- Hydrogen breath tests (glucose-H\(_2\), lactulose-H\(_2\))—not recommended because of limited sensitivity and specificity.

**CELIAC DISEASE (GLUTEN-SENSITIVE ENTEROPATHY, NONTROPICAL SPRUE, IDIOPATHIC STEATORRHEA)**

**Definition**
Celiac disease is an autoimmune multisystem disorder (principally manifested in the GI tract) in genetically susceptible persons that may be caused by a mucosal injury by a complex of gliadin (a protein from dietary gluten in wheat, rye, barley, or oats) with tissue transglutaminase (tTG), a cross-linking enzyme. Findings are caused by malabsorption and autoimmunity.

**Laboratory Findings**
Although there are no universally accepted tests for the diagnosis of celiac disease, specific serologic testing and small bowel biopsy are very sensitive and specific for making the diagnosis. All tests must be performed while patients are on a diet of food that contains gluten (Figure 5-5).

*Histology:* Biopsy of jejunum is the diagnostic gold standard; shows characteristic although not specific mucosal lesions. Establishing the diagnosis is essential; patients should not be committed to lifelong gluten-free diet without first assessing intestinal mucosal histology. False-negative results may occur because of patchy distribution of pathology.

*Stool findings:* Steatorrhea demonstrated by positive Sudan stain on \( \geq 2 \) stool samples or quantitative determination of fat in 72-hour pooled stool sample.

*Anti-human IgA tTG antibodies:* (by ELISA) has S/S = \( >90\% >95\% \). False-negative results may occur in patients with IgA deficiency (present in 2.5% of patients with celiac disease for whom corresponding IgG antibody tests may be useful). More reproducible than EMA test.
Anti-IgA deamidated gliadin IgG/IgA antibodies: Deamidated gliadin antibody (DGA) recognizes an antigen related to dietary gluten and is responsible for initiating inflammation in celiac disease. Antigliadin IgA antibodies (by ELISA) have been superseded by these more sensitive tests; has S/S = 80%/80–90%. IgA antigliadin antibodies become undetectable 3–6 months after gluten abstinence; may be used to monitor dietary compliance. May be most effective marker for children <3 years of age. Gliadin is a component of gluten. False-negative results may occur in patients on immunosuppressive therapy. If patient is IgA deficient, serology using IgG-tTG or IgG-EMA should be used.

Molecular tests: HLA variation DQ2 is expressed in approximately 95% of patients; HLA-DQ8 performed by DNA testing is expressed in approximately 5% of patients; absence of these virtually excludes this diagnosis.

Gluten challenge: No longer considered essential to establish the diagnosis. It is done if the diagnosis is uncertain and not documented by biopsy before gluten withdrawal, to determine if symptoms and mucosal changes occur.

Xylose tolerance test: Distinguishes malabsorption caused by impaired transport across diseased mucosa from that caused by impaired digestion in the lumen. Normal in many patients with mild to moderate disease not usually performed.

Considerations

- Firm diagnosis requires definite clinical response to gluten-free diet in 3–9 months, preferably with histologic documentation that the mucosa has reverted to normal by repeat biopsy. If the patient fails to respond to rigid dietary control, biopsy should be repeated to rule out GI lymphoma,
Giardiasis, hypogammaglobulinemia, and other causes of villous atrophy, as well as diet should be rechecked.

- Malabsorption may cause folate deficiency with megaloblastic bone marrow and iron deficiency with mild hypochromic macrocytic anemia. Celiac disease should always be considered in cases of iron deficiency or macrocytic anemia. May also have coagulopathy due to vitamin K deficiency and hypocalcemia and vitamin D deficiency causing osteomalacia. In patients with unexplained diarrhea or malabsorption, celiac sprue should be ruled out by small bowel biopsy.

- Malabsorption may cause folate deficiency with megaloblastic bone marrow and iron deficiency with mild hypochromic macrocytic anemia. Celiac disease should always be considered in cases of iron deficiency or macrocytic anemia. May also have coagulopathy due to vitamin K deficiency and hypocalcemia and vitamin D deficiency causing osteomalacia. In patients with unexplained diarrhea or malabsorption, celiac sprue should be ruled out by small bowel biopsy.

- Laboratory findings due to frequently associated autoimmune diseases (e.g., thyroid, liver, type 1 DM, dermatitis herpetiformis [≤20% of celiac patients], Addison disease, arthritis) and other diseases (e.g., selective IgA deficiency; hyposplenism, T-cell lymphoma of the small intestine; also Down syndrome, IgA nephropathy, IBD). Patients who should be screened include those with steatorrhea, malabsorption, or autoimmune diseases.

Suggested Readings

ENTEROPATHY, PROTEIN LOSING

- **Definition**
  This condition refers to the GI loss of plasma protein in abnormal amounts.

- **Causes**
  - Secondary (i.e., disease states in which clinically significant protein-losing enteropathy may occur as a manifestation)
    - Giant hypertrophy of gastric rugae (Ménétrier disease)
    - Eosinophilic gastroenteritis
    - Gastric neoplasms
    - Infections (e.g., Whipple disease, bacterial overgrowth, enterocolitis, shigellosis, parasitic infestation, viral infections, C. difficile infection) (See relevant sections in Chapter 11, Infectious Diseases)
    - Nontropical sprue
    - Inflammatory and neoplastic diseases of the small and large intestines, including UC, regional enteritis
    - Constrictive pericarditis
    - Immune diseases (e.g., SLE)
    - Lymphatic obstruction (e.g., lymphoma, sarcoidosis, mesenteric TB)
  - Primary (i.e., hypoproteinemia is the major clinical feature)
    - Intestinal lymphangiectasia
    - Nonspecific inflammatory or granulomatous disease of the small intestine
Laboratory Findings

Core laboratory: Serum cholesterol usually normal. Serum total protein, albumin, γ-globulin, and calcium are decreased. Serum α- and β-globulins normal. Proteinuria absent.

Hematology: Mild anemia. Eosinophilia (occasionally).

Stool findings: Steatorrhea with abnormal tests of lipid absorption.

Other: Increased permeability of the GI tract to large molecular substances shown by IV iodine-131-polyvinylpyrrolidone (131I-PVP) test (see Malabsorption).

COLITIS, COLLAGENOUS

Definition
Syndrome of chronic nonbloody diarrhea. The incidence is approximately 3/1,000 in such patients. Diagnosis is established by biopsy of the colon in patients thought to have irritable bowel syndrome.

Laboratory Findings
Hematology: ESR is increased, and anemia and hypoalbuminemia occur in some patients. Eosinophil count is increased in some patients.

COLITIS, PSEUDOMEMBRANOUS

- See Clostridium difficile in Chapter 11, Infectious Diseases.

GALLSTONE ILEUS

- Laboratory findings caused by preceding chronic cholecystitis and cholelithiasis
- Laboratory findings caused by acute obstruction of the terminal ileum (accounts for 1–2% of patients)

GASTROENTERITIS, EOSINOPHILIC

Definition
Diagnosis requires histologic evidence of predominant eosinophilic (>20 eosinophils/HPF) infiltration of the GI tract in the absence of parasitic infection or extraintestinal disease.

Laboratory Findings
Hematology: Eosinophilia in 80% of cases.

Other: Eosinophilic ascites with predominant disease of serosal layer. IgE may be increased, especially in children.

Suggested Readings
Bonis PAL, LaMont JT. Approach to the adult with chronic diarrhea in developed countries. www.uptodate.com, May 2009.
GASTROINTESTINAL BLEEDING

UPPER GASTROINTESTINAL BLEEDING (ADULT)

Definition
Upper GI bleeding is defined as emanating from a source above the ligament of Treitz. This is the most common medical emergency for gastroenterologists. The mortality is approximately 8%, and it is not usually due to exsanguination but rather due to the adverse effect on comorbid conditions.

Who Should Be Suspected?
The patient may present with stigmata of chronic blood loss (iron deficiency anemia and related symptoms) or acute blood loss (weakness or syncope).

Screening: Currently, screening for asymptomatic ulcerated lesions of the GI tract is generally recommended, especially for carcinoma of the colon and large adenomas.

Differential Diagnosis of Upper Gastrointestinal Bleeding (Table 5-3)

- PUD (see discussion of acute abdomen under Abdominal Pain) (40–50% of patients) is associated with risk factors including H. pylori infection, use of NSAIDs, stress, and increase of gastric acid. It accounts for gastritis in 10% of patients, esophagitis 6% associated with gastric reflux (GERD). Risk factors for stress-related bleeding include respiratory failure and coagulopathy. Portal hypertension and varices (18% of patients) indicate the severity of a patient’s underlying cirrhosis. These patients have an associated mortality of 50% even after control of the hemorrhage.
- Mallory-Weiss tears (5% of patients) occur in the distal esophagus, at the site of the gastroesophageal junction, usually following a bout of retching. Most tears heal uneventfully within 24–48 hours. The diagnosis is made by

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<thead>
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<th>TABLE 5–3. Differential Diagnosis of Upper Gastrointestinal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peptic ulcer disease (40–50%; idiopathic; induced by drug, toxin, or stress; related to an infection; associated with Zollinger-Ellinger syndrome)</td>
</tr>
<tr>
<td>• Erosive esophagitis, gastritis, and duodenitis 25%</td>
</tr>
<tr>
<td>• Portal hypertension and varices (10–15%; esophageal, gastric, duodenal, and portal hypertensive gastropathy)</td>
</tr>
<tr>
<td>• Mallory-Weiss tear (5%)</td>
</tr>
<tr>
<td>• Rare causes: arteriovenous malformations, Rendu-Osler-Weber syndrome, watermelon stomach (gastric antral vascular ectasia), Dieulafoy lesion, stomal ulcer, neoplasm (benign, primary, and metastatic malignancy), connective tissue disease (scleroderma, Ehlers-Danlos syndrome), aortic enteric fistula, hemobilia, uremic gastritis, foreign body</td>
</tr>
<tr>
<td>• Carcinoma of the stomach</td>
</tr>
<tr>
<td>• Heyde syndrome (acquired von Willebrand, angiodysplasia, aortic stenosis)</td>
</tr>
</tbody>
</table>
endoscopic evaluation, at which time therapeutic interventions may be utilized as well as stratifying the risk of rebleeding.

- Neoplasm of the esophagus and stomach accounts for <5% of all cases of severe bleeding. It is generally a late manifestation and represents a negative prognostic feature. Uncommonly, tumors may metastasize to the gastric mucosa.

- Anticoagulant therapy: GI hemorrhage occurs in 3–4% of patients on anticoagulant therapy; it may be spontaneous or secondary to unsuspected disease (e.g., peptic ulcer, carcinoma, diverticula, hemorrhoids). Occasionally, there is hemorrhage into the wall of the intestine with secondary ileus. PT may be in the therapeutic range or, more commonly, is increased. Warfarin (Coumadin) drug action is potentiated by administration of aspirin, antibiotics, phenylbutazone, and thyroxine and by T-tube drainage of the common bile duct, especially if pancreatic disease is present.

- Occult bleeding.

- Rendu-Osler-Weber syndrome is associated with telangiectasia of the lips, oral mucosa, and fingertips. Dieulafoy lesion correlates with a dilated aberrant submucosal vessel, which erodes the overlying mucosa in the absence of an ulcer. This should be suspected in the patient with recurrent episodes of undiagnosed upper GI bleeding (GI bleeding in 10–40% of patients).

- Causes

  - Mass (e.g., carcinoma, adenoma). In addition to the main cause of bleeding, 50% of patients have an additional lesion that could cause hemorrhage (especially duodenal ulcer, esophageal varices, hiatal hernia). With previously known GI tract lesions, 40% of patients bled from an altogether different lesion.

  - Inflammation (e.g., IBD, Crohn disease, erosive esophagitis).

  - Vascular disorders (e.g., varices, hemangioma).

  - Infections (e.g., TB, amebiasis, hookworm, whipworm, strongyloidiasis, ascariasis).

  - Other sites (e.g., hemoptysis, epistaxis, oropharynx).

  - Others (e.g., factitious, coagulopathies, long-distance running).

- Use of fecal occult blood test (See: Occult Blood, Stool, in Chapter 16. Laboratory Tests.)

- Laboratory Findings

  - Initial assessment: Assess magnitude of blood loss (CBC, vital signs).
    - Check coagulation (PT, PTT, platelets) and other tests to rule out either an acquired or a congenital bleeding disorder.
    - Type and cross-match number of units appropriate for severity of blood loss.

  - Esophagogastroduodenoscopy (EGD) is the diagnostic procedure of choice for patients presenting with acute GI bleeding. Advantages of early EGD include the following:
    - Confirmation or modification of the working diagnosis, proposed by the history and physical examination
    - Providing therapeutic measures, which lessen transfusion requirements and the need for surgery
Potentially averting the need for hospitalization

In patients with iron deficiency, recommend upper and lower endoscopy plus workup for celiac disease

**Limitations**

- Adenomas <2 cm in greatest diameter are less likely to bleed. Upper GI tract bleeding is less likely than lower GI tract bleeding to cause a positive test.
- Long-distance running is associated with positive guaiac test in ≤23% of runners.
- Stools may appear grossly normal with GI bleeding of 100 mL/day.
- Consistent melena requires 150–200 mL blood in the stomach.

**GASTROINTESTINAL BLEEDING, SMALL INTESTINE**

The small intestine is an uncommon site of hemorrhage, accounting for only 3–5% of GI bleeding. Patients usually present with occult blood loss and may have evidence of melena or hematochezia.

**Differential Diagnosis of Gastrointestinal Bleeding from the Small Intestine (Table 5-4)**

- Angiodysplasia accounts for the majority of cases of bleeding from the small intestine (70–80%). Bleeding can be either brisk or occult. An isolated episode of bleeding does not mandate therapy, as the lesions do not usually rebleed (approximately 50%). Angiodysplasia may be an incidental finding and needs to be documented to be considered as a source of blood loss.
- Tumors account for 5–10% of cases of blood from the small intestine. Of these, one third are benign (leiomyoma and adenomas most commonly) and two thirds are malignant (45% adenocarcinoma, usually of the duodenum, 30% carcinoid, 14% lymphoma, and 11% leiomyosarcoma). The three

<table>
<thead>
<tr>
<th>TABLE 5–4. Differential Diagnosis of Gastrointestinal Bleeding from the Small Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Angiodysplasia</td>
</tr>
<tr>
<td>• Small bowel tumors</td>
</tr>
<tr>
<td>• Less common causes:</td>
</tr>
<tr>
<td>• Ulcerative diseases (most commonly Crohn disease)</td>
</tr>
<tr>
<td>• Meckel diverticulum (the cause in two thirds of men younger than 30 years of age)</td>
</tr>
<tr>
<td>• Zollinger-Ellison syndrome (causes ulcerations)</td>
</tr>
<tr>
<td>• Infections (e.g., tuberculosis, syphilis, typhoid, histoplasmosis)</td>
</tr>
<tr>
<td>• Medications (e.g., potassium, nonsteroidal anti-inflammatory drugs, 6-mercaptopurine)</td>
</tr>
<tr>
<td>• Vasculitis</td>
</tr>
<tr>
<td>• Radiation enteritis (injury can occur 6–24 months after exposure, secondary to the development of occlusive vasculitis)</td>
</tr>
<tr>
<td>• Jejunal diverticula (&lt;5% actually bleed, but bleeding is usually massive, with mortality as high as 20%)</td>
</tr>
<tr>
<td>• Vascular lesions (varices, venous ectasias, telangiectasias, hemangiomas, arteriovenous malformations)</td>
</tr>
</tbody>
</table>
most common malignancies are generally associated with chronic blood loss. Metastatic disease may also occur, most commonly from melanoma and breast cancer.

