5
GASTROENTEROLOGY

Angeli Chopra

Nausea and Vomiting

DIFFERENTIAL DIAGNOSIS

NEUROLOGIC

- **ORGANIC**—infections, tumors, multiple sclerosis, vestibular nerve or brain stem lesions
- **DRUGS**—chemotherapy, SSRI, opioids, antibiotics, hormonal therapy, chronic marijuana use
- **PSYCHIATRIC**—anorexia nervosa, bulimia nervosa, rumination

GASTROINTESTINAL

- **INFECTIONS**—acute gastroenteritis, food poisoning, UTI, pyelonephritis, pneumonia
- **NEOPLASTIC**—gastric, ovarian, paraneoplastic, renal
- **OBSTRUCTION**—stomach, small bowel, colon, functional, gastric volvulus
- **POSTOP**—vagotomy, gastrectomy, fundoplication
- **INFLAMMATION**—esophagus, stomach, duodenum
- **GASTROPARESIS**—ischemic, diabetic, amyloidosis, scleroderma, drugs
- **OTHERS**—eosinophilic gastroenteritis, hepatobiliary disease, pancreatic disease, peritoneal irritation, functional gastrointestinal disorders, retroperitoneal fibrosis

METABOLIC

- **ENDOCRINE**—diabetes, adrenal insufficiency, hypercalcemia, hyperthyroidism, hyperparathyroidism, hyperemesis gravidarum, porphyria
- **OTHERS**—uremia, pregnancy, migraine

IDIOPATHIC

PATHOPHYSIOLOGY

REFLEX PATHWAY

- **AFFERENT**—(1) **humoral factors** (drugs, toxins, neurotransmitter, peptides) → area postrema in floor of 4th ventricle (chemoreceptor trigger zone) → **nucleus tractus solitarius** (NTS) in medulla serves as central pattern generator for vomiting; (2) neuronal **GI tract** stimuli → vagus nerve → NTS; (3) **nociceptive** stimuli → sympathetic nervous system → brain stem nuclei and the hypothalamus
- **EFFERENT**—NTS → **paraventricular nuclei** of the hypothalamus and the limbic and cortical regions → gastric electromechanical events are perceived as normal sensations or nausea or discomfort → vagus nerve → gastric and lower esophageal sphincter relaxation, retrograde contraction in proximal small bowel and antrum, abdominal muscle contraction and initial cricopharyngeus contraction followed by relaxation seconds before vomiting

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, AM cortisol, urinalysis
- **MICROBIOLOGY**—urine C&S
- **IMAGING**—CXR, AXR

SPECIAL

- **GASTROSCOPY, GASTRIC EMPTYING STUDY**
- **CT HEAD**

MANAGEMENT

SYMPTOM CONTROL

- **H1 ANTAGONISTS**—*dimenhydrinate* 25–50 mg PO/PR q4h, *diphenhydramine* 25–50 mg PO/IV/IM q4h, *cyclizine* 50 mg PO/IM q4h or 100 mg PR q4h, *meclizine* 25–50 mg PO daily, *promethazine* 12.5–25 mg PO/IM q4h or 12.5–25 mg PR daily
- **D2 ANTAGONISTS**—**benzamides** (*metoclopramide* 5–10 mg PO/IV/IM q4h), **phenothiazine** (*prochlorperazine* 5–10 mg PO q6–8 h, *chlorpromazine* 10–25 mg PO q4–6 h),

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_5,

MANAGEMENT (CONT'D)

butyrophenones (*droperidol* 1.25–5 mg IM q4h, *haloperidol* 0.5–1 mg IV/PO q4h)
- **5HT3 ANTAGONISTS**—*ondansetron* 4–8 mg PO/IV q8h, *granisetron* 2 mg PO or 1 mg IV, *dolasetron* 100 mg PO/IV daily
- **M1 ANTAGONISTS**—*scopolamine* 1.5 mg TD q72h
- **STEROID**—*dexamethasone* 4 mg PO/SC/IV BID–TID
- **TUBE FEED**—NJ tube, G tube

TREAT UNDERLYING CAUSE

Related Topics
Chemotherapy-Induced Nausea and Vomiting (p. 254)
Nausea and Vomiting in the Palliative Setting (p. 448)

Dysphagia

DIFFERENTIAL DIAGNOSIS

OROPHARYNGEAL (upper esophagus and pharynx, or upper esophageal sphincter dysfunction)
- **NEUROLOGICAL**—stroke, multiple sclerosis, Parkinson's, dementia, amyotrophic lateral sclerosis, Guillain–Barre, myasthenia gravis, cerebral palsy, Huntington's, tardive dyskinesia, brain stem tumors, trauma
- **MYOPATHIC**—myotonic dystrophy, dermatomyositis, connective tissue disease, sarcoidosis, paraneoplastic
- **STRUCTURAL**—cricopharyngeal bar, Zenker's diverticulum, cervical webs, oropharyngeal tumors, osteophytes and skeletal abnormality, congenital abnormality, ill-fitting dentures
- **INFECTIOUS**—syphilis, Lyme disease, botulism, mucositis
- **METABOLIC**—Cushing's, thyrotoxicosis, Wilson's, amyloidosis, Sjögren's syndrome
- **IATROGENIC**—chemotherapy, neuroleptics, postsurgical, radiation
- **FUNCTIONAL (GLOBUS SENSATION)**

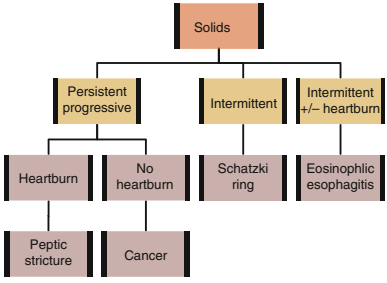
ESOPHAGEAL (body of esophagus, lower esophageal sphincter, cardia)
- **STRUCTURAL**—**tumors** (benign, malignant), **esophagitis/stricture** (reflux, caustic/erosive, infectious, eosinophilic, pill, radiation), tylosis, diverticula, **iatrogenic** (post-surgery, radiation), esophageal ring/web, **extrinsic compression** (enlarged aorta, left atrium, mediastinal mass, lung cancer, lymphoma, osteophytes, subclavian artery)
- **MOTILITY**—achalasia, scleroderma, Chagas disease, diffuse esophageal spasm, hypertensive lower esophageal sphincter, nutcracker esophagus, non-specific esophageal motility disorders

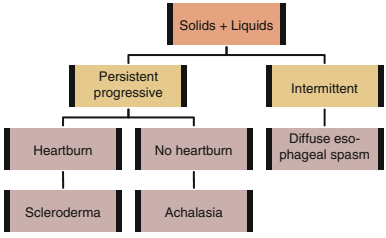
CLINICAL FEATURES

DIAGNOSTIC CLUES—history of heartburn may suggest GERD leading to erosive esophagitis, peptic stricture, or esophageal adenocarcinoma. History of atopic diseases especially in a young adult with recurrent dysphagia may suggest eosinophilic esophagitis. Also check for odynophagia, regurgitation, hematemesis, coffee ground emesis, respiratory symptoms, weight loss, and medication history (tetracycline, bisphosphonates, potassium supplements)

PRACTICAL APPROACH TO DYSPHAGIA
1. Features of oropharyngeal dysphagia (problems initiating swallowing, extending neck/arms when swallowing, changes in speech, coughing, choking, or nasal regurgitation)? Consider workup for oropharyngeal dysphagia. Otherwise, proceed to step 2
2. Difficulty swallowing both solids and liquids? If yes, consider motility disorders and proceed to step 3. If progressing from solids to liquids, consider structural disorders and proceed to step 4
3. For motility disorders, is the dysphagia progressive? If yes, consider achalasia or scleroderma. If intermittent, consider diffuse esophageal spasm or non-specific esophageal motility disorder
4. For structural disorders, is the dysphagia progressive? If yes, consider tumors and peptic stricture. If intermittent, consider esophageal ring
5. Any caustic ingestion history?

CLINICAL FEATURES (CONT'D)





INVESTIGATIONS

BASIC

- **IMAGING**—barium swallow (esophageal), videofluoroscopy (oropharyngeal)
- **SWALLOWING ASSESSMENT**—occupational therapy or speech pathology

SPECIAL

- **GASTROSCOPY**—for esophageal lesions and biopsy for eosinophilic esophagitis
- **ESOPHAGEAL MANOMETRY**—definitive for achalasia, useful for diffuse esophageal spasm
- **pH MONITORING**—for refractory GERD, especially if gastroscopy normal
- **FIBEROPTIC NASOPHARYNGEAL LARYNGOSCOPY**—for oropharyngeal dysphagia

MANAGEMENT

SYMPTOM CONTROL—postural/nutritional/behavioral modifications, swallowing rehabilitation, esophageal dilation

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

ACHALASIA

- **PATHOPHYSIOLOGY**—a motor disorder with lack of peristalsis in the body of the esophagus and incomplete relaxation of the lower esophageal sphincter on manometry
- **DIAGNOSIS**—endoscopy is essential for ruling out malignancy ("pseudoachalasia"). Barium swallow (beak-like narrowing), esophageal manometry (definitive)
- **TREATMENTS**—endoscopic intrasphincteric injection of botulinum toxin, pneumatic dilation, and surgical myotomy

INFECTIOUS ESOPHAGITIS

- **PATHOPHYSIOLOGY**—common organisms include *Candida albicans*, CMV, and HSV. Happens more commonly in immunocompromised host
- **DIAGNOSIS**—gastroscopy and biopsy/viral cultures

EOSINOPHILIC ESOPHAGITIS

- **PATHOPHYSIOLOGY**—food allergens and genetic factors leading to eosinophilic infiltration and stricture (frequently presents in young males with esophageal foreign body)
- **DIAGNOSIS**—gastroscopy (esophageal trachealization) and biopsy
- **TREATMENTS**—control reflux, dilatation, dietary modification, fluticasone (administered as MDI and swallowed), and oral steroids (viscous budesonide slurry)

Related Topics
Esophageal Cancer (p. 215)
Stroke (p. 337)

Dyspepsia

DIFFERENTIAL DIAGNOSIS

NON-GASTRIC CAUSES—cardiac (myocardial infarction), pulmonary (pneumonia), hepatobiliary (biliary colic), pancreatic (pancreatitis), colonic (irritable bowel syndrome), musculoskeletal, dietary indiscretion

PEPTIC ULCER DISEASE (PUD, 10–20%)—*H. pylori*, ASA, NSAIDs (COX-2 inhibitors slightly decreased risk), cancer, Zollinger–Ellison, smoking

MEDICATION SIDE EFFECTS—NSAIDs, ASA, theophylline, calcium channel blockers, erythromycin, metronidazole, bisphosphonates, orlistat, acarbose, iron, potassium supplements

DIFFERENTIAL DIAGNOSIS (CONT'D)

GASTROESOPHAGEAL REFLUX DISEASE (GERD, 20%)

★ACIDS★

- **A**cid hypersecretion—Zollinger–Ellison disease
- **A**lcohol abuse
- **C**onnective tissue disease—scleroderma
- **I**nfections of esophagus—CMV, HSV, candidiasis
- **D**iabetic gastroparesis
- **D**rug therapy
- **S**moking

NON-ULCER DYSPEPSIA (50%)—cause unclear. Diagnosis of exclusion (rule out organic cause)

PATHOPHYSIOLOGY

COMPLICATIONS OF PUD—perforation, hemorrhage, gastric outlet obstruction, pancreatitis

COMPLICATIONS OF GERD—esophageal complications include esophagitis, esophageal ulcer, esophageal stricture, and Barrett's esophagus. Extra-esophageal complications include asthma, aspiration, chronic cough, hoarseness, chronic laryngitis, and dental erosions

CLINICAL FEATURES

SYMPTOM DEFINITIONS

- **DYSPEPSIA**—chronic or recurrent epigastric pain, often with regurgitation, heartburn, bloating, nausea, and post-prandial fullness (indigestion)
- **HEARTBURN**—retrosternal burning sensation secondary to lower esophageal sphincter relaxation = more specific for GERD

RATIONAL CLINICAL EXAMINATION SERIES: CAN THE CLINICAL HISTORY DISTINGUISH BETWEEN ORGANIC AND FUNCTIONAL DYSPEPSIA?

	LR+	LR–
Organic dyspepsia		
Diagnosis reached by the clinician or computer model	1.6	0.46
Peptic ulcer disease		
Diagnosis reached by the clinician or computer model	2.2	0.45
Esophagitis		
Diagnosis reached by the clinician or computer model	2.4	0.5

CLINICAL FEATURES (CONT'D)

APPROACH—"functional dyspepsia is defined as pain or discomfort centered in the epigastrium with a normal endoscopy. Neither clinical impression nor computer models that incorporated patient demographics, risk factors, history items and symptoms adequately distinguished between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia"

JAMA 2006 295:13

PRACTICAL APPROACH TO DYSPEPSIA

1. Consider **non-gastric causes** of dyspepsia (cardiac, pulmonary, hepatobiliary, colonic, musculoskeletal, medications, and dietary indiscretion) and investigate those causes if likely. Otherwise proceed to step 2
2. If **age >50 or alarm symptoms ★Very BAD★** (**V**omiting, **B**leed/anemia, **A**bdominal mass/weight loss, **D**ysphagia), refer for gastroscopy to check for gastric cancer. Otherwise proceed to step 3
3. If **ASA or NSAIDs** use, stop medications if possible. If not, consider empiric proton pump inhibitor/H_2 blocker trial and proceed to step 4
4. If **GERD predominant symptoms** (heartburn, regurgitation), treat as GERD. Otherwise, proceed to step 5
5. If ***H. pylori*** **urea breath test positive**, treat with triple therapy. Otherwise, proceed to step 6
6. If none of the above, diagnosis of **non-ulcer dyspepsia**

Canadian Dyspepsia Working Group. Can J Gastroenterol 2005 19:5

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, glucose, AST, ALT, ALP, bilirubin, lipase, Ca, albumin
- **IMAGING**—upper GI series, US abd, CT abd

SPECIAL

- **UREA BREATH TEST**
- ***H. PYLORI* SEROLOGY**
- **24-H ESOPHAGEAL PH MONITORING**
- **ENDOSCOPY WITH BIOPSY**—urease test, C&S for *H. pylori*
- **PROTON PUMP INHIBITOR TEST**—sens 78% for GERD

MANAGEMENT

PEPTIC ULCER DISEASE—avoid NSAID use. Antisecretory treatment (*ranitidine* 150–300 mg PO BID, *omeprazole* 20–40 mg PO daily, *lansoprazole* 15–30 mg PO daily, *pantoprazole* 40 mg PO daily; all 30–60 min before meals; 8 week course). ***H. pylori* eradication** (★**CAO**★: *clarithromycin* 500 mg PO BID, *amoxicillin* 1 g PO BID, *omeprazole* 40 mg PO daily × 10 days; ★**CMO**★ (if penicillin allergy): *clarithromycin* 500 mg PO BID, *metronidazole* 250 mg PO QID, *omeprazole* 40 mg PO daily × 10 days; ★**BMT**★ (if macrolide allergy or failed first line): *bismuth* 30 mL PO QID, *metronidazole* 250 mg PO QID, *tetracycline* 500 mg PO QID × 2 weeks)

GERD—lifestyle changes (avoid coffee, alcohol, chocolate, high-fat meals, acidic or spicy foods. More frequent, smaller portions, exercise/weight loss, smoking cessation, elevate head of bed, loose garments). **Antisecretory treatment** (proton pump inhibitors more effective than H2 blockers for esophagitis. Use antacids as breakthrough). **Nissen fundoplication**

NON-ULCER DYSPEPSIA—lifestyle changes (avoid alcohol, caffeine, tobacco). **Antisecretory treatment** (see above). ***H. pylori* eradication** (may or may not relieve symptoms). **Promotility agent** (domperidone)

Related Topics
Esophageal Cancer (p. 215)
Gastric Cancer (p. 217)
Gastric Lymphoma (p. 193)

SPECIFIC ENTITIES

GERD

- **CAUSES**—obesity, lower esophageal sphincter pressure (transient relaxation of lower esophageal sphincter), decreased esophageal peristalsis, gastric acid hypersecretion, delayed gastric emptying, anatomic disruption lower esophageal sphincter (hiatal hernia)
- **PATHOPHYSIOLOGY**—reflux of stomach contents, leading to a multitude of symptoms including heartburn, regurgitation, dysphagia, chest pain, complicated by esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma
- **CLINICAL FEATURES**—esophageal (heartburn, regurgitation), extra-esophageal (wheeze, cough, pneumonia, waterbrash, hoarseness, sore throat, globus, dental erosions)

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—clinical based on symptoms (≥2/week). Endoscopy to look for complications and rule out other potential diagnoses

NEJM 2008 359:16

NSAIDS-INDUCED GASTROPATHY

- **PATHOPHYSIOLOGY**—NSAIDs inhibit COX-1 (normally protective effect through mucus secretion, bicarbonate secretion, mucosal circulation) and COX-2 (inducible inflammatory activity, also in kidneys). It also has direct toxic mucosal effect → dose related but even low dose baby ASA may contribute to ulcer formation. Overall ~20% patients on NSAIDs develop ulcers. Risk factors include age >60, preexisting peptic ulcer, multiple NSAIDs, high-dose NSAIDs, concomitant glucocorticoid or anticoagulant therapy
- **TREATMENTS**—primary prophylaxis includes proton pump inhibitor and misoprostol. If ulcer developed while on NSAIDs but must continue, should give proton pump inhibitor

BARRETT'S ESOPHAGUS

- **PATHOPHYSIOLOGY**—prolonged heartburn → intestinal squamous metaplasia (abnormal salmon-colored mucosa extending proximally from the gastroesophageal junction to the normal pale esophageal mucosa) → dysplasia → adenocarcinoma of esophagus and gastric cardia. Barrett's develops in 5–8% of patients with GERD. Transformation to low-grade dysplasia 4%/year, high-grade dysplasia 1%/year and cancer 0.5%/year
- **DIAGNOSIS**—screen with surveillance endoscopy every 2–3 years if age ≥50, white race, male, obese, chronic GERD, or presence of hiatal hernia. Mucosal biopsy after the initial diagnosis of Barrett's esophagus to look for dysplasia. Once diagnosed with Barrett's, endoscopy with biopsy every 3–5 years, 6–12 months if low-grade dysplasia
- **TREATMENTS**—high-grade dysplasia should be evaluated for esophagectomy, endoscopic mucosal resection, or ablative therapy

GASTROPARESIS

- **CAUSES**—systemic diseases (diabetes, scleroderma), drugs (anticholinergic agents, narcotics), idiopathic
- **PATHOPHYSIOLOGY**—impairment of gastric emptying due to dysfunction of the neuromuscular unit → dyspepsia, bloating, nausea, vomiting, and weight loss
- **DIAGNOSIS**—gastric emptying study, barium swallow, gastroscopy

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—frequent, small, low-fat, low-fiber feedings, prokinetic agents (*metoclopramide* 10 mg PO TID ac meals, *erythromycin* 250 mg PO TID ac meals, *domperidone* 10 mg PO QID), nutritional support

NEJM 2007 356:8

HELICOBACTER PYLORI

- **PATHOPHYSIOLOGY**—chronic inflammation → causative role in 50–80% of duodenal ulcers, 40–60% of gastric ulcers, 80% of gastric cancers, and 90% of gastric lymphomas

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—urea breath test (sens 90%, spc 95%. Particularly good in post-treatment setting; testing for eradication should be performed off antibiotic and proton pump inhibitor therapy), serology (sens 90%, spc 80%) is of limited value as it tests for IgG which only indicates previous exposure, endoscopy (culture, histologic assessment, urease testing)
- **TREATMENTS**—see H. PYLORI ERADICATION above

Acute Abdominal Pain

DIFFERENTIAL DIAGNOSIS

GI—peptic ulcer disease, pancreatitis, cholangitis, hepatitis, cholecystitis, inflammatory bowel disease, gastroenteritis, appendicitis, diverticulitis, bowel obstruction (small, large), volvulus
GU—pyelonephritis, renal colic, cystitis, prostatitis, testicular torsion, inguinal hernia
GYNECOLOGIC—ectopic pregnancy, ruptured ovarian cyst, pelvic inflammatory disease, fibroid torsion, endometriosis, endometritis
VASCULAR—acute mesenteric ischemia, ischemic colitis, chronic mesenteric ischemia, abdominal aortic aneurysm rupture
SYSTEMIC—Addison's disease, diabetic ketoacidosis, uremia, hypercalcemia, porphyria, familial Mediterranean fever
OTHERS—myocardial infarction, pneumonia, splenic injury, shingles, musculoskeletal, peritonitis

PATHOPHYSIOLOGY

CAUSES OF ABDOMINAL PAIN—any intra-abdominal organs (e.g. GI, GU, gynecological, spleen) × (ischemia, infection, obstruction, tumors) + systemic causes + referred pain

CLINICAL FEATURES

HISTORY—characterize abdominal pain (onset, location, duration, severity, radiation, aggravating and relieving factors), N&V, bleeding, fever, inquire about last menstrual period and pregnancy if female, past medical history (CAD, diabetes, hypertension, renal stones), past surgical history (abdominal adhesions), medication history (analgesics)
PHYSICAL—vitals, respiratory and cardiac examination, abdominal examination, CVA tenderness, pelvic and rectal examination
APPENDICITIS SEQUENCE—vague pain initially located in the epigastric or periumbilical region; anorexia, nausea, or non-sustained vomiting; migration of the initial pain to the RLQ; low-grade fever

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE APPENDICITIS?