- **Laboratory Findings**
  - Plain abdominal films may show evidence of obstruction suggestive of stricture or tumor, but they are not likely to be diagnostic.
  - Contrast radiography
    - Small bowel series have a low yield in identifying a bleeding source (i.e., a 5% detection rate). This may be increased to 10% with use of enteroclysis. If the bleeding source is a small intestine malignancy, the yield is considerably better.
    - Barium studies cannot diagnose angiodysplasias, but they may be useful in identifying mass lesions and mucosal defects.
    - Despite the low diagnostic yield, contrast radiography is the initial study in a patient where small intestinal bleeding is suspected (i.e., when the evaluation of upper and lower GI tracts are nondiagnostic).
  - Endoscopic studies
    - Routine EGD reaches the junction of the second and third portions of the duodenum.
    - Conventional push enteroscopy (either a dedicated enteroscope or a pediatric colonoscope) can reach the proximal jejunum. Yield with push enteroscopy varies from 24 to 75% in detecting a bleeding source. Push enteroscopy also has therapeutic value.
    - Sonde enteroscopy is a newer procedure that is being developed to visualize the entire jejunum and ileum. It is a flexible fiberoptic instrument carried through the bowel by peristalsis. It is not a routinely available procedure, and it is best reserved for those patients with comorbid conditions that may preclude intraoperative enteroscopy (video capsule endoscopy).
  - Angiography detects a bleeding rate of 0.5 mL/minute. It can localize the site of bleeding in 50–72% of cases if bleeding is massive, but in only 25–50% of cases if bleeding has slowed. It has a low yield in diagnosing angiodysplasias and tumors.
  - Nuclear imaging
    - Technetium-99 bleeding scan may detect bleeding at a rate as slight as 0.1 mL/minute. Like angiography, it is only of value in the setting of active bleeding. It can define a general area of bleeding, but it cannot identify the precise source.
    - Technetium-99 Meckel scan, which is taken up by ectopic gastric mucosa in the diverticulum, is not useful if the diverticulum does not contain gastric mucosa.
  - Surgical evaluation
    - Intraoperative enteroscopy is a procedure whereby the bowel is manually advanced over an endoscope. It is the most common way to examine the entire small bowel. It is successful in identifying a bleeding source 83–100% of the time.
    - Exploratory surgery is often considered in patients with recurrent GI bleeding of unclear origin. Simple exploration has a low success rate, with
a diagnostic yield of only 10% when unaccompanied by other evaluations (i.e., enteroscopy).

- Stepwise approach to evaluation: In a study of 77 patients, the interval from presentation to diagnosis was >20 months, because of the relatively asymptomatic nature of the conditions and the difficulty in evaluating small bowel bleeding sources.

- Determine the source of bleeding
  - In those with a nondiagnostic evaluation of lower and upper GI tracts, small bowel evaluation will be necessary.
  - Once the small bowel is assumed to be the bleeding source (i.e., standard examinations are nondiagnostic), proceed to small bowel series.

- If the source is not identified
  - Proceed to push enteroscopy, before considering repeat EGD or colonoscopy.
  - Sonde enteroscopy may be considered.
  - Withhold bleeding scans and angiography, unless the patient is actively bleeding.
  - Exploratory surgery can be done with intraoperative endoscopy if needed.
  - Video capsule endoscopy.

- **Neoplasms Caused by Primary Diseases of the Small Intestine**
  - Biopsy of lesions confirms the diagnosis.
  - Laboratory findings due to complications (e.g., hemorrhage, obstruction, intussusception, malabsorption).
  - Laboratory findings due to underlying conditions (e.g., Peutz-Jeghers syndrome, carcinoid syndrome).

### LOWER GASTROINTESTINAL BLEEDING (ADULT), ACUTE

- **Overview**
  - Lower GI bleeding is usually defined by bleeding originating from below the ligament of Treitz.
  - If the initial assessment does not clearly distinguish between upper and lower sources of GI bleeding, evaluation of the upper tract should be pursued, as this is the more common site of massive GI bleeding.

- **Differential Diagnosis of Lower Gastrointestinal Bleeding (Table 5-5)**
  - Angiodysplasia: In elderly patients, angiodysplasia is diagnosed with proportional greater frequency. Angiodysplasia is not visualized by barium enema. The bleeding tends to be self-limited, frequently arising from the right colon.
  - Benign anorectal pathology: In younger patients (<35 years of age), benign anorectal pathology (e.g., hemorrhoidal bleeding) is the most common etiology.
  - Diverticulosis: Less than 33% of patients with diverticulosis develop significant bleeding. The bleeding is typically painless and occurs in the absence of diverticulitis. Although diverticula are more commonly located on the left side of the colon, right-sided lesions account for a significant portion of diverticular bleeding.
Colon cancer polyps account for 19% of patients with lower gastrointestinal blood loss in patients older than 50 years of age. 
Coagulopathy usually causes bleeding in patients with a comorbid GI condition. Therefore, a patient with coagulopathy always requires further evaluation. 
Suspect upper GI bleeding in patients presenting with hematochezia. 
Hemorrhoids and bloody diarrhea from inflammation need to be ruled out.

Diagnostic Evaluation

Initial assessment
- Check coagulation studies (PT, PTT, platelets, CBC, BUN, creatinine). Bleeding in uremic patients with angiodysplasia may be a result of acquired coagulopathy. May present as iron deficiency. Perform serum ferritin.
- Type and cross-match number of units appropriate for severity of blood loss.

Endoscopic studies (assuming an upper GI bleed is excluded by virtue of nonbloody bilious fluid obtained via nasogastric lavage)
- Anoscopy may be performed to rule out bleeding hemorrhoids in appropriately selected patients.
- Colonoscopy will identify a bleeding source in approximately 80% of patients and will help control bleeding in up to 40% of patients. Other advantages include assisting in preoperative assessment.

Neoplasms, colon: Blood in stool (occult or gross). Annual screening for occult blood detects <50% of cancers and 10% of adenomas.

Suggested Readings

<table>
<thead>
<tr>
<th>TABLE 5–5. Differential Diagnosis of Lower Gastrointestinal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diverticulosis (~33%)</td>
</tr>
<tr>
<td>• Angiodysplasia (~28%)</td>
</tr>
<tr>
<td>• Neoplasia (benign and malignant ~19%)</td>
</tr>
<tr>
<td>• Colitis (ulcerative, Crohn, ischemic, pseudomembranous, infectious disease, radiation exposure approximately 18%)</td>
</tr>
<tr>
<td>• Hemorrhoid (approximately 3%)</td>
</tr>
<tr>
<td>• Less common causes:</td>
</tr>
<tr>
<td>• Solitary ulcers</td>
</tr>
<tr>
<td>• Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>• Venous lakes</td>
</tr>
<tr>
<td>• Blue rubber nevus</td>
</tr>
<tr>
<td>• Anastomotic ulcerations and suture lines</td>
</tr>
<tr>
<td>• Mechanical trauma</td>
</tr>
<tr>
<td>• Postbiopsy or polypectomy</td>
</tr>
<tr>
<td>• Coagulopathy and anticoagulation therapy</td>
</tr>
<tr>
<td>• Autoimmune disease (e.g., rheumatoid vasculitis, Henoch-Schönlein purpura)</td>
</tr>
</tbody>
</table>
HEPATOMEGALY

Definition

- Hepatomegaly refers to an enlarged liver with a vertical span >12 cm as per-cussed in the midclavicular line. Studies have suggested that by ultrasound, a midhepatic (sagittal) diameter >15.5 cm indicates hepatomegaly in 75% of the cases. By radioisotope scanning, a span of >15–17 cm in the mid-clavicular line indicates hepatomegaly.
- Hepatomegaly may occur in the absence of pathology (i.e., normal variant) or as a result of a depressed right hemidiaphragm, Riedel lobe, or subdia-phragmatic space occupying lesions.

Differential Diagnosis and Workup (Figure 5-6)

- The causes of hepatomegaly can be subdivided into processes involving the following:
  ▼ Hypertrophy or hyperplasia of cells intrinsic to the normal liver parenchyma
  ▼ Hepatomegaly secondary to infiltration of the liver by cells or organisms not normally present
  ▼ Vascular causes resulting in congestion of the liver
- Common causes: Fatty liver (nonalcoholic steatohepatitis) is a common cause of hepatomegaly. The most common cause of fatty liver in the United States is chronic alcoholism. Other causes of fatty liver include diabetes, obesity, hyperlipidemia (metabolic syndrome), protein malnutrition, and prolonged TPN.
  ▼ Other causes: In addition to infectious and drug-related causes, clinically important causes of hepatomegaly include hemochromatosis, α1-antitrypsin deficiency, Wilson disease, autoimmune hepatitis, SLE, and RA.
  ▼ Cholangiohepatitis is a rare disorder in which intrahepatic and extrahepatic bile ducts become obstructed with bile stones, leading to secondary inflammation of the liver.
  ▼ Congestion from heart failure includes all causes of elevated right heart pressures (e.g., cor pulmonale, tricuspid regurgitation, constrictive pericarditis, ventricular dysfunction).
  ▼ Hepatocellular carcinoma represents approximately 2.5% of all carcinomas in the United States and approximately 30–50% of all carcinomas in Asians living in Asia, where chronic active hepatitis due to hepatitis B virus is common. Other risk factors include chronic hepatitis C or chronic liver disease of any type.
Figure 5–6  Algorithm for the workup of hepatomegaly; if the vertical span is >12 cm by physical examination or imaging. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CT, computed tomography; FOBT, fecal occult blood test; GI, gastrointestinal; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis; PT, prothrombin time.
Benign tumors include adenomas, focal nodular hyperplasia, and hemangiomas. Adenomas are more commonly seen in women 30–40 years of age, mostly in the right lobe and can be as large as 10 cm in greatest dimension. There is often a history of oral contraceptive (estrogen) use. Focal nodular hyperplasia often presents as right-sided solid masses. Hemangiomas are most commonly benign, with hemorrhage and malignant transformation occurring rarely.

Budd-Chiari syndrome (hepatic vein thrombosis) usually presents with hepatomegaly, pain, and severe, intractable ascites. Risk factors included hypercoagulable states, polycythemia vera, myeloproliferative syndromes, paroxysmal nocturnal hemoglobinuria, and use of oral contraceptive pills.

Metastatic tumors: After lymph nodes, the liver is the second most common metastatic site, probably due to its high vascularity from a dual arterial/venous blood supply. With the exception of primary brain tumors, any primary tumor can metastasize to the liver. The most common primary tumors derive from the GI tract, lung, breast, and melanoma. The usual presentation is with nonspecific, systemic symptoms such as weight loss, fever, and loss of appetite.

A tender liver mass in a patient with an elevated WBC count and eosinophilia suggests a liver abscess and possibly parasitic infection.

Radiologic studies

Ultrasound is considered the primary screening examination for hepatic disease. In general, ultrasound is better for focal lesions than for parenchymal disease.

- The advantages include low cost, portability, and no ionizing radiation.
  - Masses as small as 1 cm can be detected, and cystic masses or abscesses can be distinguished from solid masses. Doppler ultrasonography can assess the patency and direction of blood flow in the hepatic and portal veins (without contrast).
  - The disadvantages include obscured images in the presence of bowel gas and obesity.

CT scanning: In general, anatomic definition is more complete than with ultrasound. CT scanning is also better than ultrasound for showing diffuse parenchymal liver disease (fat shows up as decreased density and hemochromatosis, or secondary iron overload shows up as increased density).

- The advantages include the ability to image in the setting of obesity and bowel gas.
  - Lesions as small as 1 cm can be distinguished.
  - With IV contrast, abscesses can usually be distinguished from tumors.
  - Dynamic scanning with IV contrast may also show cavernous hemangiomas.
  - Mass lesions can be biopsied under either ultrasound or CT guidance.
- The disadvantages include cost, radiation, and possible exposure to IV contrast.
Magnetic resonance imaging (MRI): Sensitivity is superior to CT scanning for mass lesions.
- The advantages include lack of ionizing radiation and different planes of imaging.
  - It is the technique of choice to look for hemangiomas.
  - It is useful in distinguishing between a regenerating nodule and a tumor in the cirrhotic liver.
  - MRI can be used to monitor the liver for iron and copper deposition and, with some modification, can identify fatty liver and can produce an estimated quantification of fat content.
  - It can sometimes detect Budd-Chiari syndrome (hepatic vein thrombosis) without the need for IV iodinated contrast media (gadolinium is required).
- The disadvantages include cost; slow time to acquire images, leading to more artifact; and limitations for patients with metal implants due to the use of a large magnet. MRI cannot distinguish a primary versus metastatic tumor.

Radioisotope scanning has been largely replaced by ultrasound and CT scanning.
- Technetium-99m–labeled sulfur colloid scanning depends on uptake of phagocytic cells (Kupffer) and can help assess size and shape of the liver. Any disease where Kupffer cells are replaced by tumors, cysts, and abscesses produces a cold spot (adenomas); whereas with focal nodular hyperplasias, the liver will light up. Resolution for mass lesions is approximately 2 cm. Scintigraphy using radioactively labeled antibodies to tumor antigens is being developed as a diagnostic tool.
- Gallium scanning uses gallium that is preferentially taken up in tissues synthesizing proteins (tumors or abscesses), and such areas show up as hot spots.

Imaging of the biliary tract
- ERCP allows for therapy (e.g., stone removal or stenting) as well as diagnosis.
- Percutaneous transhepatic cholangiography (PTC) allows for imaging of the proximal biliary ducts and some therapy (e.g., stent placement or percutaneous drainage) of the ducts.
- More recently, magnetic resonance cholangiopancreatography (MRCP) has demonstrated diagnostic accuracy similar to ERCP. The principal disadvantages include spatial resolution, which may not be as good as that achieved with ERCP; lack of therapeutic benefit; and decreased ability to visualize the ampulla.

FATTY LIVER
- Nonalcoholic steatohepatitis in most cases may have a history of metabolic syndrome. Nutritional (e.g., alcoholism, malnutrition, starvation, rapid weight loss)
\section*{Causes}

- Drugs (e.g., aspirin, glucocorticoids, synthetic estrogens, some antiviral agents, calcium channel blockers, cocaine, methotrexate, valproic acid)
- Metabolic/genetic (e.g., acute fatty liver of pregnancy, dysbetalipoproteinemia, Weber-Christian disease, cholesterol ester storage, Wolman disease)
- Other (e.g., HIV infection, \textit{B. cereus} toxins, liver toxins [e.g., organic solvents, phosphorus], small bowel disease [inflammatory, bacterial overgrowth], fatty liver of pregnancy)

\section*{Laboratory Findings}

- **Histology**: Biopsy of the liver establishes the diagnosis. Fatty liver may be the only postmortem finding in cases of sudden, unexpected death.
- **Core laboratory**: Most commonly, serum AST and ALT are increased 2–3×; usually ALT > AST in NAFL. Serum ALP is normal or slightly increased in <50% of patients. Other liver function tests are usually normal. Increased serum ferritin (≤5×) and transferrin saturation occur in approximately 60% of cases.
- **Serology**: Tests for viral hepatitis are negative.

\textbf{Considerations}

- Laboratory findings are due to underlying conditions (most commonly alcoholism; nonalcoholic fatty liver [NAFL] is commonly associated with type 2 DM [≤75%], obesity [69–100%], hyperlipidemia [20–81%]; hypertension malnutrition, toxic chemicals). NAFL is distinguished by negligible history of alcohol consumption and negative random blood alcohol assays. Cirrhosis occurs in ≤50% of alcoholic and ≤17% of nonalcoholic cases.

\section*{FATTY LIVER OF PREGNANCY, ACUTE}

- The incidence is ≤1 per 15,000 deliveries; usually occurs >35th week of pregnancy.
- This is a medical emergency because of high maternal and fetal mortality that is markedly improved by termination of pregnancy.
- Often associated with preeclampsia (see Chapter 8, Renal and Urinary Tract Diseases).

\section*{Laboratory Findings}

- **Histology**: Biopsy of the liver confirms the diagnosis.
- **Core laboratory**: Increased AST and ALT to approximately 300 U (rarely >500 U) is used for early screening in suspicious cases; ratio is not helpful in differential diagnosis. Serum bilirubin may be normal early but will rise unless pregnancy terminates. Serum uric acid is increased disproportionately to BUN and creatinine, which may also be increased. Blood glucose is often decreased, sometimes markedly. Blood ammonia is usually increased. Neonatal liver function tests are usually normal but hypoglycemia may occur.
- **Hematology**: Increased WBC in >80% of cases (often >15,000/μL). Evidence of DIC in >75% of patients.

\footnote{May principally cause macrovesicular steatosis due to imbalance in hepatic synthesis and export of lipids.}

\footnote{May principally cause microvesicular steatosis due to defective mitochondrial function.}

\footnote{May principally cause accumulation of phospholipids in lysosomes.}
NEOPLASMS OF THE LIVER: HEPATOCELLULAR CARCINOMA (HEPATOMA)

- **Laboratory Findings**
  - **Core laboratory**: Serum AFP may be increased for up to 18 months before symptoms; is a sensitive indicator of recurrence in treated patients, but a normal postoperative level does not ensure the absence of metastases. Levels >500 ng/dL in adults strongly suggest hepatoma. Levels >100× URL have S/S = 60%/100%. In ≤30% of hepatoma cases, AFP <4× URL; such increases are common in chronic HBC and HCV. Serum GGT hepatoma–specific band (HSBs I′, II, II′) by electrophoresis activity >5.5 U/L has S/S = 85%/97%, accuracy = 92%. Does not correlate with AFP or tumor size.
  - **Hematology**: ESR and WBC sometimes increased. Anemia is common; polycythemia occurs occasionally. Hemochromatosis (≤20% of patients die of hepatoma).
  - **Serology**: Markers of viral hepatitis are frequently present.
  - **Tumor markers**: Serum CEA is usually normal. CEA in bile is increased in patients with cholangiocarcinoma and intrahepatic stones but not in patients with benign stricture, choledochal cysts, and sclerosing cholangitis. Increases with progression of disease and declines with tumor resection.

**Considerations**
- Sudden progressive worsening of laboratory findings of underlying disease (e.g., increased serum ALP, LD, AST, bilirubin).
- Relative absence of hepatoma associated with cirrhosis of Wilson disease.
- Laboratory findings due to obstruction of hepatic (Budd-Chiari syndrome) or portal veins or the inferior vena cava may occur.

**Suggested Readings**

JAUNDICE (SEE HEPATOMEGALY)

- **Overview**
  - Jaundice is a yellowish staining of the integument, sclerae, and deeper tissues and is associated with conditions that have increased excretions of bile pigments, which are increased in the plasma.
  - **Physiology**
    - Serum bilirubin accumulates when its production from heme exceeds its metabolism and excretion.
    - An imbalance between the production and clearance of serum bilirubin results either from excess release of bilirubin into the bloodstream or
from physiologic processes that impair the hepatic uptake, metabolism, or excretion of this metabolite.

Jaundice is clinically detectable when the serum bilirubin exceeds 2.0–2.5 mg/dL. Because elastin has a high affinity for bilirubin, and scleral tissue is rich in elastin, scleral icterus is usually a more sensitive sign than generalized jaundice.

Bilirubin metabolism

Unconjugated bilirubin: More than 90% of serum bilirubin in normal individuals is in an unconjugated form, circulating as an albumin-bound complex. This is not filtered by the kidneys.

Conjugated bilirubin: The remainder is conjugated (primarily as a glucuronide), rendering it water soluble, and thus capable of being filtered and excreted by the kidney.

Hepatic phase: Hepatic metabolism has three phases: uptake, conjugation, and excretion.

- Uptake phase: Unconjugated bilirubin is bound to albumin and is presented to the hepatocyte, where the complex dissociates and bilirubin enters the cell either by diffusion or by transport across the membrane.
- Conjugation phase: Bilirubin is then conjugated in a two-step process. This occurs in the endoplasmic reticulum and is catalyzed by glucuronyl transferase. Bilirubin glucuronide is generated.
- Excretion phase: In an energy-dependent process occurring in the biliary canaliculi, conjugated bilirubin is excreted into the bile. It is important to remember that this is the rate-limiting step. When this phase is impaired, either through obstruction or through excretory defects, the conjugated bilirubin is presumed to reflux through the hepatic sinusoids into the bloodstream.

Intestinal phase: After excretion into the bile, conjugated bile is transported into the duodenum. It is not reabsorbed by intestinal mucosa. In the intestine, it is either excreted in the feces unchanged or metabolized by intestinal bacteria to urobilinogen. Urobilinogen is then reabsorbed, where a small portion is metabolized in the liver, and the remainder bypasses the liver and is excreted by the kidney.

Differential Diagnosis of Jaundice (Table 5-6)

Extrahepatic biliary obstruction

The history, physical examination, and initial laboratory assessment have a sensitivity of 90–95%. The specificity, however, is only 76%. When radiologic imaging is factored in, the specificity rises to 98%.

Approximately 40% of patients with this diagnosis present with jaundice.

In the setting of complete obstruction, alcoholic stools are seen and no urobilinogen is detected in the urine (see Cancer Head of the Pancreas, Acute Abdomen).

In patients with extrahepatic biliary obstruction, ALP would be expected to rise to levels 2–3 times normal. A normal level would be uncommon. Serum transaminases would generally be <300 U/L.
Intrahepatic cholestasis: Consider intrahepatic etiologies in the differential diagnosis because high levels may be seen in patients with primary biliary cirrhosis and granulomatous hepatitis.

This group of disorders is defined by the lack of evidence of mechanical obstruction and cannot be explained on the basis of hepatocellular injury alone. Among these disorders are those characterized by disordered enzyme function (intrinsic/acquired), infiltrative disorders, and drugs.

A diagnosis of intrahepatic cholestasis made by clinical assessment and supported by negative findings from ultrasound or CT scan offers 95% specificity. In a patient in whom extrahepatic obstruction is not strongly suspected, no further investigation of the extrahepatic biliary tree is indicated.

### TABLE 5–6. Differential Diagnosis of Jaundice

<table>
<thead>
<tr>
<th>Conjugated Hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatocellular jaundice</td>
</tr>
<tr>
<td>• Hepatitis virus</td>
</tr>
<tr>
<td>• Toxin or drugs (alcohol)</td>
</tr>
<tr>
<td>• Cirrhosis</td>
</tr>
<tr>
<td>• Ischemia</td>
</tr>
<tr>
<td>• Extrahepatic biliary obstruction</td>
</tr>
<tr>
<td>• Choledocholithias</td>
</tr>
<tr>
<td>• Ascending cholangitis</td>
</tr>
<tr>
<td>• Pancreatitis—see Abdominal Pain</td>
</tr>
<tr>
<td>• Sclerosing cholangitis</td>
</tr>
<tr>
<td>• HIV cholangiopathy</td>
</tr>
<tr>
<td>• Biliary stricture or cyst</td>
</tr>
<tr>
<td>• Malignancy</td>
</tr>
<tr>
<td>• Pancreas—see Abdominal Pain</td>
</tr>
<tr>
<td>• Ampullary carcinoma</td>
</tr>
<tr>
<td>• Cholangiocarcinoma</td>
</tr>
<tr>
<td>• Metastatic</td>
</tr>
<tr>
<td>• Intrahepatic cholestasis</td>
</tr>
<tr>
<td>• Abscess</td>
</tr>
<tr>
<td>• Tumor</td>
</tr>
<tr>
<td>• Primary biliary cirrhosis</td>
</tr>
<tr>
<td>• Cholestatic jaundice of pregnancy</td>
</tr>
<tr>
<td>• Dubin-Johnson syndrome</td>
</tr>
<tr>
<td>• Rotor syndrome</td>
</tr>
<tr>
<td>• Benign recurrent intrahepatic cholestasis</td>
</tr>
<tr>
<td>• Sepsis</td>
</tr>
<tr>
<td>• Infiltrative disease</td>
</tr>
<tr>
<td>• Sarcoid</td>
</tr>
<tr>
<td>• Amyloid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unconjugated Hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hemolysis</td>
</tr>
<tr>
<td>• Gilbert syndrome</td>
</tr>
<tr>
<td>• Ineffective erythropoiesis</td>
</tr>
<tr>
<td>• Hematoma resorption</td>
</tr>
</tbody>
</table>
HYPERBILIRUBINEMIA

UNCONJUGATED HYPERBILIRUBINEMIA

Causes

- Increased destruction of RBCs
  - Isoimmunization (e.g., incompatibility of Rh, ABO, other blood groups)
  - Biochemical defects of RBCs (e.g., G6PD deficiency, pyruvate deficiency, hexokinase deficiency, congenital erythropoietic porphyria, and α- and γ-thalassemias)
  - Structural defects of RBCs (e.g., hereditary spherocytosis, hereditary elliptocytosis, infantile pyknocytosis, hereditary xerocytosis)
  - Physiologic hemolysis of the newborn
    - Infection (viral, bacterial, and protozoal)
    - Congenital causes
    - Extravascular blood (e.g., subdural hematoma, ecchymoses, hemangiomas)
    - Erythrocytosis (e.g., maternal-to-fetal or twin-to-twin transfusion, delayed clamping of the umbilical cord)

Recommended Laboratory Evaluation

These studies are of proven benefit in determining the proximate etiologies in the patient presenting with jaundice. With this approach, the clinician can confidently assign probabilities to the major categories that most frequently account for jaundice.

- The first step is to determine the total bilirubin and the bilirubin fractions. This allows the clinician to determine whether the problem is due to an excess production or impaired conjugation (indirect/unconjugated predominant) versus impaired excretion (direct/conjugated predominant).
- ALP elevations out of proportion to the hepatic transaminases would favor extrahepatic or intrahepatic cholestasis.
- Hepatic transaminase elevations out of proportion to the alkaline phosphatase favor hepatocellular etiologies.
- The CBC can be extremely useful. The most important points include the interpretation of or for
  - Anemia (hemolysis, bleeding) (see Chapter 10, Hematologic Disorders)
  - Mean corpuscular volume (microcytosis suggests iron deficiency; round macrocytosis suggests chronic liver disease or ineffective erythropoiesis; GI malignancy)
  - Thrombocytopenia (sequestration in portal hypertension, sepsis, autoimmune disease, bone marrow suppression [alcohol])
  - Reticulocytosis (hemolysis) (see Chapter 10, Hematologic Disorders)
- Urinalysis provides information about bilirubinuria and urobilinogen. In reality, data from urinalysis add little incremental benefit to the decision-making process.
  - The presence of urobilinogen eliminates the possibility of complete biliary tract obstruction. That is, bile has entered the intestine, where it undergoes enterohepatic metabolism.
  - The presence of bilirubinuria, on the other hand, suggests that conjugation is taking place.
Coagulation studies are useful in two areas.
- If an invasive intervention is considered, coagulation studies can be used to assess bleeding risk.
- If the prothrombin time is prolonged and other causes of coagulopathy are unlikely, chronic liver disease or hepatocellular etiologies become increasingly likely.
- Serum amylase would be obtained in cases where extrahepatic obstruction is suspected on the basis of history and physical examination.

Diagnostic Imaging
- It is estimated that 25–40% of common bile duct obstructions are missed by both ultrasound and CT scanning. However, when intrahepatic cholestasis or hepatocellular etiologies are suspected, either of these noninvasive strategies is acceptable.
- Ultrasound: This is the least invasive and most inexpensive of the imaging procedures available to assess obstructive jaundice. Ultrasound determines the presence of obstructive jaundice by detecting dilated bile ducts.
  - The sensitivity is 55–93%, and the specificity is 73–96%.
  - False negatives are generally due to two factors:
    - Inability to visualize the biliary tree (often secondary to interposed bowel gas)
    - Absence of biliary dilation in the presence of obstruction
  - It may be preferable, given its lower cost and radiation exposure.
- CT scanning is slightly more sensitive (74–96%) and specific (90–94%) than ultrasound in detecting the presence of biliary obstruction.
  - A CT scan is more likely to show the site and cause of obstruction when compared with ultrasound.
  - CT scan also gives information in instances where staging a suspected neoplasm has clinical significance (see Cancer Head of the Pancreas).
  - In patients for whom mass lesions (i.e., malignancy, abscess) are suspected or where technical limitations make ultrasound difficulty to interpret, CT is preferred.
- Percutaneous transhepatic cholangiography (PTC): The technical success rate of this procedure is approximately 90–99%. Its use is limited by a major complication rate of 3–5% and has been largely supplanted by endoscopic retrograde cholangiopancreatography (ERCP). ERCP offers a lower complication rate than PTC and provides a greater number of therapeutic options (stone extraction, stent placement).
  - This test could reasonably be used in patients with a high likelihood of extrahepatic obstruction (e.g., those who have had recent biliary surgery, symptoms of cholangitis, palpable gallbladder, pain or fever, pancreatitis).
  - When palliation is the primary intent, ERCP is an appropriate initial procedure.
- Magnetic resonance cholangiopancreatography (MRCP) is a radiologic technique that produces images of the pancreaticobiliary tree, which are similar in appearance to those obtained by invasive methods. It appears to have diagnostic accuracy similar to that of ERCP.
DISEASES ASSOCIATED WITH JAUNDICE

CONJUGATED HYPERBILIRUBINEMIA/HEPATOCELLULAR JAUNDICE

CIRRHOSIS OF THE LIVER

Laboratory Findings

- **Bilirubin**: Serum levels are often increased; may be present for years. Fluctuations may reflect liver status due to insults to the liver (e.g., alcoholic debauches). Most bilirubin is of the unconjugated type unless cirrhosis is of the cholangiolic type. Higher and more stable levels occur in post-necrotic cirrhosis; lower and more fluctuating levels occur in Laennec cirrhosis. Terminal icterus may be constant and severe. Urine bilirubin is increased; urobilinogen is normal or increased.

- **AST**: Serum levels are increased (<300 U) in 65–75% of patients. Serum ALT is increased (<200 U) in 50% of patients. Transaminases vary widely and reflect activity or progression of the process (i.e., hepatic parenchymal cell necrosis).

- **ALP**: Serum levels are increased in 40–50% of patients.

- **Total protein**: Usually normal or decreased. Serum albumin parallels functional status of parenchymal cells and may be useful for following progress of liver disease, but it may be normal in the presence of considerable liver cell damage. Decreasing serum albumin may reflect development of ascites or hemorrhage. Serum globulin level is usually increased; it reflects inflammation and parallels the severity of the inflammation. Increased serum globulin (is usually gamma) may cause increased total protein, especially in chronic viral hepatitis and post-hepatitic cirrhosis.

- **Total cholesterol**: Normal or decreased. Progressive decrease in cholesterol, HDL, LDL with increasing severity. Decrease is more marked than in chronic active hepatitis. LDL may be useful for prognosis and selecting patients for transplantation. Decreased esters reflect more severe parenchymal cell damage.

- **Other core laboratory findings**: BUN is often decreased (<10 mg/dL); increased with GI hemorrhage. Serum uric acid is often increased. Electrolytes and acid–base balance are often abnormal and reflect various combinations of circumstances at the time, such as malnutrition, dehydration, hemorrhage, metabolic acidosis, respiratory alkalosis. In cirrhosis with ascites, the kidney retains increased sodium and excessive water, causing dilutional hyponatremia. Increased blood ammonia in liver coma and cirrhosis and with portacaval shunting of blood.
Jaundice

- **Hematology**: WBC is usually normal with active cirrhosis; increased (<50,000/μL) with massive necrosis, hemorrhage, and so on; decreased with hypersplenism. Anemia reflects increased plasma volume and some increased destruction of RBCs. If more severe, rule out hemorrhage in the GI tract, folic acid deficiency, and excessive hemolysis.

  *CSF findings*: CSF is normal except for increased glutamine levels, which reflect brain ammonia levels (due to conversion from ammonia). Glutamine >35 mg/dL is always associated with hepatic encephalopathy (normal = 20 mg/dL); correlates with depth of coma and is more sensitive than arterial ammonia.

**Considerations**

- See Tables 5-7 and 5-8.
- Laboratory findings due to complications or sequelae, often in combination.
- Abnormalities of coagulation mechanisms (see Chapter 10, Hematologic Disorders) such as prolonged PT (does not respond to parenteral vitamin K as frequently as in patients with obstructive jaundice). Prolonged bleeding time in 40% of cases due to decreased platelets and/or fibrinogen.
- Hepatic encephalopathy (neurologic and mental abnormalities in some patients with liver failure or portosystemic shunt). Diagnosis is clinical; characteristic laboratory findings are supportive but not specific.
- See Table 5-9.
- Markers that may indicate progression to cirrhosis include decreased albumin; increased globulins; AST/ALT ratio >1; increased bilirubin, mainly unconjugated; increased PT; and decreased platelet count.