	Sens	Spc	LR+	LR–
History				
Migration of pain to RLQ	64%	82%	3.18	0.5
RLQ pain	81%	53%	8.0	0.15
Pain before vomiting	100%	64%	2.76	–
No similar pain previously	81%	41%	1.5	0.32
Physical				
Rigidity	27%	83%	3.76	0.82
Fever	67%	79%	1.94	0.58
Rebound tenderness	63%	69%	3.7	0.4
Psoas sign	16%	95%	2.38	0.90
Obturator sign	–	–	–	–
Rectal exam	–	–	–	–

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR–
Combination of Findings				
Alvarado score ≥7	81%	74%	3.1	0.26

APPROACH—"migration of pain, RLQ pain and pain before vomit suggest appendicitis. Rigidity, positive psoas sign, fever and rebound tenderness increase likelihood of appendicitis. Absence of above and similar pain previously suggest appendicitis is less likely"

JAMA 1996 276:19

UPDATE—The Alvarado score (MANTRELS–**M**igration, **A**norexia-acetone, **Nausea-Vomiting**, **T**enderness RLQ [2 points], **R**ebound pain, **E**levation of temperature, **L**eukocytosis [2 points], **L**eft shift) is a user-friendly and powerful tool for assessing likelihood of acute appendicitis

The Rational Clinical Examination. McGraw-Hill, 2009

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PERITONITIS, SMALL BOWEL OBSTRUCTION, AND ABDOMINAL WALL PAIN

- **PERITONITIS**—rigidity (LR+ 5.1), guarding (LR+ 2.0), rebound tenderness (LR+ 2.0), positive cough test (LR+ 2.0). Other special tests include Rovsing's sign, psoas sign (flexion of hip against resistance increases abdominal pain), obturator sign (internal rotation of hip increases abdominal pain), and rectal/pelvic examination
- **SMALL BOWEL OBSTRUCTION**—visible peristalsis (LR+ 18.8), absent/tinkling/high-pitched bowel sounds (LR+ 5.0), abdominal bloating
- **ABDOMINAL WALL PAIN**—Carnett's test (palpate area of most intense tenderness while patient supine, then palpate again with patient half sitting up. If pain is intra-abdominal, the pain will not increase as tensed rectus muscles protect the underlying viscus)

Related Topic
Acute Pancreatitis (p. 156)

EXAMINATION OF ABDOMINAL MASSES

- **RIGHT UPPER QUADRANT MASS**—**liver** (downward with inspiration, left lobe, bruit/venous hum), **right kidney** (downward with inspiration, ballotable, palpable upper border), **gallbladder** (downward with inspiration, smooth and regular), **colon or gastroduodenal** (does not move with inspiration, ill-defined mass, high-pitch bowel sounds), **lymphoma** (does not move with inspiration, usually more central)

CLINICAL FEATURES (CONT'D)

- **LEFT UPPER QUADRANT MASS**—**spleen** (downward and medially with inspiration, notch, bruit), **left kidney** (downward with inspiration, ballotable, palpable upper border), **colon** (splenic flexure), **gastric or pancreatic** (ill-defined mass, difficult to clearly differentiate these masses on examination), **lymphoma** (does not move with inspiration, usually more central)
- **RIGHT LOWER QUADRANT MASS**—**colon, distal small bowel, or appendix** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)
- **LEFT LOWER QUADRANT MASS**—**colon, distal small bowel** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, lipase, amylase, lactate, INR, PTT, Ca, albumin, urinalysis, urine βhCG (if ♀ of reproductive age)
- **MICROBIOLOGY**—urine C&S, stool C&S
- **IMAGING**—CXR, AXR, US abd/pelvic

SPECIAL

- **IMAGING**—IVP, barium contrast, CT abd
- **ECG**—if suspect cardiac involvement
- **ENDOSCOPY**

DIAGNOSTIC ISSUES

APPROACH TO ABDOMINAL X-RAYS

- **FREE AIR**—pneumoperitoneum suggests perforation. Look for free air under right diaphragm on CXR view or R lateral decubitus view. On supine abd view, look for outline of bowel wall (normally can only see inside of lumen. If outside of bowel wall also seen, free air present)
- **SMALL BOWEL**—more central location, valvulae closer together, thin and cross completely. Dilated if >3 cm [1.2 in.], multiple air fluid levels suggest small bowel obstruction
- **LARGE BOWEL**—more peripheral location, colonic haustra wider apart, thick, and cross part way. Normally some air–fluid levels in ascending colon. Dilated if >5 cm [2 in.]. Thumb printing (mural edema) and dilated bowel suggest toxic megacolon. Check for air in bowel wall (pneumatosis intestinalis)
- **STOOL IN BOWEL**—cannot distinguish from abscess
- **KIDNEYS**—ureter runs along transverse processes. May see calculi along tract. If see kidney outline, suggests pneumoretroperitoneum
- **PSOAS**—air around psoas suggests perforated retroperitoneal structures (rectum, duodenum). Lack of psoas outline suggests retroperitoneal inflammation (decreased fat)
- **BILIARY STRUCTURES**—common bile duct up to 6 mm in size. Check for air in portal vein or common bile duct (bowel infarction)
- **OTHER STRUCTURES**—liver, spleen, bones

MANAGEMENT

ACUTE—ABC, O_2, IV hydration. **NPO**, NG if severe N&V/obstruction. ***Morphine*** 2.5–5 mg SC q3–4 h PRN and 1–2.5 mg IV q1h PRN. ***Dimenhydrinate*** 50 mg IM/IV q4h PRN

TREAT UNDERLYING CAUSE—early surgical consult if peritonitis. Empiric antibiotics if fever or suspect peritonitis (*ceftriaxone* 1 g IV q24h plus *metronidazole* 500 mg IV q8h, or *piperacillin-tazobactam* 3.375 g IV q6h, or *ciprofloxacin* 400 mg IV q12h plus *metronidazole* 500 mg IV q8h, or *meropenem* 1 g IV q8h)

SPECIFIC ENTITIES

GALLSTONE DISEASE SPECTRUM—asymptomatic (70%), biliary colic (20%, intermittent obstruction), acute cholecystitis (cystic duct obstruction), choledocholithiasis (common bile duct obstruction), ascending cholangitis (stasis and infection of biliary tract; may be secondary to choledocholithiasis; see p. 156 for more details), gallstone pancreatitis (pancreatic duct obstruction), gallstone ileus, gallbladder cancer

SPECIFIC ENTITIES (CONT'D)

ACUTE CHOLECYSTITIS

- **PATHOPHYSIOLOGY**—abnormalities of bile acid secretion, mucus generation, and gallbladder motility → gallstone formation → migrate to obstruct the cystic duct and even common bile duct/pancreatic duct → gallbladder inflammation and sometimes secondary infection → gallbladder necrosis and gangrene with perforation in severe cases. Risk factors include older age, obesity, fertility, women (i.e. **f**orty, **f**at, **f**ertile, **f**emale), ethnicity (Aboriginal, Hispanic), TPN, and rapid weight loss

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ACUTE CHOLECYSTITIS?

HISTORY—RUQ pain, N&V, anorexia, fever

PHYSICAL—Murphy sign (arrest of inspiration while palpating the gallbladder during a deep breath), guarding, rigidity, RUQ mass, rebound, rectal tenderness

	Sens	Spc	LR+	LR–
Murphy sign	65%	87%	2.8	0.5
RUQ tenderness	77%	54%	1.6	0.4
Bedside US with gallstones and positive sonographic Murphy sign	–	–	2.7	0.13

INVESTIGATIONS—leukocytosis, ALP >120 U/L, elevated ALT or AST, elevated bilirubin

APPROACH—"no single clinical finding or laboratory test carries sufficient weight to establish or exclude cholecystitis without further testing (i.e. ultrasound). Clinical gestalt (without ultrasound) is estimated to have LR+ 25–30, bringing the probability of cholecystitis from 5% pretest to 60% post test. The evaluation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on clinical gestalt and diagnostic imaging"

JAMA 2003 289:1

UPDATE—clinicians with training and experience in bedside ultrasound can visualize the gallbladder in most patients. For patients with low pretest probability of cholecystitis and definitively negative bedside ultrasound, formal ultrasound may not be required.

The Rational Clinical Examination. McGraw-Hill, 2009

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—US abd, endoscopic US, ERCP, percutaneous transhepatic cholangiography, MRCP, HIDA/DISIDA cholescintigraphy (acalculous cholecystitis), CT abd
- **TREATMENTS**—supportive measures include NPO, IV fluids, pain control (NSAIDs, opioids), antiemetics and antibiotics (*ceftriaxone* 1 g IV q24h plus *metronidazole* 500 mg IV q8h, or *piperacillin-tazobactam* 3.375 g IV q6h, or *ciprofloxacin* 400 mg IV q12h plus *metronidazole* 500 mg IV q8h, or *meropenem* 1 g IV q8h). Cholecystectomy (laparoscopic, open) or percutaneous cholecystostomy to facilitate drainage (if non-operative because of high risk). If biliary pain despite cholecystectomy, consider possibility of a retained common bile duct stone, sphincter of Oddi dysfunction, or functional pain

NEJM 2008 358:26

ACUTE MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—embolism in the celiac or superior mesenteric artery from valvular heart disease or atrial fibrillation, thrombosis, or shock (low flow state) → sudden and severe periumbilical pain out of proportion with physical findings, N&V, leukocytosis, ↑ lactate, ileus

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—high clinical suspicion, CT abd (+ contrast). Angiography gold standard
- **TREATMENTS**—IV fluids, immediate surgery, anticoagulation if mesenteric arterial embolism or mesenteric venous thrombosis

ISCHEMIC COLITIS

- **PATHOPHYSIOLOGY**—low-flow state in the mesentery affecting mainly the "watershed" area of the middle colic and inferior mesenteric arteries → hematochezia, diarrhea, abdominal pain
- **DIAGNOSIS**—AXR ("thumbprinting" or edematous haustral folds), CT (focal or segmental bowel wall thickening or intestinal pneumatosis with portal vein gas), colonoscopy, laparoscopy
- **TREATMENTS**—supportive (hydration), antibiotics

CHRONIC MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—↓ blood flow from atherosclerosis of the proximal mesenteric vessels → intestinal angina with post-prandial abdominal pain → fear of eating, extensive weight loss
- **DIAGNOSIS**—CT abdomen/pelvis (initial), mesenteric duplex US (sens 90% for stenosis of >50%), CT angiography
- **TREATMENTS**—angioplasty, surgical revascularization, management of vascular risk factors

Upper GI Bleed — NEJM 2008 359:9

DIFFERENTIAL DIAGNOSIS

PEPTIC ULCER DISEASE (PUD)—gastric, duodenum
INFLAMMATION—**esophagitis** (CMV, medications), **gastritis** (acute, chronic), **inflammatory bowel disease** (Crohn's)
VARICES—esophagus, stomach
TUMORS—esophagus, stomach, duodenum
STRUCTURAL—Mallory–Weiss tear, Boerhaave's syndrome, Dieulafoy's lesion, arteriovenous malformation, aortoduodenal fistula, hemobilia
OTHERS—epistaxis, hemoptysis

CLINICAL FEATURES

HISTORY—volume of hematemesis, melena, and hematochezia, vomiting, past medical history

CLINICAL FEATURES (CONT'D)

(PUD, *H. pylori* infection, alcohol-related disorders, liver cirrhosis with varices, renal failure, metastatic cancer, heart disease/HF), medication history (anticoagulants, NSAIDs)
PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), cirrhosis (facial telangiectasia, palmar erythema, spider angiomas, gynecomastia, abdominal wall veins, Terry's nails/leukonychia, peripheral edema). Perform a rectal examination and test for fecal occult blood. Examine vomitus or nasogastric aspirate and test for occult blood
BLACK STOOL THAT MAY MIMIC MELENA—bismuth subsalicylate, iron, spinach, charcoal

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A SEVERE UPPER GASTROINTESTINAL BLEED?

	LR+	LR–
Clinical Factors Distinguishing UGIB vs. LGIB		
Prior history of UGIB	6.2	0.81
Age <50 years	3.5	0.80
Cirrhosis	3.1	0.97
History of melena	5.1–5.9	0.06–0.27
Melenic stool on examination	25	0.52
Nasogastric lavage with blood or coffee grounds	9.6	0.58
Clots in stool	0.05	1.2
Serum urea nitrogen:creatinine ratio >30	7.5	0.53
Clinical Factors Determining Need for Urgent Evaluation of UGIB		
History of malignancy or cirrhosis	3.7	0.83
Cirrhosis	3.2	0.89
Syncope	3.0	0.95
Pulse rate >100/min	4.9	0.34
Nasogastric lavage with red blood	3.1	0.32
Hemoglobin level <8 g/dL	4.5–6.2	0.36–0.41
Serum urea nitrogen >90 mg/dL	3.6	0.45
Blatchford score = 0	1.2	0.02

BLATCHFORD SCORE: determined by blood urea, hemoglobin, systolic blood pressure, pulse > 99 beats/min, presentation with melena, presentation with syncope, hepatic disease, cardiac failure

APPROACH—"tachycardia (pulse rate of >100/min; LR, 4.9), a history of cirrhosis or malignancy (LR+ 3.7), hemoglobin level of less than 8 g/dL (LR+ range, 4.5-6.2), or a nasogastric lavage with red blood (LR+ 3.1) increase the likelihood of severe bleeding. All patients with a UGIB should have a Blatchford score, which does not require a nasogastric lavage, to help assess the severity (Blatchford score = 0; LR- 0.02 for identifying patients requiring urgent evaluation). When negative, prediction rules combining symptoms, signs, and routine laboratory test results almost definitively rule out severe UGIB, thereby identifying at least some patients who can be safely evaluated as an outpatient"

JAMA 2012 307:10

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HYPOVOLEMIC? HYPOVOLEMIA DUE TO ACUTE BLOOD LOSS

	Sens	Spc
For moderate blood loss		
Postural pulse increment ≥30/min or severe postural dizzines	22%	–
Postural hypotension ≥20 mmHg SBP drop	9%	94%
Supine tachycardia	0%	96%
Supine hypotension	13%	97%
For large blood loss		
Postural pulse increment ≥30/min or severe postural dizziness	97%	98%
Supine tachycardia	12%	96%
Supine hypotension	33%	97%

NOTE: postural change is measured first with supine vitals counting pulse for 30 s (after waiting 2 min), then standing vitals (after waiting 1 min)

JAMA 1999 281:11

Related Topic
Shock (p. 108)

CLINICAL FEATURES (CONT'D)

HYPOVOLEMIA DUE TO VOMITING, DIARRHEA, DECREASED INTAKE, DIURETICS

	Sens	Spc	LR+	LR–
Symptoms				
Postural pulse increment ≥30/min	43%	75%	1.71	0.8
Postural hypotension ≥20 mmHg	29%	81%	1.5	0.9
Dry axilla	50%	82%	2.8	0.6
Dry oral/nasal mucous membrane	85%	58%	2.0	0.3
Dry tongue	59%	73%	2.1	0.6
Tongue with furrows	85%	58%	2.0	0.3
Sunken eyes	62%	82%	3.4	0.5
Confusion	57%	73%	2.1	0.6
Upper/lower extremity weakness	43%	82%	2.3	0.7
Speech not clear or expressive	56%	82%	3.1	0.5
Capillary refill time > normal	34%	95%	6.9	0.7

APPROACH—"for patients with suspected acute blood loss, severe postural dizziness (preventing upright vitals measurements) or postural pulse increment are predictive. Postural hypotension has no incremental value. For patients with suspected hypovolemia not due to blood loss, severe postural dizziness, postural pulse increment, or dry axilla can be helpful. Moist mucous membranes and tongue without furrows argue against it. Capillary refill time and poor skin turgor have no proven diagnostic value"

JAMA 1999 281:11

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/cross-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin, fecal occult blood
- **IMAGING**—CXR, AXR
- **GASTROSCOPY**

PROGNOSTIC ISSUES

RISK STRATIFICATION FOR PEPTIC ULCER DISEASE

- **CLINICAL ROCKALL SCORING**—age 60–79 = 1; age ≥80 = 2; heart rate >100 beats/min = 1; systolic BP <100 mmHg = 2; co-existing illnesses (ischemic heart disease, HF, other major illness) = 2; co-existing illnesses (renal failure, hepatic failure, metastatic cancer) = 3
- **COMPLETE ROCKALL SCORING**—in addition to clinical Rockall score, add the following based on endoscopic findings: no lesion observed, Mallory–Weiss tear = 0; peptic ulcer, erosive disease, esophagitis = 1; cancer of upper GI tract = 2; clean base ulcer, flat pigmented spot = 0; blood in upper GI tract, active bleeding, visible vessel, clot = 2
- **INTERPRETATION**—low risk for bleeding or death = clinical Rockall score 0 or complete Rockall score ≤2

PROGNOSTIC ISSUES (CONT'D)

RISK OF ULCER RE-BLEED

- **HIGH-RISK FEATURES**—active spurting/oozing during endoscopy (90% chance), non-bleeding visible vessel (50% chance), adherent clot (25–30% chance). If none of above factors and clinically not severe bleed, very low chance of rebleed and may consider discharging shortly after. Other factors include size and location of ulcer
- **LOW-RISK FEATURES**—flat spot (10% chance), clean ulcer base (3–5% chance)

MANAGEMENT

ACUTE—**ABC**, O_2, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hemoglobin <70 g/L [<7 g/dL], platelets $<50 \times 10^9$). NPO, consider NG tube. **Hold** antihypertensive and diuretic therapy. If prolonged PT/PTT, ***vitamin K*** 10 mg IV (small risk of anaphylaxis) and ***FFP*** 2–4 U IV or ***unactivated prothrombin complex concentrates (PCC)*** 1000–3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on heparin, consider ***protamine*** infusion (1 mg antagonizes 100 U of heparin—beware of excessive protamine which can cause paradoxical coagulopathy). If suspect varices, ***octreotide*** 50 μg IV bolus, then 25–50 μg/h. ***Pantoprazole*** 80 mg IV bolus, then 8 mg/h until endoscopy. If cirrhosis and acute variceal hemorrhage, **transfuse** platelet and FFP PRN, antibiotics for 7 days (*ceftriaxone*

MANAGEMENT (CONT'D)

1 g IV q24h, *cefotaxime* 1 g IV q8h, *ciprofloxacin* 400 mg IV q12h, *ciprofloxacin* 500 mg PO BID, or *norfloxacin* 400 mg PO BID). **Consult GI** for gastroscopy and consider ***erythromycin*** 250 mg IV 30–90 min before endoscopy for clot lavage

TREAT UNDERLYING CAUSE—**avoid** ASA, NSAIDs. **Peptic ulcer** (endoscopic hemostasis with thermal coagulation/fibrin sealant/endoclips plus 1:10,000 ratio epinephrine injection. After endoscopy, start *pantoprazole* 80 mg IV bolus if not given already, then 8 mg/h × 72 h [if high-risk lesion], switch to 40 mg PO BID × 1 month then daily). **Varices** (endoscopy within 12 h with ligation/band/glue/sclerotherapy → balloon tamponade → transjugular intrahepatic portosystemic shunt (TIPS) → portacaval/distal splenorenal shunt, or liver transplant. Continue octreotide for 3 days. Repeat endoscopy every 2–4 weeks until varices obliterated, then at 1–3 months and again every 6–12 months afterward. Consider non-selective β-blocker such as *nadolol* 40–80 mg PO daily or *propranolol* 20 mg PO BID. **Mallory–Weiss tear** (*omeprazole* 20 mg PO daily). ***H. pylori*** eradication (see DYSPEPSIA p. 125 for treatment). **Intractable or recurrent bleed** (consult surgery. See TREATMENT ISSUES below)

MANAGEMENT (CONT'D)

TREATMENT ISSUES

CRITERIA FOR SURGICAL CONSULT FOR ULCER BLEED—hemodynamic instability despite resuscitation (>3 U PRBC), shock, recurrent hemorrhage after two endoscopic attempts, continued slow bleed requiring >3 U PRBC/day), high-risk endoscopic lesion

COMPLICATIONS OF ENDOSCOPY—perforations, bleeding, sedation-related respiratory failure

DISCHARGE DECISIONS FOR PATIENTS' PEPTIC ULCER DISEASE—patients with low-risk of rebleed (complete Rockall score ≤2, low risk endoscopic features), with Hb >80–100 g/L [>8–10 g/dL] without further need of transfusions, normal INR/PTT, and have adequate social support may be safely discharged home shortly after endoscopy with follow-up, while patients with high-risk features should be admitted and monitored closely

Lower GI Bleed

DIFFERENTIAL DIAGNOSIS

UPPER GI SOURCE WITH BRISK BLEEDING (10%)

INFECTIOUS—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* (EHEC, EIEC), *C. difficile*, *Amoeba*

TUMORS—colorectal cancer, small bowel cancer, polyp

INFLAMMATORY—inflammatory bowel disease (IBD)

ISCHEMIC—ischemic colitis

STRUCTURAL—angiodysplasia, diverticulosis, radiation colitis, hemorrhoids, anal fissure, intussusception, Meckel's diverticulum

CLINICAL FEATURES

HISTORY—volume of bleed, melena, abdominal pain, past medical history (IBD, cancer, diverticulosis), medication history (anticoagulants, antiplatelet drugs, NSAIDs)

PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), abdominal tenderness. Perform a rectal examination and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/X-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- **MICROBIOLOGY**—stool C&S, fecal occult blood
- **ENDOSCOPY**—colonoscopy, gastroscopy

SPECIAL

- **IMAGING**—for obscure bleed, consider ^{99}Tc RBC scan (detects 0.1 mL/min), angiography (detects 0.5 mL/min), capsule endoscopy, push enteroscopy, double balloon enteroscopy, MR enterography and/or Meckel's scan

DIAGNOSTIC ISSUES

OCCULT BLEED—no obvious melena or bright red blood per rectum (BRBPR), but possible bleed as fecal occult blood or fecal immunochemical test positive

OBSCURE BLEED—obvious bleeding but source cannot be found

OVERALL APPROACH—gastroscopy and/or colonoscopy (start with the end with the most likely source of bleed, then scope the other end if no yield) → if negative, repeat panendoscopy → if negative, small bowel

DIAGNOSTIC ISSUES (CONT'D)

follow-through → if negative, consider angiography, RBC scan, capsule, push or double balloon endoscopy, or laparotomy

MANAGEMENT

ACUTE—ABC, O_2, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hemoglobin <70 g/L [<7 g/dL], platelets $<50 \times 10^9$/L). NPO. **Hold** antihypertensive and diuretic therapy. If prolonged

MANAGEMENT (CONT'D)

PT/PTT, ***vitamin K*** 10 mg IV (small risk of anaphylaxis) [see above comment for UGIB] and ***FFP*** 2–4 U IV or ***unactivated prothrombin complex concentrates (PCC)*** 1000–3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on unfractionated heparin, ***protamine*** infusion (1 mg antagonizes 100 U of heparin). **Consult GI** for endoscopy

TREAT UNDERLYING CAUSE

Inflammatory Bowel Disease Exacerbation

DIFFERENTIAL DIAGNOSIS

SEE DIFFERENTIAL DIAGNOSIS FOR ACUTE ABDOMINAL PAIN (p. 128) **LOWER GI BLEED** (p. 134) and **CHRONIC DIARRHEA** (p. 138)

PATHOPHYSIOLOGY

TYPES

- **CROHN'S—mild to moderate** (relatively asymptomatic, tolerating oral diet), **moderate to severe** (failed treatment for mild disease, symptomatic), **severe to fulminant** (failed steroid treatment, very symptomatic)
- **ULCERATIVE COLITIS—ulcerative proctitis** (limited to rectum), **distal colitis/protosigmoiditis** (extending up to mid-sigmoid colon), **left-sided colitis** (extending up to splenic flexure), **extensive colitis** (extending up to but not including cecum), **pancolitis** (extending up to cecum)

CLINICAL FEATURES

EXTRAINTESTINAL MANIFESTATIONS—fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's only), arthritis (spondylitis; type I arthropathy: pauciarticular and related to IBD activity; type II arthropathy: polyarticular and unrelated to IBD activity), erythema nodosum, pyoderma gangrenosum, DVT, amyloidosis