**TABLE 5–7. Causes of Liver Disease with Associated Conditions**

<table>
<thead>
<tr>
<th>Laboratory Findings Due to Causative/Associated Diseases or Conditions</th>
<th>Frequency in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>60–70%</td>
</tr>
<tr>
<td>Biliary disease (e.g., primary biliary cirrhosis and sclerosing cholangitis)</td>
<td>5–10%</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>10–15%</td>
</tr>
<tr>
<td>Chronic viral hepatitis (HBV with or without HDV; HCV)</td>
<td>10%</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>5%</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Alpha1-antitrypsin deficiency</td>
<td>Rare</td>
</tr>
<tr>
<td>Autoimmune chronic active hepatitis</td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td></td>
</tr>
<tr>
<td>Glycogen storage diseases</td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
</tr>
<tr>
<td>Fructose intolerance</td>
<td></td>
</tr>
<tr>
<td>Tyrosinosis</td>
<td></td>
</tr>
<tr>
<td>Infections (e.g., congenital syphilis, schistosomiasis)</td>
<td></td>
</tr>
<tr>
<td>Gaucher disease</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
</tr>
<tr>
<td>Osler-Weber-Rendu disease</td>
<td></td>
</tr>
<tr>
<td>Venous outflow obstruction (e.g., Budd-Chiari syndrome, venoocclusive disease, congestive heart failure)</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 5–8. Comparison of Different Mechanisms of Jaundice

<table>
<thead>
<tr>
<th>Disease Example</th>
<th>Cholestasis</th>
<th>Hepatocellular</th>
<th>Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, ALT (U/mL)</td>
<td>6–20 mg/dL*</td>
<td>4–8 mg/dL</td>
<td>Usually &lt;4 mg/dL, often normal</td>
</tr>
<tr>
<td>Serum ALP</td>
<td>May be slightly I, &lt;200</td>
<td>Markedly I, often 500–1,000</td>
<td>May be slightly I, &lt;100</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>3–5 times N</td>
<td>1–2 times N</td>
<td>2–4 times N</td>
</tr>
<tr>
<td>Response to parenteral vitamin K</td>
<td>Yes</td>
<td>I in severe disease</td>
<td>N</td>
</tr>
</tbody>
</table>

N, normal; I, increase.
*Serum bilirubin >10 mg/dL is rarely seen with common duct stone and usually indicates carcinoma.

Increased serum ALP <3× normal in 15% of patients with extrahepatic biliary obstruction, especially if obstruction is incomplete or due to benign conditions. Occasionally, AST and LD are markedly increased in biliary obstruction or liver cancer.

### TABLE 5–9. Comparison of Three Main Types of Liver Disease Due to Drugs

<table>
<thead>
<tr>
<th>Example of drugs</th>
<th>Predominantly Cholestatic</th>
<th>Predominantly Hepatocellular</th>
<th>Mixed Biochemical Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic steroids,* estrogens*</td>
<td>Cinchophen</td>
<td>Isonicotinic acid hydrazide</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Cinchophen</td>
<td>Organic arsenicals, antithyroid drugs (e.g., methimazole), chlorpromazine, PAS, erythromycin, sulfonamide derivatives (including sulfonamides, phenothiazine tranquilizers, oral diuretics, antidiabetic drugs)</td>
<td>Monamine oxidase inhibitors (particularly iproniazid)</td>
<td>Phenotoin</td>
</tr>
<tr>
<td>Cinchophen</td>
<td>May be ≥30 mg/dL</td>
<td>More markedly increased</td>
<td>PAS and other antituberculosis agents</td>
</tr>
<tr>
<td>Cinchophen</td>
<td>Mild to moderate increase</td>
<td>Less markedly increased</td>
<td></td>
</tr>
<tr>
<td>Cinchophen</td>
<td>More markedly increased; may remain increased for years after jaundice has disappeared</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ALP, AST, and ALT are not increased as much compared with other drugs.
INFECTIONIOUS DISEASE: VIRAL HEPATITIS

Definition

Five hepatitis viruses cause the majority of clinically important viral infections of the liver: HAV, HBV, HCV, HDV, and HEV. They are all RNA viruses except for HBV, which is a DNA virus. All of these viruses can cause acute hepatitis; only HBV, HCV, and HDV are able to cause chronic hepatitis infections in immunologically normal patients. Coinfection with two hepatitis viruses or hepatitis virus infection in patients with preexisting liver disease is frequently associated with greater disease severity (Table 5-10). Other viruses or infectious agents may cause liver infection associated with systemic or localized infections. Agents include herpes viruses—like HSV, CMV, and EBV—rubella, M. tuberculosis, ameba, and leishmania. See the discussions for these agents in Chapter 11. Infectious Diseases. A variety of hepatotoxins, autoimmune diseases, and other diseases may also cause hepatitis that is clinically similar to diseases caused by the hepatitis viruses.

Viral hepatitis may be suspected in patients with nonspecific symptoms (see Prodromal Phase) or specific symptoms, like jaundice or RUQ pain (see Acute Phase). Viral hepatitis may also be considered in asymptomatic patients in whom liver function abnormality, like hyperbilirubinemia or elevated levels of AST or ALT, is detected by screening tests. For these patients, evaluation with an acute hepatitis panel is recommended; the different viral agents cannot be reliably distinguished by clinical signs and symptoms. The acute hepatitis panel includes hepatitis A IgM antibody, hepatitis B core IgM antibody, hepatitis B surface antigen, and hepatitis C antibody. Further testing, as described below, is recommended on the basis of results of the tests in the acute hepatitis panel.

Laboratory Overview

- The results for acute hepatitis panel, and additional virus-specific tests, are discussed with the agents below.
- Because the signs and symptoms of infection with other infectious agents and hepatotoxins may be indistinguishable from those caused by the hepatitis viruses, specific testing to rule out other causes of liver damage is recommended, based on clinical history, epidemiology, laboratory, and other relevant information.
- In addition to testing for specific viral markers of infection, the patient’s hematologic, coagulation, and hepatic function should be evaluated over the course of illness.
- The earliest laboratory signs of acute viral hepatitis include elevations in ALT and AST, which typically precede elevation of bilirubin levels. In acute illness, the degree of ALT elevation typically exceeds AST elevation. Peak aminotransferase levels >1,000 U/L are common. The level of aminotransferase elevation does not reliably predict the severity or prognosis of disease. Total bilirubin may increase to 5–20 mg/dL at peak. ALP is normal or mildly elevated in most cases.
- CBC may show mild neutropenia with a relative lymphocytosis, often with atypical lymphocytes. Serum globulins are normal or mildly elevated. In severe liver disease, synthesis of albumin and coagulation factors may be compromised, resulting in increased PT.
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>ssRNA</td>
<td>dsDNA</td>
<td>ssRNA</td>
<td>ssRNA</td>
</tr>
<tr>
<td>Classification</td>
<td>Picornaviridae</td>
<td>Hepadnaviridae</td>
<td>Flaviviridae</td>
<td>Unclassified</td>
</tr>
<tr>
<td>New cases in the United States, 2007 (<a href="http://www.cdc.gov">www.cdc.gov</a>)</td>
<td>25,000</td>
<td>43,000</td>
<td>17,000</td>
<td>Uncommon. Always associated with HBV; 4% of acute HBV cases have HDV coinfection</td>
</tr>
<tr>
<td>Incubation period (days)</td>
<td>15–60</td>
<td>45–160</td>
<td>14–180</td>
<td>42–180</td>
</tr>
<tr>
<td>Transmission Enteric</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sexual</td>
<td>No</td>
<td>Yes</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Perinatal</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Rare</td>
<td>1 case per 137,000 units transfused</td>
<td>1 case per 2 million units transfused</td>
<td>Virtually eliminated by HBV screening</td>
</tr>
<tr>
<td>Posttransfusion incidence (%)</td>
<td>None</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Viremia</td>
<td>Transient</td>
<td>Abrupt</td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Fecal excretion of virus</td>
<td>Transient</td>
<td>Insidious</td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Onset Course</td>
<td>Mild, often subclinical, self-limited</td>
<td>Acute* and chronic infection</td>
<td>Acute infection typically mild; high incidence of chronic infection &lt;75%</td>
<td>Increases severity of underlying HBV infection</td>
</tr>
<tr>
<td>Asymptomatic Most children</td>
<td>Most children; 50% adults</td>
<td>Varies</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Jaundice Child: 10% Adult: 70–80%</td>
<td>15–40%*</td>
<td>10–25%</td>
<td>Varies</td>
<td>25–50%</td>
</tr>
<tr>
<td>Chronic hepatitis after acute infection (%)</td>
<td>0%</td>
<td>1–10% (90% of neonates)</td>
<td>70–85%</td>
<td>Common; high in superinfection</td>
</tr>
<tr>
<td>Hepatocellular carcinoma association</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>1–2%</td>
<td>0.1–1%</td>
<td>Very rare</td>
<td>5%</td>
</tr>
</tbody>
</table>

*≤20% have serum sickness-like prodroma.
†Resembles hepatitis A. Case fatality 1–2% except ≤20% in pregnancy; usually milder infection and biochemical abnormalities than HBV or HAV infection.
‡A nonicteric patient is more likely to progress to chronic hepatitis. One percent of icteric cases become fulminant (<8 weeks) and 90% die within 2–4 weeks; associated with encephalopathy; renal, electrolyte, acid–base imbalances; hypoglycemia; coagulation derangements.
Disease Manifestations

Viral hepatitis infections may show many and varied clinical features, but most patients with acute viral hepatitis are asymptomatic or experience minimal constitutional symptoms. On the other hand, any of the hepatitis viruses may cause fulminant disease with extensive liver damage and hepatic failure. One cannot distinguish different types of viral hepatitis by clinical features or routine chemistries; specific serologic tests are needed. Hepatitis virus infections demonstrate the following clinical phases.

Prodromal Phase

- After a variable, virus-specific incubation period, patients may develop non-specific symptoms, including low-grade fever, headache, fatigue and malaise, and arthralgias. Anorexia, nausea, and vomiting are common and may be associated with abdominal pain (epigastric or right upper quadrant).
- Prodromal symptoms typically last 1–2 weeks before the onset of signs and symptoms of acute liver disease. Dark urine may precede the onset of jaundice. Acholic stools may be seen in HAV and HEV infections.
  - During the prodrome:
    - Specific serologic markers appear in serum (see Figure 5-7).
    - ESR is normal.
    - Leukopenia (lymphopenia and neutropenia) is noted with onset of fever, followed by relative lymphocytosis and monocytosis. Plasma cells and <10% atypical lymphocytes may be seen.
    - Urinary urobilinogen and total serum bilirubin increase just before the onset of jaundice.
    - Serum AST and ALT levels increase during the prodromal phase and show very high peaks (>500 U) during the acute phase.

Acute Hepatitis Phase

- Signs and symptoms of the prodromal phase usually abate with the onset of jaundice and the acute phase of hepatitis.
- Acute hepatitis may be icteric or anicteric. The majority of cases of acute HCV infections and HAV and HBV infections in children are anicteric.
  - Asymptomatic: Many patients infected with hepatitis viruses may remain clinically asymptomatic or show only mild or transient symptoms. The diagnosis of viral hepatitis may be suspected by finding abnormal LFT or other tests collected for other reasons.
  - Symptomatic, icteric:
    - Patients develop jaundice; examination of the sclerae may provide the most sensitive site for detection. LFT and other laboratory testing demonstrates liver cell damage and the extent of hepatic function compromise. The levels of conjugated and unconjugated bilirubin are typically comparable. In acute hepatitis, there is usually marked elevation of aminotransferases, with ALT > AST; the degree of elevation does not correlate with the extent of hepatic cellular damage. LD may be mildly elevated. Serum AST and ALT fall rapidly in the several days after jaundice appears and become normal 2–5 weeks later with resolution of infection.
**Figure 5–7** Hepatitis serologic profiles. **A,** Antibody response to hepatitis A. **B,** Hepatitis B core window identification. **C,** **D,** Hepatitis B chronic carrier profiles: no seroconversion (**C**); late seroconversion (**D**). (Reproduced with permission of Hepatitis Information Center, Abbott Laboratories, Abbott Park, IL.)
Other laboratory tests may be abnormal, depending on severity of the disease. ALP and albumin levels are usually normal. Serum protein electrophoresis may show mild elevation of the \( \gamma \)-globulin fraction. Serum cholesterol-to-ester ratio is usually depressed early; total serum cholesterol is decreased only in severe disease. Serum phospholipids are increased in mild but decreased in severe hepatitis. Urine urobilinogen is increased in the early icteric period; at peak of the disease, it disappears for days or weeks; urobilinogen simultaneously disappears from stool.

Severe hepatocellular damage is predicted by prolonged PT, markedly elevated bilirubin, hypoglycemia, or decreased serum albumin concentration. A prolonged and complicated course is more common in the elderly, in patients with significant underlying medical (especially hepatic) conditions, and in patients presenting with severe symptoms, like peripheral edema or encephalopathy during the acute phase.

Symptomatic, anicteric: Laboratory abnormalities are usually mild compared to patients with icteric hepatitis; there is slight or no increase in serum bilirubin.

Nonspecific laboratory abnormalities may be associated with the acute phase of viral hepatitis. ESR is increased but decreases during convalescence. Serum iron is often increased. Urine examination may show cylinduria, and albuminuria occurs occasionally. The renal concentrating ability is sometimes decreased.

**Acute Fulminant Hepatitis/Acute Liver Failure (ALF)**

Acute fulminant hepatitis may be recognized by triad of prolonged PT, increased PMNs, and nonpalpable liver. A prolonged PT, especially >20 seconds, indicates the likely development of acute hepatic insufficiency; therefore, the PT should be performed with the initial patient evaluation.

Acute fulminant hepatitis is associated with failure of liver function. Patients present with hepatic encephalopathy and hepatic synthetic dysfunction. The manifestations of encephalopathy may range from drowsiness and confusion to stupor and coma. Synthetic dysfunction is usually manifested by coagulopathy. Multiorgan failure may ensue. Ascites is typical. Bacterial superinfection, especially with streptococci and \( S. aureus \), may occur.

ALF is more common with coinfection with two hepatitis viruses, like HBV and HDV, or with hepatitis infections in patients with preexisting liver disease. HBV infection is the most common cause of ALF (approximately 1–3% of adults). HAV is associated with ALF only in adults and occurs in 1.8% of patients >60 years of age. ALF after HEV is rare, except for pregnant women, where up to 20% of patients may develop ALF. ALF is an extremely rare complication of acute HCV infection. ALF may occur as a complication of systemic HSV infection. There is a high mortality associated with ALF, but if the patient survives, complete biochemical and histologic recovery are the rule.

In addition to clinical signs of hepatic failure, significant metabolic derangement and laboratory abnormalities are common:

- As the patient’s condition deteriorates, titers of HBsAg and HBeAg often fall and disappear.
- Serum bilirubin progressively increases and may reach very high levels.
Increased serum AST and ALT levels are seen, but levels may fall abruptly terminally; serum ALP and GGT may be increased.

- Serum cholesterol and cholesterol esters are markedly decreased.
- Albumin and total protein levels are decreased.
- Increased ammonia level in blood.
- Hematologic abnormalities.
- Evidence of DIC is common.
  - Decreased factors II, V, VII, IX, and X cause prolonged PT and aPTT.
  - Decreased antithrombin III.
  - Platelet count <100,000 in two thirds of patients.
  - Hemorrhage, especially in the GI tract.

- Metabolic markers are typically abnormal, including
  - Hypokalemia (early), with metabolic alkalosis
  - Respiratory alkalosis
  - Lactic acidosis
  - Hyponatremia, hypophosphatemia
  - Hypoglycemia in approximately 5% of patients
- Renal function tests may be abnormal. Hepatorenal syndrome may develop.

Postacute Hepatitis Phase

In uncomplicated viral hepatitis, symptoms of the acute phase should resolve within 1 to 6 months, depending on the virus, with correction of the biochemical abnormalities in the subsequent months. Persistence of clinical or biochemical abnormalities suggests progression to chronic hepatitis in hepatitis B, C, or D infections.

- Resolution: During recovery, systemic symptoms abate. Liver tenderness and biochemical abnormalities may persist. Complete clinical and biochemical recovery occurs 1–2 months after HAV and HEV infections and 3–6 months after uncomplicated HBV. HAV and HEV infections are not associated with progression to chronic infection. HBV, HCV, and HDV may progress to chronic infection. Recovery from acute HBV infection is more likely after clinically apparent (icteric) versus subclinical infection

- Chronic infection
  - The persistence of clinical and laboratory abnormalities for >6 months after acute hepatitis is characteristic of chronic infection. Chronic liver infection may develop with HCV, HBV, or HBV plus HDV infections. The clinical presentation varies from asymptomatic disease through progression to end-stage liver failure. Signs and symptoms may be fairly constant or marked by flares in severity, increasing the progression of liver injury. Cirrhosis may develop. Liver damage is influenced by virus factors, as discussed later, and host factors. Host factors include coexisting diseases, especially liver disease, the host immune response, and alcohol consumption or exposure to other hepatotoxins.
  - The degree of laboratory abnormalities may not accurately reflect the degree of histologic changes. Aminotransferase elevation may be variable. In mild disease, ALT elevation is typically greater than the degree of AST elevation. Marked elevation of bilirubin levels is associated with
advanced liver damage and cirrhosis. In advanced cirrhosis, the pattern of aminotransferase elevation is usually reversed, with the degree of AST elevation exceeding that of ALT elevation. The synthetic function of the liver decreases with advanced chronic disease and cirrhosis, with resulting clinical manifestations of coagulopathy, metabolic derangements, and so on.

- **Hepatocellular carcinoma:** Hepatocellular carcinoma (HCC) may occur as a complication of chronic viral hepatitis. In HBV infection, HCC may occur in patients with or without cirrhosis. Risk factors for the development of HCC in HBV-infected patients include infection early in life, coexisting immunocompromising diseases, and HDV coinfection. HCC may also complicate HCV infection but occurs only in patients with cirrhosis.

### HEPATITIS VIRUSES

Most cases of acute viral hepatitis in the United States are caused by HAV, HBV, and HCV. In a CDC surveillance survey in 2012, there were an estimated 69,000 new cases of acute hepatitis caused by these agents (50% HBV; 25% HAV; 25% HCV).

- The acute hepatitis panel (HBsAg, total anti-HBc, IgM anti-HBc, IgM anti-HAV, and total anti-HVC) is recommended for evaluation of patients with suspected acute infectious hepatitis. Repeat testing to confirm negative results may be considered in patients at high risk for viral hepatitis. In addition, testing for rheumatoid factor may be considered if false-positive antibody tests are suspected. Further testing is determined by results of the initial screening tests. Repeat screening after negative results should be considered for patients with a high clinical suspicion or prior risk in order to rule out false-negative results due to a window period. Window periods represent intervals prior to immune response or during a transition from phases of antigen predominance to antibody predominance (e.g., HBsAg positive → anti-HBs positive). There are no FDA-approved diagnostic tests for HDV or HEV; diagnostic testing, when indicated, may be pursued through the CDC/Public Health Laboratory or Reference Laboratories. Specific testing for HDV is not necessary if HBV infection has been ruled out. Testing for HEV is usually unneeded unless a patient has recently traveled to an area where HEV infection is endemic. Specific hepatitis viruses and diagnostic testing are presented in subsequent text of this chapter.

- **Hepatitis Viruses Transmitted by Enteric Routes (HAV and HEV)**
  - **HAV**
    - HAV infections, caused by a nonenveloped, single-stranded RNA picornavirus, occur worldwide.
    - Only approximately 25% of patients with acute HAV infection report risk factors in the 2–6 weeks prior to onset of symptoms. Risk factors include close contact with a patient with documented HAV infection or person at increased risk for HAV infection, employment or attendance at a nursery, day care center or preschool, exposure to a foodborne or waterborne outbreak, or high-risk sexual practices.
Overall, 68% of patients develop jaundice. Childhood infections are most commonly anicteric (>90%), whereas infections in adults are often severe, with icteric infection occurring in approximately 80% of patients. Most symptomatic infections resolve in 1–2 months. Rare cholestatic variants may remain symptomatic for months but eventually resolve completely. The fatality rate for HAV infection is <1% (0.02/100,000 population), most commonly in patients >75 years of age.

The prodromal period after exposure is approximately 4 weeks (range 2 to 7 weeks). Fecal excretion of virus begins late in the prodromal phase. IgM appears in the late prodrome; IgM may remain detectable for 6–12 months. After 3 months, IgM levels usually begin to drop, whereas rising IgG levels are detected. IgG levels persist indefinitely. Acute liver failure is uncommon in HAV infection (0.1%). Chronic infection does not occur in HAV infections.

**HAV diagnosis:**

- **Anti-HAV-IgM positive: Acute infection**
  - Anti-HAV-IgM appears at the same time as symptoms in >99% of cases and peaks within the 1st month. IgM becomes undetectable within 12 (usually 6) months.
  - The presence of anti-HAV-IgM confirms diagnosis of recent acute infection. Serial testing is usually not needed for diagnosis.
  - Serum bilirubin is usually 5–10 times the normal level. Jaundice lasts a few days to 12 weeks. Patients are usually not infectious after the onset of jaundice.
  - Serum AST and ALT are increased for 1–3 weeks.
  - Relative lymphocytosis is frequent.

- **Anti-HAV-IgG positive: Remote infection/immune**
  - Anti-HAV-IgG is usually detectable for life after resolution of acute HAV infection and indicates immunity to HAV infection.

- **Anti-HAV-total may be predominantly IgG or IgM, depending on infection status.** A negative anti-HAV-total effectively excludes acute HAV but does not distinguish recent from past infection, for which anti-HAV-IgM test is needed. Tests for anti-HAV-total (minimum detection approximately 100 mU/mL) may be insensitive for detection of protective antibody after HAV vaccine (minimum protective antibody concentration is <10 mU/mL).

- **Nonspecific elevation of IgM is common in acute HAV infection.**

**HEV**

- HEV infections are caused by an unenveloped, single-stranded RNA virus of the Caliciviridae family and are clinically similar to HAV infections.

- HEV infection is most common in developing countries with inadequate sanitation and limited access to clean water supplies, including countries in Asia, Africa, and Central America; symptomatic infection is rare in the United States and usually occurs in persons with recent travel to an endemic region.

- HEV infections are transmitted by the fecal–oral route. The symptoms of acute HEV infection are similar to those of acute hepatitis caused by other viruses; specific testing is needed to establish HEV infection.
Asymptomatic infection occurs in approximately 60–90% of patients during outbreaks. Symptomatic infections are most common in young adults (20–40 years); acute liver failure may occur in 1–2% of patients overall but in 10–20% of pregnant women with HEV infection. A cholestatic presentation (duration of infection >3 months), with prolonged jaundice, fatigue, and pruritus, occurs more frequently in HEV infections compared to HAV, but infection eventually resolves completely.

**HEV diagnosis**

- Anti-HEV-IgM positive: Acute infection.
- Anti-HEV-IgG positive: Remote infection.
- Recent travel to an endemic area should be documented (e.g., Mexico, India, Africa, or Russia).

**Hepatitis Viruses Transmitted by Blood-Borne Routes (HBV, HCV, and HDV)**

HBV, HCV, and HDV are most commonly transmitted by exposure to blood, semen, or infected body fluids. Infection may also be transmitted by perinatal/vertical (especially in HBV in areas with high endemic rate) and sexual routes (now the most common exposure for HBV infection). Transmission by transfusion or transplantation has fallen as a result of screening.

**HBV**

- HBV is a double-stranded DNA Hepadnavirus. HBV infection occurs worldwide.
- In a 2010 CDC survey, only 36% of patients with acute HBV infection reported any high-risk behavior or known exposure in the 6 months prior to illness. Specific high-risk behaviors or exposure risks include employment in health care settings involving contact with blood or potential needle-stick injury, dialysis or kidney transplant, transfusion of blood products, recent surgery, injection drug use, high-risk sexual practices, or close contact with any person at high risk for HBV infection. The case fatality rate for acute HBV infection is approximately 1.5% (1.1 case/100,000 population). It is highest in patients 30–39 years of age.
- Symptoms and disease: Symptomatic disease occurs in a minority of patients with acute HBV infection (<1 year old: <1%; 1–5 years old: 5–15%; >5 years old: 30–50%). Symptoms and evidence of active infection occurs approximately 2–3 months (range 2 to 5 months) after exposure. HBsAg, anti-HBc IgM, and HBeAg appear late in the prodromal phase. In patients who recover without progression to chronic infection, the titer of these markers, as well as the ALT, begin to fall during the phase of active disease, usually returning to normal within 4 to 6 months. Most patients with acute HBV infection recover completely. The risk of chronic infection depends on the age of acquisition of HBV infection (>90% of infants; 25–50% of children aged 1 to 5 years; 6–10% of older children and adults).

**HBV Diagnosis and Laboratory Testing**
A number of laboratory tests are used to different stages of HBV infection:

- **Hepatitis B surface antigen (HBsAg)** is the earliest indicator of active HBV infection. HBsAg is usually detectable within 27–41 days (as early as 14 days) of the onset of infection. HBsAg appears 7–26 days before transaminase abnormalities and peaks as ALT rises. HBsAg detection persists during the acute illness. HBsAg usually disappears 12–20 weeks after onset of symptoms in uncomplicated HBV infection.

- Detection of HBsAg for >6 months defines chronic infection or a chronic carrier state. Hepatitis B vaccination does not cause a positive HBsAg. HBsAg titers are not of clinical value and may never be detected in some patients; diagnosis of acute HBV infection is based on detection of HBe-IgM.

- **Anti-HBs** is the only antibody produced in response to vaccine. Its presence indicates immunity. Antibody develops in approximately 95% of healthy adults after a three-dose immunization series. Seroreactivity may wane in vaccinated individuals, but immunity to infection is typically preserved. Escape mutants, which lack the “a” determinant of the vaccine, may cause infection in vaccinated patients who demonstrate anti-HBs.

- Antibodies to hepatitis B core antigens (anti-HBc) are the first antibodies to appear after HBV infection. Total and IgM antibodies typically appear 4–10 weeks after appearance of HBsAg. Anti-HBc-total remains detectable for years or for lifetime. In chronic HBV infection, total anti-HBc and HBsAg are always present, and anti-HBs is absent.

- **Anti-HBc-IgM** is the earliest specific antibody to develop in response to HBV infection. It is found in high titer for a short time during the acute disease stage and is the sole marker of HBV infection during the window between HBsAg and anti-HBs detection. Anti-HBe-IgM declines to low levels during recovery. Because this is the only test unique to recent infection, it may be used to differentiate acute from chronic HBV. However, because some patients with chronic Hepatitis B infection become positive for anti-HBc-IgM during flares, it is not an absolutely reliable marker of acute illness. Before anti-HBc-IgM disappears, anti-HBc-IgG appears and lasts indefinitely.

- **Hepatitis B e-antigen (HBeAg)** indicates virus replication and a highly infectious state. HBeAg appears within 1 week after HBsAg. HBeAg disappears prior to the disappearance of HBsAg during resolution of acute infection. HBeAg is detected only when HBsAg and HBV DNA are detectable in the circulation. HBeAg occurs early in disease, before biochemical changes, and disappears after the serum ALT peaks. Levels are usually detectable for 3–6 weeks in uncomplicated HBV infection. It is a marker of active HBV replication in the liver. HBeAg at the time of delivery is an accurate predictor of risk (approximately 90%) of vertical transmission to neonates.
HBeAg may be used to determine resolution of HBV infection. Persistence >20 weeks suggests progression to chronic carrier state and possible chronic hepatitis. Antibody to HBe (anti-HBe) appears after HBeAg disappears and remains detectable for years. Detection of anti-HBe is associated with decreasing infectivity and suggests a good prognosis for resolution of acute infection. A positive reaction for anti-HBe and anti-HBc, in the absence of HBsAg and anti-HBs, confirms recent acute infection (2–16 weeks).

Detection of HBV DNA by PCR indicates active infection. It is the most sensitive and specific assay for early diagnosis of HBV infection and may be detected when all other markers are negative (e.g., in immunocompromised patients). Detection of HBV DNA indicates active viral replication, even if HBeAg is not detectable. HBV DNA viral load may be used to assess disease status and prognosis or to monitor the response to therapy. A level of 100,000 copies per mL has been proposed for initiation of therapy in HBeAg-positive patients. DNA levels decrease in patients who respond to therapy. An increased risk for the development of HCC and cirrhosis is seen in chronically infected patients with persistently elevated HBV DNA levels (>10⁵ copies/mL).

HBV genotype analysis may be useful for management of patients with chronic HBV infection who are treated with antiviral agents. The replication of the HBV genome is prone to misreading, resulting in a pool of “quasispecies” in the patient’s circulating pool of HBV. A quasispecies resistant to the antiviral agent may become the predominant circulating form of virus in the presence of antiviral selection, resulting in failure of therapy. Genotype analysis may identify quasispecies with specific mutations of the HBV polymerase gene that confer resistance to the antiviral agents used to treat chronic HBV. If identified early, therapy may be changed before hepatitis reactivation occurs.

Correlation of HBV Serologic Test Results and Disease Status

Typical patterns of HBV serologic tests for different disease status are given below. Atypical patterns may be due to testing during transitions between disease phases but may also be caused by false-positive or false-negative test results. Unexpected test results should be confirmed and, if confirmed, repeated after several months to see if the pattern resolves. Additional testing, like genetic analysis, may be performed, if relevant, for resolution.

- No HBV infection: Negative reactions for HBsAg and anti-HBc IgM rule out acute HBV infection.

- HBV immune status: Anti-HBs may be added to assess a patient’s immune status. Patients with immunity due to natural infection show positive reactions for anti-HBs and anti-HBc and a negative reaction for HBsAg. Patients with immunity due to hepatitis B vaccination are positive for anti-HBs and negative for HBsAg and anti-HBc.

- Acute HBV infection: HBsAg and anti-HBc antibodies (total and IgM) are positive, and anti-HBs is negative. HBV DNA is detectable.

Acute HBV infection usually lasts for 1–6 months with mild or no symptoms. Aminotransferases are increased >10-fold. HBsAg gradually arises to high titers during the active phase; HBeAg also appears. Serum bilirubin is
Digestive Diseases usually normal or only slightly increased in acute disease. Immune complex–mediated diseases may be seen in 10–20% of patients (e.g., serum sickness, arthritis, dermatitis, glomerulonephritis, vasculitis). Immune complex–mediated glomerulonephritis or nephrotic syndrome may progress to chronic renal failure. Acute HBV usually resolves in 3–6 months in uncomplicated infection. In patients who recover from acute HBV infection, titers of HBsAg fall to undetectable levels, followed by the emergence of anti-HBs after 4 to 8 weeks. During this “window,” anti-HBc total and IgM antibodies are detectable; HBV DNA is also usually detectable.

▼ Acute HBV infection with recovery: After complete resolution of HBV infection, patient testing shows HBsAg negative, anti-HBs positive, HBeAg negative, anti-HBe positive, anti-HBc-IgG positive, and HBV DNA falls to undetectable levels. Full recovery is more common after clinically apparent acute HBV infection. Acute liver failure is uncommon, occurring in 0.1–1% of patients.

▼ Chronic HBV infection: Chronic infection is uncommon, occurring in 1–10% of patients overall, but approximately 90% perinatal infections. The typical pattern of HBV markers shows that HBsAg and total anti-HBc are positive, while anti-HBc-IgM and anti-HBs are negative.

▼ Laboratory Evaluations for Patients with Chronic HBV Infection:
- Tests for HBV active replication (e.g., HBeAg/anti-HBe, HBV viral load) are used for initial assessment and ongoing monitoring of patients.
- Laboratory tests to assess impact of infection (e.g., CBC, PT, hepatic function panel) are used for initial assessment and ongoing monitoring of patients.
- Laboratory tests to rule out coinfection with other viruses (e.g., HCV, HDV, HIV).
- Consider liver biopsy to stage liver disease histologically.
- Consider screening for hepatocellular carcinoma (e.g., AFP, ultrasound).