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN CROHN'S DISEASE AND ULCERATIVE COLITIS

	Crohn's disease	Ulcerative colitis
Degree of involvement	Segmental ("skip lesions") Rectal sparing	Continuous
Symptoms	Abd pain Diarrhea Anorexia Perianal disease	Bloody diarrhea Tenesmus Fever
Serology	Anti-*Saccharomyces cerevisiae* IgG antibody (sens 77%, spec 92%, PPV 82%)	p-ANCA (sens 70%, spc 88%, PPV 75%)
Pathology	Transmural granuloma	Mucosal inflammation No granulomas
Complications	Obstruction Strictures Fistulas Fissures Abscesses Colorectal cancer	Toxic megacolon (1–2%) Colorectal cancer (1%/year after 10 years)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR, CRP, Fe, TIBC, ferritin, % sat, AST, ALT, ALP, bilirubin, albumin, Ca, Mg, PO_4, vitamin B12, folate, fecal calprotectin, fecal lactoferrin
- **MICROBIOLOGY**—stool C&S, fecal occult blood, stool for *C. difficile* toxin assay
- **SEROLOGY**—antineutrophil cytoplasmic antibodies (pANCA), anti-*Saccharomyces cerevisiae* antibodies (ASCA)
- **IMAGING**—AXR, CT/MR enterography, contrast-enhanced US
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy, double-balloon enteroscopy

MANAGEMENT

SUPPORTIVE THERAPY

- **DIET AND NUTRITION**—if mild, low-fiber diet, elemental diet; if severe, TPN and bowel rest
- **ANTIDIARRHEAL AGENTS**—contraindicated in severe exacerbation and toxic megacolon

ANTIINFLAMMATORY AGENTS

- **5ASA SUPPOSITORIES**—if localized (i.e. rectal/left-sided) disease. *Mesalamine* 1 g PR qhs, glucocorticoid enema/suppositories daily-BID
- **SYSTEMIC 5ASA**—for induction and maintenance (*sulfasalazine* induction 0.5 g PO BID, then titrate to 0.5–1.5 g PO QID, maintenance 1 g PO BID–QID; *mesalamine* 800–1600 mg PO TID maintenance 400–800 mg PO TID; *olsalazine*)
- **GLUCOCORTICOIDS**—for flares (*methylprednisolone* 30 mg IV BID, *prednisone* 50 mg PO daily, reduce by 5 mg/week)
- **IMMUNOSUPPRESSIVE AGENTS**—*azathioprine* 50 mg PO daily, increase by 25 mg daily every 2 weeks to a max of 2–2.5 mg/kg/day as tolerated (monitor CBC, liver enzymes), *methotrexate* 25 mg IM weekly
- **ANTIBIOTICS**—*metronidazole* 500 mg PO TID, *ciprofloxacin* 500 mg PO BID
- **BIOLOGICAL AGENTS**—*infliximab* IV infusions of 5 mg/kg at 0, 2, 6 weeks, followed by 5–10 mg/kg every 8 weeks for maintenance; or *adalimumab* 160 mg SC initially then 80 mg SC at 2 weeks, 40 mg SC at 4 weeks, followed by 40 mg SC every other week for maintenance. Drug coverage for anti-TNF therapy differs between Canadian provinces

MANAGEMENT (CONT'D)

SURGERY

Related Topics
Clostridium difficile Colitis (p. 137)
Inflammatory Arthritis (p. 321)

TREATMENT ISSUES

CROHN'S COLITIS

- **STEPWISE TREATMENT**—oral 5ASA or sulfasalazine for 3–4 weeks. If failed, add metronidazole and ciprofloxacin. If failed, add oral steroids for 4 weeks. If failed, consider immunosuppressive therapy. Consider metronidazole and ciprofloxacin, biologic therapy for treatment of perianal fistula

ULCERATIVE COLITIS

- **ULCERATIVE PROCTITIS**—5ASA suppositories or enemas for 2–4 weeks for active treatment. If failed, add steroid foams. Consider oral 5ASA if patient cannot tolerate suppositories. Maintenance therapy may be required
- **DISTAL COLITIS/PROTOSIGMOIDITIS AND LEFT-SIDED COLITIS**—similar treatment to ulcerative proctitis, push to maximal dose if necessary. If failed, add budesonide enemas. If failed, add oral prednisone. Maintenance therapy is recommended
- **EXTENSIVE AND PANCOLITIS** (mild-moderate)—oral 5ASA or sulfasalazine, plus topical 5ASA or steroid enemas. Add oral prednisone if failed or severe symptoms. Maintenance therapy is required
- **EXTENSIVE AND PANCOLITIS** (severe)—hospitalize with bowel rest, hydration, nutrition, parenteral steroids, and adjunctive rectal and oral therapy. Consider adding metronidazole, ciprofloxacin, and infliximab or cyclosporine. May need surgical consult

TOXIC MEGACOLON

- **PATHOPHYSIOLOGY**—a potential complication of inflammatory bowel disease, infectious colitis (*C. difficile*, other inflammatory organisms), ischemic colitis, and obstructive colon cancer
- **CLINICAL FEATURES**—the combination of abdominal distension and diarrhea (may be bloody) should prompt investigations for toxic megacolon. Patient usually toxic with fever, hypotension, delirium, and abdominal pain

TREATMENT ISSUES (CONT'D)

- **DIAGNOSIS**—**dilated colon on X-ray** (usually transverse or right colon, >6 cm), plus **three of the following** (fever >38 °C [100.4 °F], tachycardia >120/min, leukocytosis $>10.5 \times 10^9$/L, anemia), plus **one of the following** (dehydration, delirium, electrolyte disturbances, hypotension)
- **TREATMENTS**—supportive therapy (NPO, IV fluids, hold all opioids, antidiarrheal and anticholinergic agents). For IBD-related toxic megacolon, give *hydrocortisone* 100 mg IV q6h and antibiotics (ceftriaxone plus metronidazole). For *C. difficile*-related toxic megacolon, treat aggressively with IV metronidazole and PO/NG vancomycin. Patients with toxic megacolon who do not respond to therapy within 72 h should be considered for colectomy. ICU admission for monitoring. Serial blood tests and AXR daily to assess progress

TREATMENT ISSUES (CONT'D)

Acute Diarrhea NEJM 2004 350:1

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY/INVASIVE (fever, bloody diarrhea, tenesmus)

- **INVASIVE INFECTIONS**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *Vibrio parahaemolyticus*, *Clostridium difficile*, *Entamoeba*
- **INFLAMMATORY**—ulcerative colitis, Crohn's
- **ISCHEMIC COLITIS**
- **RADIATION COLITIS**

NON-INFLAMMATORY

- **NON-INVASIVE INFECTIONS**—**bacterial** (*Vibrio cholera*, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*, *C. difficile*, ETEC, EPEC), **viral** (Rotavirus, norovirus, CMV), **parasites** (*Giardia*, *Cryptosporidium*, *Amoeba*)
- **MEDICATIONS**—antibiotics, laxatives, chemotherapy

PATHOPHYSIOLOGY

DEFINITION OF DIARRHEA—3 bowel movements/day or at least 200 g of stool/day. Acute diarrhea is defined as <2 weeks, whereas chronic diarrhea is defined as ≥2 weeks duration

DIARRHEA AND ASSOCIATED SYNDROMES

- ***SALMONELLA***—may cause septicemia in patients with sickle cell anemia or AIDS
- ***SHIGELLA***—precedes reactive arthritis
- ***CAMPYLOBACTER***—precedes 10–30% of Guillain–Barre syndrome
- ***YERSINIA***—mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis, bacteremia, may mimic appendicitis

DIARRHEA AT VARIOUS SETTINGS

- **COMMUNITY ACQUIRED**—*Salmonella* (prevalence 16/100,000), *Campylobacter* (13/100,000), *Shigella* (10/100,000), *E. coli* O157:H7 (1.7/100,000), *Cryptosporidium* (1.4/100,000)

PATHOPHYSIOLOGY (CONT'D)

- **TRAVELER'S**—ETEC
- **NOSOCOMIAL**—*C. difficile*
- **PERSISTENT DIARRHEA** (>7 days)—*Giardia*, *Isospora belli*, *Cyclospora*, *Cryptosporidium*
- **IMMUNOCOMPROMISED**—*Microsporidia*, MAC, CMV

NATURAL HISTORY—most diarrheal illnesses are self-limited or viral-induced and nearly 50% last <1 day

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contacts, recent food intake, abdominal pain, past medical history (IBD, lactose intolerance), medication history (laxatives, antibiotics), travel history

PHYSICAL—vitals and check for dehydration. Abdominal tenderness. Perform a rectal examination. Inspect stool sample if available

SALMONELLA* AND *CAMPYLOBACTER—although they are classified as inflammatory, patients usually only develop fever and severe diarrhea and not bloody diarrhea

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, lactate
- **MICROBIOLOGY**—stool C&S (sens 1.5–5.6%), O&P, C. diff toxin A + B, viral culture

SPECIAL

- **FECAL TESTING**—fecal leukocytes (inflammatory, sens 73%, spc 84%), fecal lactoferrin (inflammatory, sens 92%, spc 79%), Giardia toxin, fecal occult blood
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy

MANAGEMENT

SYMPTOM CONTROL—IV hydration. Antidiarrheal agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg × 1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—*Shigella, Salmonella, Campylobacter, E. coli* other than EHEC (*ciprofloxacin* 500 mg PO BID × 3 days, *levofloxacin* 500 mg PO daily × 3 days). ***Vibrio cholera*** (*tetracycline* 500 mg PO QID × 3 days, *doxycycline* 300 mg PO × 1 dose, or *azithryomycin* 1 g PO × 1 dose). ***Isospora* and *Cyclospora*** (*trimethoprim–sulfamethoxazole* 160/800 PO BID × 7–10 days). ***C. difficile, Giardia,* and *Entamoeba*** (*metronidazole* 500 mg PO TID × 10 days)

Related Topic
Acute Abdominal Pain (p. 128)

SPECIFIC ENTITIES

ANTIBIOTICS-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS

- **PATHOPHYSIOLOGY**—organisms include *C. difficile* (particularly with clindamycin, cephalosporins, penicillins) and non-*C. difficile* organisms (*Salmonella*, *C. perfringens*, *S. aureus*, *Candida*). Relapse occurs in 20–25% of patients and typically between 3 and 21 days after discontinuation of treatment: 3–5% of patients have more than 6 relapses. Note emergence of virulent *C. difficile* strain NAP-1/027 characterized by increased secretion of toxins A/B, binary toxin production and fluoroquinolone resistance, and associated with increased outbreaks and mortality
- **RISK FACTORS**—onset of diarrhea ≥6 days after the initiation of antibiotic therapy, hospital stay ≥2 weeks, fecal leukocytes, semi-formed stools, cephalosporin use