Continued transaminase elevation for >6 months is seen in chronic hepatitis. Chronic HBV infection may last for only 1 year or for several decades with mild or severe symptoms. Most patients resolve spontaneously, but some develop progressive liver failure and cirrhosis. AST and ALT fall to 2–10 times normal range. Detection of HBeAg indicates continuing active viral replication, but patients with active HBV replication, as demonstrated by HBV DNA, may be HBeAg negative. A chronic carrier state with nonreplicating virus may also develop. Patients are usually asymptomatic. AST and ALT fall to normal or <2 times normal levels. Anti-HBe is detectable; HBeAg is negative. HBsAg is present but at decreasing titers. HBV viral load may be negative or low positive. Total anti-HBc is usually present in high titer (>1:512). HBV carrier patients may experience flares of active, symptomatic hepatitis accompanied by a change in their serologic markers: HBsAg positive, anti-HBc-IgM positive, anti-HBs negative, anti-HBe negative, and HBeAg may be detected. The development of anti-HBs marks the end of the carrier stage. Chronic replicative infection may be caused by hepatitis B viruses with mutations that affect normal HBeAg expression, resulting in an atypical pattern of HBV markers. Patients infected with precore or core promoter mutants tend to have more severe disease, more flares, and more rapid progression to cirrhosis. Patients
are HBsAg positive, anti-HBs negative, anti-HBc-IgG positive, anti-HBc-IgM negative, HBeAg negative, and anti-HBe positive. Effective treatment of chronic HBV hepatitis causes ALT, HBeAg, and HBV DNA to become normal.

■ HDV

▼ HDV, delta agent, is a small defective single-stranded RNA virus enveloped by hepatitis B surface antigens. HDV requires simultaneous HBV infection but relies on HBV only for envelope protein (HBs). The epidemiology of HDV infection is similar to HBV except that sexual and perinatal infection is less efficient. Although uncommon in the United States, HDV is distributed worldwide, with perhaps 5% of HBV-infected patients coinfected with HDV.

▼ HDV infection may be transmitted simultaneously with HBV infection. In these patients, clinical manifestations may be similar to patients with HBV infection alone, but coinfection is often more severe in terms of clinical signs and symptoms. In HBV/HDV coinfection, the risk for progression to chronic hepatitis is no greater than is seen in HBV infection alone.

▼ HDV may also be transmitted to patients with preexisting chronic HBV infection. Such HDV superinfections usually lead to clinical deterioration, increased chronicity, and may lead to ALF.

▼ HDV infection may be suspected on the basis of exposure in regions of high endemicity, history of injection drug abuse, unusually severe HBV disease, or deterioration in chronic HBV infections.

● Antigen detection is the most reliable laboratory test for diagnosis, but levels may be variable. Serum HDVAg and HDV-RNA appear during the incubation period after the appearance of HBsAg and before a rise in ALT, which often shows a biphasic elevation. HBsAg and HDVAg are transient; HDVAg resolves with clearance of HBsAg. Total anti-HDV supports a diagnosis; anti-HDV-IgM is not reliable for distinguishing between acute and chronic infection but is detectable more often than anti-HDV-IgG. In HBV/HDV coinfections, detectable anti-HDV elevations are not clearly predictable, may be of low titer, and often disappear with resolution of acute infection. In superinfection, however, high anti-HDV levels are seen, and these last indefinitely. Determination of the class of anti-HBc, IgG versus IgM, can help distinguish between HDV coinfection and superinfection. Chronic HDV infection is more severe and has higher mortality than other types of viral hepatitis. The risk of HCC is threefold greater in patients with chronic HBV infection in whom anti-HDV is detected compared to patients who are negative.

■ HDV diagnosis (see Tables 5-11 and 5-12)

Commercial assays for detection of HDV antigen, antibody, and RNA are commercially available but not FDA approved in the United States.

▼ Anti-HDV positive: HDV infection

● Anti-HDV positive, HBsAg positive, anti-HBc-IgM positive: HBV/HDV coinfection. HDAg, anti-HDV-IgM, and HDV RNA may be detected. Low titer anti-HDV-total appears late.
TABLE 5–1 2. Serologic Diagnosis of Hepatitis B Virus (HBV) and Hepatitis D Virus (HDV)

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg,+</td>
<td>Acute HBV and acute HDV*</td>
</tr>
<tr>
<td>HBcAb-IgM,+</td>
<td>Chronic HBV and chronic HDV</td>
</tr>
<tr>
<td>Anti-HDV-IgM*</td>
<td>Transient low titer</td>
</tr>
<tr>
<td>HDV-RNA (HDAg)</td>
<td>Transient low titer</td>
</tr>
<tr>
<td>Liver HDAg,+</td>
<td>Usually persistent</td>
</tr>
</tbody>
</table>

- Anti-HDV-total positive, anti-HBc-IgM negative, HBsAg positive, anti-HBc-IgG positive, HDV RNA positive, total, and IgM anti-HDV rapidly increase: Acute HDV superinfection. HDAg may be missed. HDAg can be demonstrated on liver biopsy by immunohistochemical staining. HDAg is not detected in chronic HDV infection.

HCV

- HCV is an enveloped, single-stranded RNA Flavivirus. HCV infections occur worldwide but with geographic variation in prevalence of infection.

TABLE 5–11. Comparison of Types of Hepatitis D Virus (HDV) Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Coinfection</th>
<th>Superinfection</th>
<th>Chronic HDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV infection</td>
<td>Acute</td>
<td>Chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td>HDV infection</td>
<td>Acute</td>
<td>Acute to chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Chronicity rate</td>
<td>&lt;5%</td>
<td>&gt;75%</td>
<td>Cirrhosis in &gt;70%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
</tr>
<tr>
<td>HBcAb-IgM</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HDV-total</td>
<td>Negative or low titer</td>
</tr>
<tr>
<td>Anti-HDV-IgM*</td>
<td>Transient+</td>
</tr>
<tr>
<td>HDV-RNA (HDAg)</td>
<td>Transient+</td>
</tr>
<tr>
<td>Liver HDAg</td>
<td>Transient+</td>
</tr>
</tbody>
</table>

+, Positive.

*Decrease in anti-HDV-IgM usually predicts resolution of acute HDV. Persistent anti-HDV-IgM typically predicts progression to chronic HDV infection. High titer correlates with active liver inflammation.

HCV

- HBV does not resolve, HDV can continue to replicate indefinitely.

- Anti-HDV-total positive, anti-HBc-IgM negative, HBsAg positive, anti-HBc-IgG positive, HDV RNA positive, total, and IgM anti-HDV rapidly increase: Acute HDV superinfection. HDAg may be missed. HDAg can be demonstrated on liver biopsy by immunohistochemical staining. HDAg is not detected in chronic HDV infection.

- HCV is an enveloped, single-stranded RNA Flavivirus. HCV infections occur worldwide but with geographic variation in prevalence of infection.
Transmission is almost exclusively by percutaneous exposure. Transmission by sexual and perinatal exposure is rare.

\[\text{In 2011, a CDC study showed the rate of newly diagnosed HCV infection of 85 per 100,000 population. Among newly diagnosed patients, only 50% had testing for active infection (i.e., HCV RNA detection). The highest prevalence and percentage of deaths were seen in patients born during the period 1945–1965.}\]

\[\text{In 2012, the CDC published revised recommendations for HCV testing, as described below. The new recommendations were issued (1) to reflect changes in diagnostic tests, like improved immunoassays and unavailability of RIBA HCV confirmatory testing; (2) to expand one-time screening of everyone born between 1945 and 1965, regardless of specific risk factors; (3) to include initial evaluation for active infection (HCV viremia detection) in all patients with positive HCV serology to facilitate optimal treatment. The recommendations stress the impact of new direct-acting antivirals for improved outcome in patients with chronic HCV infection and likely decreased transmission of infection.}\]

\[\text{Specific risk factors are well described for HCV acquisition, but 38% of patients report no known risk for exposure. Significant risk factors for HCV infection include the following:}\]

- Any person born from 1945 through 1965
- HIV infection
- History of IV drug abuse
- History of blood product transfusion or organ transplantation before July 1992 or clotting factor concentrate before 1987
- History of long-term hemodialysis
- Known exposure to HCV, like health care workers exposed to HCV-positive blood by needle-stick injury or the recipient of blood or organ transplant from a patient subsequently shown to be HCV positive
- Children born to HCV-positive mothers
- Persistently elevated serum ALT

HCV risk may also be increased in noninjection illicit drug use, like intranasal cocaine use, patients with tattoos or body piercing, patients with a history of STD or multiple sex partners, patients with a long-term sexual relationship with an HCV-positive partner.

\[\text{The acute phase of HCV infection usually occurs 2 months after exposure (range: 2–26 weeks) and is typically mild; 70–80% of patients remain anicteric and asymptomatic. ALF is very rarely seen as a complication of acute HCV infection.}\]

\[\text{The reported rate of spontaneous recovery after acute HCV infection has varied between 14% and 50%; the variability is likely due to the patient population studied and mode of acquisition of infection. Reinfection after spontaneous clearance, in some patient populations, may also be misinterpreted as chronic infection. Patients with symptomatic infection during the acute phase are more likely to spontaneously recover; most patients who recover after acute HCV infection do so within 3 months after the onset of acute infection. Because the HBV RNA viral load may vary over}\]
time, even to undetectable levels, a single negative value should not be relied on as a marker of recovery; several repeat laboratory evaluations to confirm recovery should be performed at 3-month intervals.

■ Chronic HCV infection develops in 75–85% of infected patients, but in most patients, it is associated with relatively mild clinical disease, in spite of progressive hepatic damage. Risk factors for more severe disease and rapid progression include alcohol abuse (or other hepatotoxin exposure); coexisting liver disease; immunocompromised status, especially HIV infection; and genetic and other factors. The risk of progression to cirrhosis is markedly increased in patients with hypogammaglobulinemia. Transaminase elevations are typically lower than in HBV infection; episodic fluctuations are common. Occult HBV infection is present in about one third of patients with chronic HCV liver disease.

■ Initial HCV Diagnostic Tests

▼ Serology: Patients with suspected HCV infection should first be tested for HCV antibody. Current “second-generation” EIA assays are very sensitive; tests are positive at presentation in half of patients and within 1 month of presentation in approximately 95% of patients. False-negative results may be seen in dialysis, transplant, or immunocompromised patients (e.g., HIV-infected patients) in spite of circulating HCV RNA. The specificity of HCV serology tests is also very high (>99%), but false-positive reactions must be ruled out in asymptomatic patients with a low prior probability of infection, as in blood donor screening.

▼ The FDA has approved several waived, rapid diagnostic tests for HCV antibody detection. These tests have sensitivities comparable to laboratory-based EIA tests. These assays may improve care by providing direct testing with immediate results at the point of patient encounter, like a physician’s office, clinic, or emergency room.

▼ A negative result for HCV antibody rules out infection in immunologically intact patients. In patients who might not mount a solid antibody response, testing for HCV RNA should be performed.

▼ A positive result for HCV serology testing indicates HCV infection or a false-positive result. In antibody-positive patients with a low prior probability of HCV infection, like healthy blood donors, unexpectedly positive HCV serology screens should be followed by repeat HCV antibody testing using a different test method from the one used for initial testing.

▼ Positive HCV serology tests cannot distinguish between resolved versus active infection, which requires testing for HCV RNA.

▼ Molecular diagnostic testing: Molecular testing for HCV RNA should be performed on all patients with positive HCV serology to determine the presence of active HCV replication. The recombinant immunoblot assay (RIBA HCV) is no longer available for routine diagnostic testing.

▼ HCV RNA detection tests may be qualitative or quantitative. The most sensitive method available should be used to rule out active infection. Real-time (RT) PCR and other quantitative assays may now provide reliable quantification to levels as low as those provided by qualitative assays. An advantage of the use of quantitative HCV (viral load) assays to confirm HCV infection is that they can provide information to predict likely
response to antiviral therapy and to determine response to antiviral therapy. Even though HCV RNA assays are calibrated to an international standard, results may vary across different assays. Therefore, the use of a single assay is recommended for serial testing of a patient's HCV viral load.

- Anti-HCV positive (confirmed), HCV RNA negative: Resolved HCV infection.
- Anti-HCV positive (confirmed), HCV RNA positive: Active HCV infection.

**HCV genotype analysis**: HCV genotype should be determined for patients with acute or chronic HCV infection. There are six different HCV genotypes and many subtypes. The prevalence of different genotypes shows geographic variability; genotype 1 is most common in the United States.

There are genotype-specific differences in response to therapy; the HCV genotype is a factor used to determine the dose and duration of antiviral treatment for chronic HCV infection. Genotypes 2 and 3 have better response rates than genotypes 1 and 4.

**Laboratory testing in chronic HCV infection**: A number of medical conditions may impact the severity of chronic HCV infection and affect response to treatment. In addition, chronic HCV infection may have disease manifestations outside the liver. In addition to HCV viral load testing, tests to evaluate patients for treatment and to monitor response to therapy include the following:

- Testing to rule out other chronic diseases, including infection (like HIV, hepatitis A, and hepatitis B), genetic condition (like hemochromatosis, Wilson disease, α₁-antitrypsin deficiency), or autoimmune disease (like positive reactions for ANA, AMA, or antiactin antibody).
- A patient IL28B genotype predicts a more favorable response to therapy.
- Hepatic function panel: Serum aminotransferase levels typically increase within 2–8 weeks after infection but commonly show significant variability and may return to almost-normal levels (formerly called acute “relapsing” hepatitis). The degree of ALT elevation is an unreliable predictor of histology in HCV infection; biopsy is needed to define the severity of liver damage. Abnormal bilirubin and alkaline phosphatase levels suggest a cholestatic process.
- CBC and PT.
- Metabolic assessment: including renal and thyroid function panels and 25-hydroxy-vitamin D3 level.
- Assess the patient for alcohol and drug abuse; consider drug screen.
- Abdominal ultrasound and AFP to assess the patient for liver tumor and ascites.
- Liver biopsy to assess fibrosis, inflammation, iron overload, steatosis, or other histologic abnormality.

**Assessment of response to HCV antiviral therapy**: The goal of antiviral treatment is a sustained virologic response (SVR), which is defined as undetectable HCV RNA 6 months after the end of therapy.

**Patient factors**: Pretreatment factors associated with a lower rate of SVR include inability to comply with the treatment regimen, diabetes or insulin resistance, increased body weight, older age, increased portal hypertension.
or abnormal liver histopathology (fibrosis, cirrhosis, steatosis), statin use, increased triglyceride or HDL, and decreased LDL.

**Baseline:** Patients with pretreatment HCV viral loads >800,000 IU/mL are less likely to achieve SVR, compared to patients with lower baseline viral loads.

**Rapid virologic response (RVR):** Monitoring HCV viral load should begin as early as 2–4 weeks after initiation of antiviral therapy with pegylated interferon/ribavirin or triple therapy (e.g., pegIFN/RBV plus telaprevir or boceprevir). The rate of fall of the HCV viral load is an important predictor of SVR, especially for genotype 1 virus. Patients with negative HCV RNA at 4 weeks have high (>90%) rates of SVR and may be eligible for a shortened duration of therapy.

**Early virologic response (EVR):** HCV viral load should be assessed at 12 weeks in patients who did not achieve RVR. SVR is seen in 65% of patients overall in whom the HCV viral load shows a >2 log₁₀ reduction compared to baseline; SVR >70% is seen in patients with undetectable HCV RNA at 12 weeks.

- Patients who do not show a >2 log₁₀ reduction in HCV viral load, compared to their baseline, are unlikely to achieve an SVR (<2%).