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—usually watery diarrhea (may be bloody if severe colitis), abdominal pain. In patients with severe *C. difficile* infection, significant leukocytosis, pseudomembranous colitis, toxic megacolon (see p. 135), acute renal failure, and hypotension may develop
- **DIAGNOSIS**—*C. difficile* toxin A/B from stool sample, flexible sigmoidoscopy (pseudomembranous colitis). *C. difficile* toxin levels are usually unnecessary immediately after treatment completion as up to one-third of patients have positive assays despite successful treatment
- **TREATMENTS**—**IV hydration. Discontinue** implicated antibiotics. **Avoid** use of antiperistaltic agents (opiates, loperamide). ***C. difficile* treatment** (*metronidazole* 250 mg PO QID × 10–14 days, *metronidazole* 500 mg PO TID × 10–14 days, or *vancomycin* 125–500 mg PO QID × 10–14 days). For severe cases, consider oral vancomycin as first-line agent. If significant ileus or toxic megacolon, give vancomycin via NG or enema and *add* metronidazole 500 mg IV QID. Avoid repeating stool assays after treatment unless patient has moderate or severe diarrhea. A positive *C. difficile* toxin without significant symptoms should not prompt treatment. For ***C. difficile* recurrence**, consider retreatment with 14-day course and minimize use of other antibiotics. For further recurrences, consider tapering doses of *vancomycin* 125 mg PO QID × 1 week, then BID × 1 week, then daily × 1 week, then every other day × 1 week, then every 3 days × 2 weeks. Alternatives include *vancomycin* 125 mg PO QID in combination with *rifampin* 600 mg BID × 7 days, or *Saccharomyces boulardii* 250 mg PO QID in combination with metronidazole or vancomycin, or *fidaxomicin* 200 mg PO BID × 10 days

NEJM 2002 346:5; NEJM 2008 359:18

Chronic Diarrhea

NEJM 1995 332:11

DIFFERENTIAL DIAGNOSIS

★MISO★

MOTILITY—hyperthyroidism, diabetic neuropathy, bacterial overgrowth, irritable bowel syndrome (IBS), scleroderma

INFLAMMATORY

- **INFECTIONS**—*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *E. coli* (EHEC, EIEC), *C. difficile*, Amoeba

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **INFLAMMATORY**—ulcerative colitis, Crohn's, ischemic, radiation, toxic

SECRETORY

- **INFECTIONS**—Cholera, *Staphylococcus*, *B. cereus*, *C. perfringens*, *E. coli* (ETEC, EPEC), Rotavirus, norovirus, CMV, Giardia, Cryptococcus, Amoeba

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **NEUROENDOCRINE TUMORS**—carcinoid, VIPoma, calcitonin excess, gastrinoma, somatostatinoma
- **MEDICATIONS**—laxatives
- **OTHERS**—bile salt enteropathy, fatty acid induced, collagenous colitis, lymphocytic colitis

OSMOTIC

- **MALDIGESTION/MALABSORPTION**—pancreatic insufficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula
- **MEDICATIONS**—antacids, antibiotics, Mg citrate, Mg hydroxide, lactulose, sorbitol (i.e. "chewing gum diarrhea"), colchicine, metformin

Related Topics
Inflammatory Bowel Disease (p. 135)
Irritable Bowel Syndrome (p. 142)

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contact, abdominal pain, weight loss, past medical history (diabetes, hyperthyroidism, IBS, lactose intolerance, bowel surgery, scleroderma), medication history (laxatives)

PHYSICAL—obtain body weight and inspect stool sample. Abdominal tenderness. Perform a rectal examination and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, albumin, TSH, antitransglutaminase antibody, endomysial antibody
- **MICROBIOLOGY**—stool C&S, O&P, C. diff toxin A + B, Giardia toxin

SPECIAL

- **FECAL TESTING**—fecal leukocytes, fecal fat, fecal lytes, fecal occult blood, stool for phenothalin (laxative abuse), α-1 antitrypsin
- **IMAGING**—SBFT, CT abd
- **ENDOSCOPY**—upper and lower, for biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES

- **INFLAMMATORY**—bloody stool, fecal leukocytes
- **SECRETORY**—fecal osmotic gap <50 mOsm/kg, >500 g of stool with fasting

INVESTIGATION ISSUES (CONT'D)

- **OSMOTIC**—fecal osmotic gap >50 mOsm/kg; <500 g of stool with fasting

FECAL OSMOTIC GAP—280 − 2 × (stool Na + K)

MANAGEMENT

SYMPTOM CONTROL—**hydration** and **nutritional support**. Empiric treatment with **antidiarrheal** agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg × 1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—cholestyramine for bile acid-induced diarrhea

SPECIFIC ENTITIES

CELIAC DISEASE

- **PATHOPHYSIOLOGY**—sensitivity to gluten in **B**arley, **R**ye, **O**at, **W**heat ★**BROW**★ → T-cell-mediated immune reaction to gliadin → intestinal epithelial cell death → villous atrophy, crypt hyperplasia → malabsorption in small bowel. More common in females (2–3:1). Associated with type 1 diabetes, dermatitis herpetiformis (p. 409), IgA deficiency, liver dysfunction, and small bowel lymphoma (especially if no response to celiac diet)
- **CLINICAL FEATURES**—abdominal bloating (especially after inadvertent ingestion of gluten), isolated weight loss, iron-deficiency anemia in the absence of gastrointestinal blood loss, nutritional deficiency, osteoporosis (sometimes osteomalacia), diarrhea (sometimes), liver dysfunction
- **DIAGNOSIS**—antitransglutaminase IgA (sens 94%, spc 99%), antiendomysial IgA, antigliadin IgG (celiac patients with IgA deficiency may not be antitransglutaminase positive). Small bowel biopsy recommended for confirmation of diagnosis (intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and good response to gluten-free diet). HLA DQ2 (~95%) and HLA DQ8 (~5%) may be present (absence of both DQ2/DQ8 makes celiac disease highly unlikely). Once diagnosed, a bone mineral density scan is recommended
- **TREATMENTS**—gluten-free diet lifelong. Steroids, if symptoms persist despite gluten-free diet, and consider workup for enteropathy-associated lymphoma

Malabsorption Syndromes

DIFFERENTIAL DIAGNOSIS

SALIVARY (lipase, amylase; rare cause)—radiation, sicca
STOMACH (intrinsic factor, R factor; rare cause)—pernicious anemia, gastrectomy, vagotomy
HEPATOBILIARY (bile acids; 10% of extracolonic cases)—hepatic failure, cholestasis, biliary obstruction, terminal ileal resection
PANCREAS (lipase, amylase, HCO_3; 90% of extra-colonic causes)—cancer, chronic pancreatitis, cystic fibrosis
SMALL INTESTINE (brush border/enterocytes)—celiac disease, lymphoma, infectious colitis, inflammatory colitis, ischemic colitis, radiation colitis
OTHERS—β-lipoprotein (abetalipoproteinemia), lymphatics (lymphoma)

PATHOPHYSIOLOGY

COMPLICATIONS OF MALNOURISHMENT—infections (sepsis, abscess, pneumonia), poor wound healing, respiratory failure, death

CLINICAL FEATURES

HISTORY—diarrhea (watery, steatorrhea), flatus, abdominal distension, abdominal pain (suggests chronic pancreatitis, Crohn's disease, or pseudo-obstruction as otherwise uncommon in malabsorption), N&V, symptoms in relation to meals (may occur within 90 min of carbohydrate ingestion), anorexia, weight loss, diet, past medical history (type 1 diabetes, celiac disease, IBD, recurrent peptic ulcer disease, previous surgery, psychiatric disorders, alcohol), medications (laxatives, diuretics, illicit drugs)

Related Topics
Cachexia (p. 449)
Celiac Disease (p. 139)
Vitamin B12 Deficiency (p. 459)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT MALNOURISHED?
HISTORY—**weight change** (overall loss in past 6 months, change in past 2 weeks), **dietary intake change** relative to normal (duration, types include suboptimal solid diet, hypocaloric liquids, full liquid diet, starvation), **gastrointestinal symptoms** >**2 weeks** (nausea, vomiting, diarrhea, anorexia), **functional capacity** (duration, working suboptimally, ambulatory, bedridden)
PHYSICAL—**loss of subcutaneous fat** (triceps, chest), **muscle wasting** (quadriceps, deltoids), **swelling** (ankle edema, sacral edema, ascites)

RISK OF MAJOR POSTOPERATIVE COMPLICATIONS BASED ON SUBJECTIVE GLOBAL ASSESSMENT (SGA)

	LR+
Well nourished	
Defined as <5% weight loss or >5% total weight loss but recent gain and improvement in appetite	0.66
Moderately malnourished	
Defined as 5–10% weight loss without recent stabilization or gain, poor dietary intake, and mild (1+) loss of subcutaneous tissue	0.96
Severely malnourished	
Defined as ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting often with edema	4.44

APPROACH—"SGA is an accurate predictor of patients who are at higher risk of developing complications such as infection or poor wound healing"

JAMA 1994 271:1

UPDATE—several markers have been compared to the SGA for predicting malnutrition. Serum albumin <3.0 g/dL increases likelihood of moderate/severe malnutrition (LR + 3.3), but is not specific. A positive simplified Malnutrition Screening Tool (have you lost weight without trying, how much weight have you lost [kg], and have you been eating poorly because of decreased appetite) increases likelihood of malnutrition (LR+ 13)

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- LABS—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, fasting lipid profile, Ca, Mg, PO_4, albumin, pre-albumin,

INVESTIGATIONS (CONT'D)

carotene, Fe, ferritin, antitransglutaminase antibody, vitamin B12, RBC folate
- **IMAGING**—US abd

SPECIAL
- **COLONOSCOPY**—for Crohn's
- **GASTROSCOPY**—for Celiac disease
- **MRCP/ENDOSCOPIC US**—if suspect chronic pancreatitis
- **STOOL FAT**— > 6 g/day suggests steatorrhea
- **D-XYLOSE TEST**—if suspect malabsorption
- **BREATH TEST**—for carbohydrate malabsorption, small bowel bacterial overgrowth and lactose intolerance, including H_2, $^{14}CO_2$, or $^{13}CO_2$
- **ANTIINTRINSIC FACTOR ANTIBODY**—for vitamin B12 deficiency (has replaced historical Schilling test)

MANAGEMENT

SYMPTOM CONTROL—dietician consult. Consider supplemental nutrition

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

MARASMUS SYNDROME—deficiency of calories resulting in stunted growth in children, loss of body fat, and generalized wasting of lean body mass without significant edema

SPECIFIC ENTITIES (CONT'D)

KWASHIORKOR SYNDROME—deficiency of protein with preserved adipose tissue but significant edema, muscle atrophy, and amenorrhea

FAT-SOLUBLE VITAMIN DEFICIENCY ★KADE★
- **VITAMIN K DEFICIENCY**—increased bleeding tendencies
- **VITAMIN A DEFICIENCY**—follicular hyperkeratosis, night blindness
- **VITAMIN D DEFICIENCY**—paresthesia, tetany, weakness, fractures due to osteomalacia
- **VITAMIN E DEFICIENCY**—skeletal myopathy, spinocerebellar ataxia, pigmented retinopathy, and hemolysis

WATER-SOLUBLE VITAMIN DEFICIENCY
- **VITAMIN B1 (THIAMINE) DEFICIENCY**—Wernicke syndrome, Korsakoff syndrome, Leigh's syndrome (subacute necrotizing encephalomyopathy)
- **VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY ★DDDD★**—**D**ermatitis (photosensitive, pigmented, pellagra), **D**iarrhea, **D**ementia, **D**eath
- **VITAMIN B6 (PYRIDOXINE) DEFICIENCY**—cheilosis, painless glossitis, acrodermatitis, angular stomatitis
- **VITAMIN C DEFICIENCY**—scurvy with impaired collagen synthesis leading to ecchymoses, gum bleeding, petechiae, hyperkeratosis, impaired wound healing, arthralgia, weakness, neuropathy, and depression

Constipation NEJM 2003 349:14

DIFFERENTIAL DIAGNOSIS

★DUODENUM★

DIET—low fiber, dehydration

ΨSYCHIATRY—depression, somatization, obsessive compulsive disorder

OBSTRUCTION—cancer, strictures, adhesions

DRUGS—opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids

ENDOCRINE—diabetes, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia

NEUROLOGIC—spinal cord compression/injury, Parkinson's, multiple sclerosis, stroke, autonomic neuropathy (cachexia–anorexia syndrome)