**Suggested Readings**


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**VASCULAR AND ISCHEMIC DISORDERS OF THE LIVER**

**BUDD-CHIARI SYNDROME**

**Definition**

Heterogeneous group of disorders due to obstruction of hepatic venous outflow...
Causes

- Thrombosis due to hypercoagulable states (e.g., polycythemia vera [10–40% of cases], essential thrombocythemia, myelofibrosis; antiphospholipid syndrome; and deficiencies of protein C, protein S, and antithrombin III) (See Chapter 10, Hematologic Disorders, Paroxysmal Nocturnal Hemoglobinuria)
- Membranes and webs
- Others (e.g., neoplasms, collagen vascular diseases, cirrhosis, and polycystic liver disease)

Laboratory Findings

- Core laboratory: Due to parenchymal cell necrosis and malfunction (e.g., increased serum AST), ALT may be increased >5 times in acute and fulminant forms. ALP and bilirubin may be increased and serum albumin decreased. Ascitic fluid total protein is usually >2.5 g/dL.
- Radiologic visualization (e.g., ultrasound, CT scan, MRI, hepatic angiography).
- Liver biopsy.

Suggested Reading


CONGESTIVE HEART FAILURE

Laboratory Findings Related to Altered Liver Function

- Core laboratory: Pattern of abnormal liver function tests is variable depending on severity of heart failure; the mildest show only slightly increased ALP and slightly decreased serum albumin; moderately severe also show slightly increased serum bilirubin and GGT; one fourth to three fourths of the most severe will also show increased AST and ALT (≤200 U/L) and LD (≤400 U/L). All return to normal when heart failure responds to treatment. Serum ALP is usually the last to become normal, and this may be weeks to months later. AST and ALT may be increased 2–3× normal in less than one third of cases but much higher in severe acute heart failure. Serum albumin is slightly decreased in <50% of patients but is rarely. Serum bilirubin is increased in ≤70% of cases (unconjugated more than conjugated); usually <3 mg/dL but may be >20 mg/dL. It usually represents combined right- and left-sided failure with hepatic engorgement and pulmonary infarcts. Serum bilirubin may suddenly rise rapidly if superimposed myocardial infarction occurs. Serum cholesterol and esters may be decreased. Serum ammonia may be increased. Urine urobilinogen is increased. Urine bilirubin is increased in the presence of jaundice.
- Hematology: PT may be slightly increased in 80% of cases, with increased sensitivity to anticoagulant drugs. Fails to correct with vitamin K.

PORTAL HYPERTENSION

- This condition may be
  - Prehepatic (e.g., portal vein thrombosis, splenic arteriovenous fistula)
  - Intrahepatic
Presinusoidal (e.g., metastatic tumor, granulomas such as sarcoid, schistosomiasis)
- Sinusoidal (e.g., cirrhosis)
- Postsinusoidal (e.g., hepatic vein thrombosis, alcoholic hepatitis)
- Posthepatic (e.g., pericarditis, tricuspid insufficiency, inferior vena cava web)

**BILIARY EXTRAHEPATIC OBSTRUCTION, COMPLETE**

**DISEASES OF THE GALLBLADDER AND BILIARY TREE (INTRAHEPATIC OR EXTRAHEPATIC) (SEE ABDOMINAL PAIN)**

- **Laboratory Findings**
  - Liver enzymes: AST is increased (£300 U/L), and ALT is increased (£200 U/L); they usually return to normal within 1 week after relief of obstruction. In acute biliary duct obstruction (e.g., due to common bile duct stones or acute pancreatitis), AST and ALT are increased >300 U/L (and often >2,000 U/L) and decline 58–76% in 72 hours without treatment; simultaneous serum total bilirubin shows less marked elevation and decline, and ALP changes are inconsistent and unpredictable. Typical pattern of extrahepatic obstruction includes increased serum ALP (>2–3× normal), AST <300 U/L, and conjugated serum bilirubin. In extrahepatic type, the increased ALP is related to the completeness of obstruction. Normal ALP is extremely rare in extrahepatic obstruction. Very high levels may also occur in cases of intrahepatic cholestasis.
  - Conjugated serum bilirubin is increased; unconjugated serum bilirubin is normal or slightly increased. Urine bilirubin is increased; urine urobilinogen decreased. There is decreased stool bilirubin and urobilinogen (clay-colored stools).
  - Lipids: Serum phospholipids are increased. Serum cholesterol is increased (acute, 300–400 mg/dL; chronic, £1,000 mg/dL).
  - Hematology: PT is prolonged, with response to parenteral vitamin K more frequent than in hepatic parenchymal cell disease.

**Considerations**
- Laboratory findings due to underlying causative disease are noted (e.g., stone, carcinoma of duct, metastatic carcinoma to periductal lymph nodes).
- Bile duct obstruction (one): Characteristic pattern is serum bilirubin that remains normal in the presence of markedly increased serum ALP.

**CANCER OF THE GALLBLADDER AND BILE DUCTS**

- **Laboratory Findings**
  - Laboratory findings of duct obstruction are of progressively increasing severity in contrast to the intermittent or fluctuating changes due to duct obstruction caused by stones. A papillary intraluminal duct carcinoma may undergo periods of sloughing, producing the findings of intermittent duct obstruction.
These reflect varying location and extent of tumor infiltration that may cause partial intrahepatic duct obstruction or obstruction of the hepatic or common bile duct, metastases in the liver, or associated cholangitis; 50% of patients have jaundice at the time of hospitalization.

- **Hematology**: Anemia is present.
- **Cytology**: Examination of aspirated duodenal fluid may demonstrate malignant cells.
- **Stool findings**: Silver-colored stool due to jaundice combined with GI bleeding may be seen in carcinoma of the duct or ampulla of Vater.

### CHOLANGITIS, ACUTE

- **Laboratory Findings**
  - **Culture**: Blood culture positive in approximately 30% of cases; 25% of these are polymicrobial. Infection of bile ducts usually due to gram-negative (e.g., *E. coli*, *Klebsiella* sp., gram-positive, and anaerobic [*Streptococcus faecalis*, enterococcus, *Bacteroides fragilis*]) organisms usually associated with obstruction
  - **Hematology**: Marked increase in WBC (≤30,000/μL) with increase in granulocytes
  - **Core laboratory**: Increased serum AST and ALT. Increased urine urobilinogen

#### Considerations
- Laboratory findings of incomplete duct obstruction due to inflammation or of preceding complete duct obstruction (e.g., stone, tumor, scar). See Choledocholithiasis
- Laboratory findings of parenchymal cell necrosis and malfunction

### CHOLANGITIS, PRIMARY SCLEROSING

- Chronic fibrosing cholestatic inflammation of intra- and extrahepatic bile ducts predominantly in men younger than age 45; rare in pediatric patients; ≤75% are associated with IBD, especially UC. Slow, relentless, progressive course of chronic cholestasis to death (usually from liver failure). Twenty-five percent of patients are asymptomatic at the time of diagnosis.

- **Diagnostic Criteria**
  1. Cholestatic biochemical profile for >6 months
    - Serum ALP may fluctuate but is always increased (usually ≥3 times upper limit of normal).
    - Serum GGT is increased.
    - Serum AST is mildly increased in >90%. ALT > AST in three fourths of cases.
    - Serum bilirubin is increased in 50% of patients; occasionally is very high; may fluctuate markedly; gradually increases as disease progresses. Persistent value >1.5 mg/dL is a poor prognostic sign that may indicate irreversible medically untreatable disease.
2. Compatible clinical history (e.g., IBD) and exclusion of other causes of sclerosing cholangitis (e.g., previous bile duct surgery, gallstones, suppurative cholangitis, bile duct tumor or damage due to floxuridine, AIDS, congenital duct anomalies)

3. Characteristic cholangiogram to distinguish from primary biliary cirrhosis
   ▼ Increased γ-globulin in 30% and increased IgM in 40–50% of cases
   ▼ Antineutrophil cytoplasmic antibody (ANCA) is present in approximately 65% of cases, and antinuclear antibodies are noted in <35% of cases and are present at higher levels than in other liver diseases, but diagnostic significance is not yet known.
   ▼ In contrast to primary biliary cirrhosis, antimitochondrial antibody, smooth muscle antibody, rheumatoid factor, and ANA are negative in >90% of patients.
   ▼ HBsAg is negative.
   ▼ Liver biopsy provides only confirmatory evidence in patients with compatible history, laboratory, and x-ray findings. Liver copper is usually increased, but serum ceruloplasmin is also increased.

Other Considerations
- Laboratory findings due to sequelae.
- Cholangiocarcinoma in 10–15% of patients may cause increased serum CA 19-9.
- Portal hypertension, biliary cirrhosis, secondary bacterial cholangitis, steatorrhea and malabsorption, cholelithiasis, and liver failure.
- Laboratory findings due to underlying disease (e.g., ≤7.5% of UC patients have this disease; much less often with Crohn disease). Associated with syndrome of retroperitoneal and mediastinal fibrosis.

**CHOLECYSTITIS, ACUTE**

- **Laboratory Findings**
  - *Hematology:* Increased ESR, WBC (average 12,000/μL; if >15,000, suspect empyema or perforation), and other evidence of acute inflammatory process.
  - *Core laboratory:* Serum AST is increased in 75% of patients. Increased serum bilirubin in 20% of patients (usually >4 mg/dL; if higher, suspect associated choledocholithiasis). Increased serum ALP (some patients) even if serum bilirubin is normal. Increased serum amylase and lipase in some patients

**Considerations**
- Laboratory findings of associated biliary obstruction if such obstruction is present
- Laboratory findings of preexisting cholelithiasis (some patients)
- Laboratory findings of complications (e.g., empyema of the gallbladder, perforation, cholangitis, liver abscess, pyelophlebitis, pancreatitis, gallstone ileus)

**CHOLECYSTITIS, CHRONIC**

- May be mild laboratory findings of acute cholecystitis or no abnormal laboratory findings
May be laboratory findings of associated cholelithiasis
Laboratory findings of sequelae (e.g., carcinoma of the gallbladder)

**CHOLEDOCHOLITHIASIS**

- Gallstones in bile ducts due to passage from the gallbladder or anatomic defects (e.g., cysts, strictures)

- **Laboratory Findings**
  - *Core laboratory:* Increased serum and urine amylase. Increased serum bilirubin in about one third of patients. Increased urine bilirubin in about one third of patients. Increased serum ALP
  - *Hematology:* Increased WBC

- **Considerations**
  - Laboratory evidence of fluctuating or transient cholestasis. Persistent increase of WBC, AST, and ALT suggests cholangitis.
  - Laboratory findings due to secondary cholangitis, acute pancreatitis, obstructive jaundice, stricture formation, and so on.
  - In duodenal drainage, crystals of both calcium bilirubinate and cholesterol (some patients); 50% accurate (only useful in nonicteric patients).

- **Cholelithiasis**
  - Laboratory findings of underlying conditions causing
    - Hypercholesterolemia (e.g., DM, malabsorption)
    - Chronic hemolytic disease (e.g., hereditary spherocytosis)
  - Laboratory findings due to complications (e.g., cholecystitis, choledocholithiasis, gallstone ileus)

**ATRESIA, EXTRHEPATIC BILIARY, CONGENITAL**

- Conjugated serum bilirubin increased in early days of life in some infants but not until 2nd week in others. Level is often <12 mg/dL during the first few months, with subsequent rise later in life.
- Laboratory findings as in complete biliary obstruction.
- Liver biopsy to differentiate from neonatal hepatitis.
- Laboratory findings due to sequelae (e.g., biliary cirrhosis, portal hypertension, frequent infections, rickets, hepatic failure).
- $^{131}$I-rose bengal excretion test.

**OTHER CONSIDERATIONS**

- Most important to differentiate this condition from neonatal hepatitis, for which surgery may be harmful.
- More than 90% of cases of extrahepatic biliary obstruction in newborns are due to biliary atresia; occasional cases may be due to choledochal cyst (causes intermittent jaundice in infancy), bile plug syndrome, or bile ascites (associated with spontaneous perforation of the common bile duct).
INTRAHEPATIC OBSTRUCTION CHOLESTASIS

- Causes of intrahepatic cholestasis:
  - Intrahepatic obstruction
    - Space-occupying lesions (e.g., amyloidosis, sarcoidosis, metastases; non-Hodgkin lymphoma more often than Hodgkin disease)
    - Drugs (e.g., estrogens, anabolic steroids)—most common cause (Table 5-13)
    - Normal pregnancy
    - Alcoholic hepatitis
    - Infections (e.g., acute viral hepatitis, gram-negative sepsis, toxic shock syndrome, AIDS, parasitic, fungal)
    - Sickle cell crisis
    - Postoperative state following long procedure and multiple transfusions
    - Benign recurrent familial intrahepatic cholestasis—rare condition
  - Autosomal recessive condition; attacks begin after age 8, last weeks to months, complete resolution between episodes, may recur after months or years; exacerbated by estrogens

- Laboratory Findings
  - Core laboratory: Increased serum ALP, but GGT is usually normal. Serum direct bilirubin may be normal or ≤10 mg/dL. Transaminase usually <100 U.
  - Histology: Liver biopsy shows centrolobular cholestasis without inflammation, bile pigment in hepatocytes and canaliculi; little or no fibrosis.

CIRRHOSIS, PRIMARY BILIARY (CHOLANGIOLITIC CIRRHOSIS, HANOT HYPERTROPHIC CIRRHOSIS, CHRONIC NONSUPPURATIVE DESTRUCTIVE CHOLANGIITIS, ETC.)

- Slow progressive multisystem autoimmune disease; chronic nonsuppurative inflammation and asymmetric destruction of small intrahepatic bile ducts producing chronic cholestasis, cirrhosis, and ultimately liver failure

<table>
<thead>
<tr>
<th>TABLE 5–13. Comparison of Various Types of Cholestatic Disease</th>
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<tbody>
<tr>
<td>Disorder</td>
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<tr>
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<tr>
<td>CBD obstruction</td>
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<tr>
<td>Stone</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Intrahepatic</td>
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<tr>
<td>Drug-induced</td>
</tr>
<tr>
<td>Acute viral hepatitis</td>
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<tr>
<td>Alcoholic liver disease</td>
</tr>
</tbody>
</table>

CBD, common bile duct; N, normal; sl D, slightly decreased.
*Serum value, times normal.
Diagnostic Criteria

- Definitive diagnosis requires all three criteria; probable diagnosis requires two criteria.
  - Antimitochondrial autoantibodies present
  - Cholestatic pattern (increased ALP) of long duration (>6 months) not due to known cause (e.g., drugs)
  - Compatible histologic findings on liver biopsy
- Serum ALP is markedly increased; is of liver origin. Reaches a plateau early in the course and then fluctuates within 20% thereafter; changes in serum level have no prognostic value. $S'\text{-N}$ and GGT parallel the ALP. *This is one of the few conditions that will elevate both serum ALP and GGT to striking levels.*
- Serum mitochondrial antibody titer is strongly positive in approximately 95% of patients (1:40–1:80) and is hallmark of disease (98% specificity); titer $\geq 1:160$ is highly predictive of primary biliary cirrhosis (PBC), even in the absence of other findings. Does not correlate with severity or rate of progression. Titers differ greatly in patients. Similar titers occur in 5% of patients with chronic hepatitis; low titers occur in 10% of patients with other liver disease; rarely found in normal persons. Titer may decrease after liver transplantation but usually remains detectable.
- Serum bilirubin is normal in early phase but increases in 60% of patients with progression of disease and is a reliable prognostic indicator; an elevated level is a poor prognostic sign. Conjugated serum bilirubin is increased in 80% of patients; levels $>5 \text{ mg/dL}$ in only 20% of patients; levels $>10 \text{ mg/dL}$ in only 6% of patients. Unconjugated bilirubin is normal or slightly increased.
- Laboratory findings show relatively little evidence of parenchymal damage.
  - AST and ALT may be normal or slightly increased ($\leq 1–5$ times normal), fluctuate within a narrow range, and have no prognostic significance.
  - Serum albumin, globulin, and PT normal early; abnormal values indicate advanced disease and poor prognosis; not corrected by therapy.
- Marked increase in total cholesterol and phospholipids with normal triglycerides; serum is not lipemic; serum triglycerides become elevated in late stages. Associated with xanthomas and xanthelasmas. In early stages, LDL and VLDL are mildly elevated and HDL is markedly elevated (thus atherosclerosis is rare). In advanced stage, LDL is markedly elevated with decreased HDL and presence of lipoprotein-X (nonspecific abnormal lipoprotein seen in other cholestatic liver disease).
- Serum IgM is increased in approximately 75% of patients; levels may be very high (four to five times normal). Other serum immunoglobulins are also increased.
- Hypocomplementemia.
- Polyclonal hypergammaglobulinemia. Serum IgM is increased in approximately 75% of patients with failure to convert to IgG antibodies; levels may be very high (four to five times normal). Other serum immunoglobulins are also increased.
- Biopsy of the liver categorizes the four stages and helps assess prognosis, but needle biopsy is subject to sampling error because the lesions may be spotty; findings consistent with all four stages may be found in one specimen.
- Serum ceruloplasmin is characteristically elevated (in contrast to Wilson disease).
Liver copper may be increased 10–100 times normal; correlates with serum bilirubin and advancing stages of disease.

ESR is increased one to five times normal in 80% of patients.

Urine contains urobilinogen and bilirubin.

Laboratory findings of steatorrhea:
- Serum 25-hydroxyvitamin D and vitamin A are usually low.
- PT is normal or restored to normal by parenteral vitamin K.

Laboratory findings due to associated diseases:
- More than 80% have one, and >40% have at least two, other circulating antibodies to autoimmune disease (e.g., RA, autoimmune thyroiditis [hypothyroidism in 20% of patients], Sjögren syndrome, scleroderma) although not useful diagnostically.

**CONGENITAL CONJUGATED HYPERBILIRUBINEMIA**

**DUBIN-JOHNSON SYNDROME (SPRINZ-NELSON DISEASE)**

An autosomal recessive disease (gene located on chromosome 10q24) due to inability to transport bilirubin–glucuronide through hepatocytes into canaliculi, but conjugation of bilirubin–glucuronide is normal. Characterized by mild chronic, recurrent jaundice. May have hepatomegaly and right upper quadrant abdominal pain. Usually is compensated except in periods of stress. Jaundice (innocuous and reversible) may be produced by estrogens, birth control pills, or last trimester of pregnancy; may resemble mild viral hepatitis.

**Laboratory Findings**

- See Table 5-14.

**Histology:** Liver biopsy shows large amounts of yellow-brown or slate-black pigment in centrolobular hepatic cells (lysosomes) and small amounts in Kupffer cells.

**Core Laboratory:** Serum total bilirubin is increased (1.5–6.0 mg/dL); rarely ≤25 mg/dL during intercurrent illness; significant amount is conjugated. Normal in heterozygotes. Other liver function tests are normal. No evidence of hemolysis. Urine contains bile and urobilinogen.

**Other:** Urine total coproporphyrin is usually normal, but approximately 80% is coproporphyrin I (normally 25% is coproporphyrin I and 75% is coproporphyrin III); diagnostic of Dubin-Johnson syndrome. Not useful to detect individual heterozygotes. Fecal coproporphyrins are normal. BSP excretion is impaired with late (normal at 45 minutes; increased at 90 and 120 minutes); virtually pathognomonic but is no longer performed.

**ROTOR SYNDROME**

Autosomal recessive, familial, asymptomatic, benign defective uptake, and storage of conjugated bilirubin and possibly in transfer of bilirubin from the liver to bile or in intrahepatic binding; usually detected in adolescents or adults. Jaundice may be produced or accentuated by pregnancy, birth control pills, alcohol, infection, or surgery.

- See Table 5-14.
<table>
<thead>
<tr>
<th>Unconjugated Hyperbilirubinemias</th>
<th>Crigler-Najjar Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crigler-Najjar Syndrome</strong></td>
<td><strong>Type I</strong></td>
</tr>
<tr>
<td>Incidence</td>
<td>Very rare</td>
</tr>
<tr>
<td>Inheritance mode</td>
<td>AD</td>
</tr>
<tr>
<td>Serum bilirubin usual total</td>
<td>&gt;20</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
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<tr>
<td>Defect in bilirubin metabolism</td>
<td></td>
</tr>
<tr>
<td>Impaired excretion of dyes</td>
<td>Mostly indirect; increases with fasting</td>
</tr>
<tr>
<td>requiring conjugation</td>
<td>Hepatic UDP-glucuronyl transferase activity</td>
</tr>
<tr>
<td>(e.g., BSP)</td>
<td>All indirect</td>
</tr>
<tr>
<td>Effect of phenobarbital</td>
<td>Marked decrease</td>
</tr>
<tr>
<td>Urine coproporphyrin total</td>
<td>Absent</td>
</tr>
<tr>
<td>I/III*</td>
<td></td>
</tr>
<tr>
<td>Age at onset of jaundice</td>
<td></td>
</tr>
<tr>
<td>Usual clinical features</td>
<td></td>
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<tr>
<td>Oral cholecystogram</td>
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<tr>
<td>Liver biopsy</td>
<td></td>
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<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Animal model</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 5–14. Differential Diagnosis of Hereditary Jaundice with Normal Liver Chemistries and No Signs or Symptoms of Liver Disease**

- **Crigler-Najjar Syndrome**
  - Incidence: Very rare
  - Inheritance mode: AD
  - Serum bilirubin usual total (mg/dL): >20
  - Defect in bilirubin metabolism: Mostly indirect; increases with fasting Hepatic UDP-glucuronyl transferase activity
  - Effect of phenobarbital: Marked decrease
  - Urine coproporphyrin total I/III*: Absent
  - Age at onset of jaundice: Infancy
  - Usual clinical features: Jaundice, kernicterus in infants, young adults
  - Oral cholecystogram: Normal
  - Liver biopsy: Liver transplant; no response to phenobarbital
  - Treatment: Gunn rat
  - Animal model: Phenobarbital

- **Dubin-Johnson Syndrome**
  - Incidence: Uncommon
  - Inheritance mode: AR
  - Serum bilirubin usual total (mg/dL): 2–7; ≤25
  - Defect in bilirubin metabolism: Direct ~60%
  - Impaired excretion of dyes requiring conjugation (e.g., BSP): Yes; initial rapid fall, then rise in 45–90 minutes
  - Effect of phenobarbital: Normal
  - Urine coproporphyrin total I/III*: Normal
  - Age at onset of jaundice: Childhood, adolescence
  - Usual clinical features: Asymptomatic jaundice in young adults
  - Oral cholecystogram: GB usually not visualized
  - Liver biopsy: Characteristic pigment
  - Treatment: Not needed
  - Animal model: Corriedale sheep

- **Rotor Syndrome**
  - Incidence: Rare
  - Inheritance mode: AR
  - Serum bilirubin usual total (mg/dL): 2–7; ≤20
  - Defect in bilirubin metabolism: Direct ~60%
  - Impaired excretion of dyes requiring conjugation (e.g., BSP): Yes; slow clearance; no later increase
  - Effect of phenobarbital: Decreased
  - Urine coproporphyrin total I/III*: Normal
  - Age at onset of jaundice: Adolescence, early adulthood
  - Usual clinical features: Asymptomatic jaundice
  - Oral cholecystogram: Normal
  - Liver biopsy: No pigment
  - Treatment: None
  - Animal model: None

- **Gilbert Disease**
  - Incidence: ≤7% of population
  - Inheritance mode: AD
  - Serum bilirubin usual total (mg/dL): <3; ≤6
  - Defect in bilirubin metabolism: Mostly indirect
  - Impaired excretion of dyes requiring conjugation (e.g., BSP): May be slightly impaired in ≤40% of patients
  - Effect of phenobarbital: Decreased
  - Urine coproporphyrin total I/III*: >80%
  - Age at onset of jaundice: Adolescence
  - Usual clinical features: Appearance in early adulthood; often first recognized with fasting; very mild hemolysis in ≤40% of patients
  - Oral cholecystogram: Normal
  - Liver biopsy: Normal
  - Treatment: None
  - Animal model: None

*AD, autosomal dominant; AR, autosomal recessive; BSP, sulfobromophthalein; GB, gallbladder; UDP-glucuronyl transferase, uridine diphosphate–glucuronosyl transferase.

*Normally coproporphyrin III, 75% of total.
CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA

UNCONJUGATED BILIRUBINEMIA

Causes

- Increased destruction of RBCs
  - Isoimmunization (e.g., incompatibility of Rh, ABO, other blood groups)
  - Biochemical defects of RBCs (e.g., G6PD deficiency, pyruvate deficiency, hexokinase deficiency, congenital erythropoietic porphyria, α- and γ-thalassemias)
  - Structural defects of RBCs (e.g., hereditary spherocytosis, hereditary elliptocytosis, infantile pyknocytosis, xerocytosis)
  - Physiologic hemolysis of the newborn
  - Infection

PHYSIOLOGIC JAUNDICE

Definition

Transient unconjugated hyperbilirubinemia (physiologic jaundice) that occurs in almost all newborns resulting from physiologic hemolysis

Laboratory Findings

- In a normal full-term neonate, average maximum serum bilirubin is 6 mg/dL (≤12 mg/dL is in physiologic range) that occurs during the 2nd to 4th day and then rapidly falls to approximately 2.0 mg/dL by 5th day (phase I physiologic jaundice). Declines slowly to <1.0 mg/dL during the 5th to 10th day but may take 1 month to fall to <2 mg/dL (phase II physiologic jaundice). Phase I due to deficiency of hepatic bilirubin glucuronyl transferase activity, and sixfold increase in bilirubin load presented to the liver. In Asian and Native American newborns, the average maximum serum levels are approximately double (10–14 mg/dL) the levels in non-Asians, and kernicterus is more frequent. Serum bilirubin >5 mg/dL during the first 24 hours of life is indication for further workup because of risk of kernicterus.
- In older children (and adults), icterus is apparent clinically when serum bilirubin is >2 mg/dL, but in newborns, clinical icterus is not apparent until serum bilirubin is >5–7 mg/dL; therefore, only half of the full-term newborns show clinical jaundice during the first 3 days of life.
- In premature infants—average maximum serum bilirubin is 10–12 mg/dL and occurs during the 5th to 7th day. Serum bilirubin may not fall to normal until 30th day. Further workup is indicated in all premature infants with clinical jaundice because of risk of kernicterus in some low birth weight infants with serum levels of 10–12 mg/dL.
- In postmature infants and half of small-for-date infants—serum bilirubin is <2.5 mg/dL, and physiologic jaundice is not seen. When mothers have received phenobarbital or used heroin, physiologic jaundice is also less severe.
- When a pregnant woman has unconjugated hyperbilirubinemia, similar levels occur in cord blood, but when the mother has conjugated hyperbilirubinemia (e.g., hepatitis), similar levels are not present in cord blood.
NONPHYSIOLOGIC JAUNDICE

Cause should be sought for underlying pathologic jaundice if
- Total serum bilirubin >7 mg/dL during the first 24 hours or increases >5 mg/dL/day or visible jaundice
- Peak total serum bilirubin >12.5 mg/dL in white or black full-term infants or >15 mg/dL in Hispanic or premature infants
- Conjugated serum bilirubin >1.5 mg/dL

HEREDITARY AND/OR CONGENITAL CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA

CRIGLER-NAJJAR SYNDROME (HEREDITARY GLUCURONYL TRANSFERASE DEFICIENCY)
- A rare familial autosomal recessive disease due to marked congenital deficiency or absence of glucuronyl transferase, which conjugates bilirubin to bilirubin glucuronide in hepatic cells (counterpart is the homozygous Gunn rat)

- **Laboratory Findings**
  - See Table 5-14.
  - **Type I**
    - **Histology:** Liver biopsy is normal.
    - **Core laboratory:** Unconjugated serum bilirubin is increased; it appears on the 1st or 2nd day of life, rises in 1 week to peak of 12–45 mg/dL and persists for life. No conjugated bilirubin in serum or urine. Liver function tests are normal; BSP is normal. Fecal urobilinogen is very low.

- **Other Considerations**
  - Untreated patients often die of kernicterus by age 18 months.
  - Nonjaundiced parents have diminished capacity to form glucuronide conjugates with menthol, salicylates, and tetrahydrocortisone.
  - Type I should always be ruled out when there are persistent unconjugated bilirubin levels of 20 mg/dL after 1 week of age without obvious hemolysis and especially after breast milk jaundice has been ruled out.

GILBERT DISEASE
- Chronic, benign, intermittent, familial (autosomal dominant with incomplete penetrance), nonhemolytic unconjugated hyperbilirubinemia with evanescent increases of unconjugated serum bilirubin, which is usually discovered on routine laboratory examinations; due to defective transport and conjugation of unconjugated bilirubin.
- Jaundice is usually accentuated by pregnancy, fever, exercise, and various drugs, including alcohol and birth control pills.
- Rarely identified before puberty.
- May be mildly symptomatic; 3–7% prevalence in total population.
NEONATAL JAUNDICE: BREAST MILK JAUNDICE

- Due to the presence in mother’s milk of pregnanediol, which inhibits glucuronyl transferase activity.

Laboratory Findings

- Severe unconjugated hyperbilirubinemia. Develops in 1% of breast-fed infants by the 4th to 7th day. May reach peak of 15–25 mg/dL by the 2nd to 3rd week; then gradually disappears in 3–10 weeks in all cases. If nursing is interrupted, serum bilirubin falls rapidly by 2–6 mg/dL in 2–6 days and may rise again if breast-feeding is resumed; if interrupted for 6–9 days, serum bilirubin becomes normal.
- No other abnormalities are present.
- Kernicterus does not occur.

LUCEY-DRISCOLL SYNDROME (NEONATAL TRANSIENT FAMILIAL HYPERBILIRUBINEMIA)

- Syndrome is due to some factor in mother’s serum only during the last trimester of pregnancy that inhibits glucuronyl transferase activity; disappears about 2 weeks postpartum.
- Newborn infants have severe nonhemolytic unconjugated hyperbilirubinemia usually ≤20 mg/dL during the first 48 hours and a high risk of kernicterus.

WILSON DISEASE

- Autosomal recessive defect that impairs copper excretion by the liver, which may cause copper accumulation in the liver and brain resulting in cirrhosis, neuropsychiatric disease, and corneal pigmentation.
- Heterozygous gene for Wilson disease occurs in 1 of 200 in the general population; 10% of these have decreased serum ceruloplasmin; liver copper is not increased (<250 μg/g of dry liver). Serum copper and ceruloplasmin and urine copper are inadequate to detect heterozygous state.
- Homozygous gene (clinical Wilson disease) occurs in 1 of 200,000 in the general population.
- Liver biopsy may show no abnormalities, moderate to marked fatty changes with or without fibrosis, or active or inactive mixed micronodular–macronodular cirrhosis.

Laboratory Findings

- Findings of liver function tests may not be abnormal, depending on the type and severity of the disease. In patients presenting with acute fulminant hepatitis, Wilson disease is suggested if there is a disproportionately low serum ALP and relatively mild increase in AST and ALT. ALP is frequently decreased; ALP/bilirubin ratio <2.0 is said to distinguish Wilson disease as cause of fulminant liver failure with S/S = 100%/100%.
Radiocopper incorporation into ceruloplasmin is reduced significantly compared with heterozygotes or normal persons. $^{64}$Cu is administered IV or PO and serum concentration is plotted against time. Serum $^{64}$Cu disappears within 4–6 hours and then reappears in persons without Wilson disease; secondary reappearance is absent in Wilson disease because incorporation of $^{64}$Cu into ceruloplasmin is decreased. Useful when liver biopsy is contraindicated but rarely used since advent of transjugular liver biopsy. Can use mass spectroscopy rather than radioactive Cu.

Chelating agent (e.g., d-penicillamine) produces urine Cu excretion of 2–4 mg/day.

**Other Considerations**

Diagnosis should be ruled out in any patient with hepatitis with negative serology for viral hepatitis, Coombs-negative hemolysis (due to copper released from necrotic liver cells), or neurologic symptoms to allow for early diagnosis and treatment of Wilson disease.

**Suggested Reading**


**TRAUMA**

May be laceration, hematoma, or vascular

**Laboratory Findings**

Core laboratory: Serum LD is frequently increased (>1,400 units) 8–12 hours after major injury. Shock due to any injury may also increase LD. Other serum enzymes and liver function tests are not generally helpful.