UNKNOWN

MISCELLANEOUS—irritable bowel syndrome (IBS), amyloidosis, scleroderma, immobility

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, Ca, Mg
- **IMAGING**—AXR

DIAGNOSTIC ISSUES

CONSTIPATION SCORE—based on flat abdominal X-ray. Divide into four quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount of stool in each quadrant from 0–3. A total score >6/12 suggests constipation

MANAGEMENT

LIFESTYLE CHANGES—wheat **bran**, high-bran cereals, ***psyllium/Metamucil*** 2–3 teaspoon/day, **exercise**, **hydration** (8–10 glasses/day)

SYMPTOM CONTROL—**laxatives** (in order of increasing potency: *docusate* 100–240 mg PO

MANAGEMENT (CONT'D)

daily-QID, *senna* 1–4 tabs PO daily-QID, *milk of magnesia* 15–30 mL PO BID, *sorbitol* 15–30 mL PO daily-BID, *lactulose* 15–60 mL PO daily, *magnesium citrate* 150–300 mL PO daily, *bisacodyl/dulcolax suppositories* 1 PR PRN, *tap water enema* 500 mL PR PRN, *mineral oil enema* 100–250 mL PR PRN, *polyethylene glycol electrolyte solution [PEG]* 250–4000 mL PO PRN). **Manual disimpaction**. For patients with spinal cord injury, it is important to use rectal measures (enemas, suppositories) as significant diarrhea/leakage could occur with oral medications alone

TREAT UNDERLYING CAUSE—stop potentially constipation-causing medications if possible

SPECIFIC ENTITIES

IRRITABLE BOWEL SYNDROME (IBS)

- **PATHOPHYSIOLOGY**—heightened response to noxious visceral stimuli, such as balloon distention of the rectum and sigmoid colon
- **CLINICAL FEATURES**—Rome criteria define IBS as >3 months of abdominal pain relieved with defecation, associated with a change in the frequency or consistency of stool, plus two of the following for >25% of days: disturbed defecation (>3 bowel movements/day or <3 bowel movements/week), altered stool formation, altered stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, bloating, or feeling of abdominal distention

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: WILL THE HISTORY AND PHYSICAL EXAMINATION HELP ESTABLISH THAT IRRITABLE BOWEL SYNDROME IS CAUSING THIS PATIENT'S LOWER GASTROINTESTINAL TRACT SYMPTOMS?

MANNING CRITERIA—abdominal pain relieved by defecation, more frequent stools with onset of pain, looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, patientreported visible abdominal distension

ROME I CRITERIA—abdominal pain or discomfort relieved with defecation or associated with a change in stool frequency or consistency for ≥3 months, plus ≥2 of the following on at least 25% of occasions or days: (1) altered stool frequency, (2) altered stool form, (3) altered stool passage, (4) passage of mucus per rectum, (5) bloating or distension

KRUIS MODEL—a computer model based on a number of symptoms and signs. Symptoms include (1) abdominal pain, flatulence, or bowel irregularity for >2 years; (2) description of abdominal pain as "burning, cutting, very strong, terrible, feeling of pressure, dull, boring, or not so bad"; and (3) alternating constipation and diarrhea. Signs include (1) abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS, (2) ESR >10 mm/h, (3) leukocytosis $>10\times10^9$/L, (4) hemoglobin <120 g/L [<12 g/dL] for females or <140 g/L [<14 g/dL] for males, (5) impression by the physician that the patient's history suggests blood in the stool

	Sens	Spc	LR+	LR–
Symptoms				
Lower abd pain	90%	32%	1.3	0.29
Passage of mucus	45%	65%	1.2	0.88
Feeling of incomplete evacuation	74%	45%	1.3	0.62
Looser stools at onset of pain	59%	73%	2.1	0.59
More frequent stools at onset of pain	53%	72%	1.9	0.67
Pain relieved by defecation	60%	66%	1.8	0.62
Patient reported visible abdominal distension	39%	77%	1.7	0.79
Diagnostic criteria				
Manning criteria	78%	72%	2.9	0.29
Rome I criteria	71%	85%	4.8	0.34
Kruis system	77%	89%	8.6	0.26

APPROACH—"absence of abdominal pain reduced the likelihood of IBS. Overall, individual symptoms have limited accuracy for diagnosing IBS in patients referred with lower GI symptoms. The accuracy of the Manning criteria, Rome I criteria and Kruis scoring system were only modest"

JAMA 2008 300:15

Related Topics
Acute Abdominal Pain (p. 128)
Constipation in the Palliative Setting (p. 448)
Nausea and Vomiting (p. 123)
Opioid Use (p. 443)

SPECIFIC ENTITIES (CONT'D)

- **ASSOCIATIONS**—patients with IBS are more likely to have functional dyspepsia, urinary symptoms, dysmenorrhea, dyspareunia, sexual dysfunction, proctalgia fugax, a history of physical or sexual abuse, and fibromyalgia
- **DIAGNOSIS**—IBS is a diagnosis of exclusion. Consider flexible sigmoidoscopy/colonoscopy, evaluation for celiac sprue (p. 139), and stool cultures to rule out other diseases

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—reassurance, stress reduction, fiber supplementation. For constipation-prone IBS, consider osmotic laxatives (first-line), and *linaclotide* 290 μg PO daily (for persistent constipation). For diarrhea-prone IBS, consider *loperamide* 2–4 mg PO daily (first-line), and *alosetron* 0.5–1 mg PO BID × 12 weeks (for ♀ with severe diarrhea; 5HT3 antagonist). For abdominal pain, consider antispasmodics (*hyoscyamine* 0.125–0.25 mg PO q4–6 h PRN), TCAs (*amitriptyline* 10–75 mg qhs), *desipramine* 25–150 mg PO daily, and SSRIs for abdominal pain. Cognitive behavioral therapy may also be useful

NEJM 2008 358:16

Acute Liver Failure

DIFFERENTIAL DIAGNOSIS

HEPATOCELLULAR INJURY PATTERN (↑↑ AST/ALT ± ↑ ALP/bili)

- **INFECTIOUS**—HAV, HBV, HCV (rare), HDV, HEV, EBV, CMV, HSV, VZV, schistosomiasis, toxoplasmosis, bacterial cholangitis
- **FATTY LIVER**—alcoholic, non-alcoholic steatohepatitis (NASH)
- **TOXIC**—acetaminophen, NSAIDs, amiodarone, labetalol, statins, phenytoin, valproic acid, fluoroquinolones, amoxicillin/clavulanate, sulfonamides, tetracyclines, isoniazid, azoles, halothane, glyburide, propylthiouracil, Amanita phalloides mushroom, heavy metals, anabolic steroids, cocaine, ecstasy, phencyclidine
- **VASCULAR**—ischemic ("shock liver"), Budd–Chiari, congestive, venoocclusive disease (BMT, chemotherapy, OCP)
- **NEOPLASTIC**—hepatoma
- **AUTOIMMUNE**—autoimmune hepatitis
- **HEREDITARY**—Wilson's, hemochromatosis, α1-antitrypsin deficiency, glycogen storage disease
- **PREGNANCY**—acute fatty liver of pregnancy, HELLP
- **OTHERS**—liver surgery, Reye's syndrome with viral illness, and ASA use
- **NON-HEPATIC**—celiac sprue, adrenal insufficiency, myopathy, strenuous exercise

CHOLESTATIC PATTERN (↑↑ ALP/bilirubin ± ↑ AST/ALT)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **BACTERIAL CHOLANGITIS**
- **BILIARY EPITHELIAL DAMAGE**—hepatitis, cirrhosis, biliary colic
- **INTRAHEPATIC CHOLESTASIS**—sepsis, drugs (amoxicillin–clavulanate, erythromycin, trimethoprim–sulfamethoxazole, indinavir, nevirapine, allopurinol, carbamazepine, captopril, chlorpromazine, diltiazem, estrogens, fluphenazine, gold, imipramine), TPN, primary biliary cirrhosis
- **BILIARY DUCTAL OBSTRUCTION**—choledocholithiasis, pancreatic cancer, cholangiocarcinoma, pancreatitis, primary sclerosing cholangitis

INFILTRATIVE PATTERN (↑↑ ALP with ↑ GGT ± ↑ bili/AST/ALT)

- **INFECTIOUS**—TB, histoplasmosis, abscess (bacterial, amoebic)
- **NEOPLASM**—hepatoma, lymphoma
- **GRANULOMATOUS DISEASE**—sarcoidosis, TB, fungal
- **OTHERS**—amyloidosis

ISOLATED HYPERBILIRUBINEMIA (↑↑ bilirubin only)—see JAUNDICE (p. 155)

PATHOPHYSIOLOGY

DEFINITIONS

- **ABNORMAL LIVER ENZYMES**—defined as ±2 standard deviations, so 5% of the population would have abnormal liver enzymes by definition

PATHOPHYSIOLOGY (CONT'D)

- **ACUTE (FULMINANT) LIVER FAILURE**—development of jaundice, coagulopathy, and encephalopathy within 8 weeks of onset of hepatocellular injury; subclassified into hyperacute (day 0–7), acute (day 8–28) and subacute (day >28)
- **CHRONIC HEPATITIS**—↑ ALT >6 months

Related Topics
Acetaminophen Overdose (p. 115)
Alcohol-Related Issues (p. 117)
Hemochromatosis (p. 482)
Hepatitis B (p. 145)
Hepatitis C (p. 147)
Hepatoma (p. 227)
Liver Diseases in Pregnancy (p. 471)
Wilson's Disease (p. 150)

LIVER ENZYMES BY CATEGORY

- **SYNTHETIC FUNCTION**—INR (dependent on factors I, II, V, VII, IX, X), bilirubin (heme breakdown product), albumin (synthesis), fibrinogen
- **HEPATIC INJURY**—AST (intracellular; liver, heart, skeletal, kidneys, brain, pancreas, lungs, RBC, WBC), A**L**T (intracellular; specific for **L**iver), ALP (liver, gut, bone, placenta), GGT, 5'NT, LDH (bone, muscle, liver, lungs)

COMPLICATIONS OF HEPATIC FAILURE

★SCREAM★

- **S**epsis
- **C**oagulopathy
- **R**enal failure
- **E**ncephalopathy
- **A**scites
- **M**etabolic changes (hypoglycemia, electrolyte abnormalities, acidosis)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, HBcIgG, lactate
- **IMAGING**—US abd (with Doppler), CT abd

SPECIAL

- **LABS**—EBV, CMV, HSV, ANA, anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), quantitative immunoglobulin, ferritin, Fe, TIBC, % sat, ceruloplasmin, α1-antitrypsin, AFP, antitransglutaminase antibody, lipase, amylase, LDH, haptoglobin, acetaminophen, CK, TSH
- **ERCP/MRCP**
- **GASTROSCOPY**
- **LIVER BIOPSY**

DIAGNOSTIC AND PROGNOSTIC ISSUES

↑ **AST/SGOT**—do panel of liver function tests. If isolated rise, consider non-hepatic causes. Otherwise, same as ALT workup. AST > ALT suggests alcoholic liver disease, fatty liver, or cirrhosis

↑ **ALT/SGPT**—if symptomatic and presence of risk factors for liver disease, liver dysfunction (↓ albumin, ↑ INR, ↑ bili), ↑ ALT or AST >3× upper limit of normal, or ↑ ALT >6 months, consider basic workup including abdominal US with Doppler, viral serologies, ANA, ASMA, quantitative Ig, ceruloplasmin, iron studies, antitransglutaminase antibody, and possibly liver biopsy

↑ **ALP/BILI**—ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGT, 5'NT, abdominal US, AMA, and quantitative Ig. Consider MRCP/ERCP/EUS and liver biopsy

MONITORING—INR and bilirubin are much more useful to monitor liver function compared to transaminases

SURVIVAL IN ACUTE HEPATIC FAILURE—35% in hyperacute, 7% in acute, and 14% subacute

MANAGEMENT

SYMPTOM CONTROL

- **ACUTE**—ABC, O_2, IV hydration
- **ELEVATED INTRACRANIAL PRESSURE**—for cerebral edema, consider prophylactic phenytoin, raise head of bed, hyperventilate, dexamethasone, mannitol, avoid excessive fluids
- **SEPSIS**—antibiotics
- **COAGULOPATHY**—*vitamin K* 10 mg IV/PO, FFP 2–4 U IV (only if active bleeding or invasive procedures, or difficult to follow INR afterward)
- **ACUTE RENAL FAILURE**—supportive renal replacement. Consider midodrine, octreotide, and albumin
- **ENCEPHALOPATHY**—limit protein intake up to 1 g/kg/day. *Lactulose* 30 g PO QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider lactulose 300 mL (mixed with 700 mL of H_2O or NS) PR via rectal balloon catheter QID until awake

MANAGEMENT (CONT'D)

- **ACIDOSIS**—3 amp $NaHCO_3$ diluted in 1000 mL D5W (i.e. 150 mmol/L of HCO_3^-) as continuous IV infusion at 150–250 mL/h. Give with caution as risk of cerebral edema with increased fluid
  - **HYPOGLYCEMIA**—D10W, tube feed, TPN
  - **DETOXIFICATION**—*N-acetylcysteine* 150 mg/kg IV (~60 mL) in 200 mL D5W over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W over 4 h, then 100 mg/kg (~40 mL) in 1 L D5W over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses. May continue *N*-acetylcysteine until INR normalized

PREVENTION—**hepatitis B vaccine** (0, 1, 6 months), **HBIG** (post-exposure), hepatitis A vaccine (see p. 305)

TREAT UNDERLYING CAUSE—**hepatitis B** (if acute liver failure from HBV, provide supportive care only without active HBV treatment). **Hepatitis C** (pegylated interferon ± ribavirin). **Alcoholic hepatitis** (abstinence, nutrition, *prednisolone* 40 mg PO × 28 days but avoid if pancreatitis, GI bleed, renal failure, or active infection; *pentoxifylline* 400 mg PO TID × 28 days [expect ↓ bilirubin on day 7 vs. day 1. A lack of response suggests limited survival benefit]). **Autoimmune hepatitis** (steroids). **Wilson's disease** (D-penicillamine, trientine)

LIVER TRANSPLANT—patients with fulminant liver failure should be transferred to acute care centers with liver transplant expertise

TREATMENT ISSUES

LIVER TRANSPLANT

- **ALLOCATION**—based on ABO blood type, body size, wait designation, and degree of urgency
- **KING'S COLLEGE CRITERIA FOR TYLENOL OVERDOSE ACUTE HEPATIC FAILURE** (rule of **3**'s)—either arterial pH <**7.3** or grade **III** or IV encephalopathy, plus Cr >**300** μmol/L [>**3.3** mg/dL], plus INR >**6.5** (or PT >100 s)
- **KING'S COLLEGE CRITERIA FOR NON-TYLENOL ACUTE HEPATIC FAILURE**—INR >3 or any 3 of following: age <10 or >40, non-A non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions, duration of jaundice before onset of encephalopathy >7 days, INR >1.5, bilirubin >308 μmol/L [179 mg/dL]
- **CONTRAINDICATIONS**—malignancy (except hepatocellular carcinoma), irreversible cardiopulmonary comorbidities, neuropsychiatric comorbidities, sepsis, substance abuse, noncompliance, HIV

SPECIFIC ENTITIES

AST/ALT THOUSAND CLUB—viral hepatitis, ischemic liver (hypotension, hypoxia, sepsis), drugs/toxins (acetaminophen/paracetamol), autoimmune hepatitis, gallstone disease (acute bile duct obstruction), acute Budd–Chiari syndrome, hepatic artery ligation

ALCOHOLIC LIVER DISEASE

- **SUBTYPES**—fatty liver, alcoholic hepatitis, micronodular cirrhosis
- **DIAGNOSIS**—AST:ALT = 2:1 (low ALT activity due to alcohol-related pyridoxal 5-phosphate deficiency), rare for AST to be >8× normal and for ALT to be >5× normal. GGT ↑, ALP ↑, bilirubin ↑
- **TREATMENTS**—abstinence, nutrition, *prednisolone* 40 mg PO × 28 days, *pentoxifylline* 400 mg PO TID × 4 weeks

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

- **ASSOCIATIONS**—obesity, hyperlipidemia, diabetes, Cushing's, TPN, high-protein diets for weight loss, amiodarone, tamoxifen
- **DIAGNOSIS**—liver biopsy
- **TREATMENTS**—weight loss (diet, exercise), omega 3-6-9 fatty acids, metformin for diabetes, statins for dyslipidemia

Hepatitis B

NEJM 2004 350:11; NEJM 2008 359:14

PATHOPHYSIOLOGY

NATURAL HISTORY—acute hepatitis → chronic disease develops in >90% of neonates, in 10% if 12 years old, and in <1% if >12 years old → 12–20% with chronic hepatitis progress to cirrhosis in 5 years → 20% with compensated cirrhosis progress to decompensation in 5 years and 6–15% with compensated cirrhosis progress

PATHOPHYSIOLOGY (CONT'D)

to hepatocellular carcinoma. Lifetime risk of hepatocellular carcinoma/death in patients with chronic hepatitis is 40% for ♂ and 15% for ♀

ACUTE HEPATITIS B—may range from subclinical/anicteric hepatitis (70%) to icteric hepatitis (30%) and even fulminant hepatic failure (0.5–1%). Symptoms may include fever, anorexia, rash,

PATHOPHYSIOLOGY (CONT'D)

nausea, jaundice, RUQ tenderness, arthralgia, and arthritis. ↑↑ ALT and AST

CHRONIC HEPATITIS B

- **REPLICATIVE PHASE WITH IMMUNE TOLERANCE** (only if vertical transmission)—HBeAg positive, asymptomatic as lack of immune response in children. May last 10–30 years
- **REPLICATIVE PHASE WITH IMMUNE CLEARANCE**—HBeAg positive with seroconversion to HBeAb, may be symptomatic with increased liver enzymes due to immune response against HBV
- **NON-REPLICATIVE PHASE**—HBeAb positive, low level of viral replication. Usually normal liver enzymes
- **SUSPECT PROGRESSION TO CIRRHOSIS**—if hypersplenism or impaired synthetic function (↑ INR, ↑ bilirubin, hypoalbuminemia)

GENOTYPES—there are currently eight different genotypes (A to H)

RISK FACTORS—vertical transmission, endemic areas, transfusions, dialysis, healthcare workers, IDU, high-risk sex/homosexuals, body piercing, tattoos, organ transplantation

Related Topics
Acute Liver Failure (p. 143)
Chronic Liver Failure (p. 149)
HBV/HIV Co-infection (p. 291)
Hepatitis C (p. 147)
Hepatoma (p. 227)

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (family history, sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HCV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease (see p. 149), weight

EXTRAHEPATIC MANIFESTATIONS OF HBV—polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBV serology (HBsAb, HBsAg, HBcIgM, HBcIgG to determine infection/immune status, HBeAg, HBeAb, HBV DNA to see if active replication), HAV serology, HCV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—US abd

SPECIAL

- **LIVER BIOPSY**
- **FIBROSCAN**—non-invasive assessment of liver fibrosis using ultrasound

DIAGNOSTIC ISSUES

HEPATITIS B SEROLOGY

- **HBsAg**—hepatitis B surface antigen. Positive if active infection
- **HBcIgM**—IgM antibody against hepatitis B core antigen. Suggestive of early infection (indicates the window period) or reactivation
- **HBsAb**—antibody against hepatitis B surface antigen. Positive if immunized (through past infection or vaccination)
- **HBcIgG**—IgG antibody against hepatitis B core antigen. Suggestive of hepatitis B exposure
- **HBeAg**—hepatitis B envelope protein. HBeAg positivity suggests high viral replication with high infectivity. However, HBeAg negativity without HBeAb positivity suggests chronic HBV infection with pre-core mutants/promoter mutations, with a more aggressive phenotype than HBeAg + HBV, more treatment failures, and progressive hepatic injury. HBeAg negative infection is associated with fluctuating ALT and lower levels of HBV DNA. By definition, HBeAg seroconversion cannot occur
- **HBeAb**—antibody against hepatitis B envelope protein. Suggests low/no viral replication, usually with low infectivity
- **HBV DNA**—direct determination of hepatitis B virus DNA. HBV DNA level reflects viral replication activity and is associated with the risk of cirrhosis and hepatoma. HBV DNA determination is important in both HBeAg+ and HBeAg– individuals to determine need for antiviral therapy

DIAGNOSTIC ISSUES (CONT'D)

	HBsAg	HBcIgM	HBsAb	HBcIgG	HBeAg	HBeAb
Acute infection						
Early	+	–	–	–	+	–
Window	–	+	–	–	+	–
Late	–	+/–	+	–	+	–
Immunity						
Vaccinated	–	–	+	–	–	–
Cured	–	–	+/–	+	–	+
Chronic infection						
Infectious/active	+	–	–	+	+	–
Pre-core mutant	+	–	–	+	–	–
Low replicative	+	–	–	+	–	+

MANAGEMENT

LIFESTYLE CHANGES—avoid alcohol use, sexual education, HBV vaccination

TREAT UNDERLYING CAUSE—interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir

VACCINATION—household and sexual contacts

TREATMENT ISSUES

TREATMENT DECISION FOR CHRONIC HEPATITIS B INFECTIONS

- **HBeAg positive patients**—consider treatment if HBV DNA level >20,000 IU/mL and elevated ALT >1× upper limit of normal for 3–6 months; or significant inflammation and fibrosis on biopsy, FibroScan, Fibrotest, or US abd regardless of HBV DNA or ALT levels
- **HBeAg negative patients (pre-core or core promoter mutations)**—consider treatment if HBV DNA >2000 IU/mL and elevated ALT >1× upper limit of normal for 3–6 months; or significant inflammation and fibrosis on biopsy, FibroScan, Fibrotest, or US abd regardless of HBV DNA or ALT levels

Please see **Can J Gastroenterol 2012 21:12** at www.hepatology.ca for consensus statement on management of hepatitis B

Hepatitis C NEJM 2001 345:1

PATHOPHYSIOLOGY

NATURAL HISTORY—acute infection → 55–85% of total will develop chronic infection → 50% of total will develop chronic hepatitis → 5–20% of total will develop cirrhosis → 3–5%/year of acute decompensation, also 1–5%/year of developing hepatocellular carcinoma (after 10–30 years)

RISK FACTORS FOR TRANSMISSION

- **high**—IDU, transfusions, immigration from endemic regions
- **low**—perinatal transmission, transfusion before 1992, body piercing, long-term dialysis, occupational exposure, intranasal drug use, multiple sexual partners

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HBV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease, weight. Also examine for extrahepatic manifestations of HCV

Related Topics
Acute Liver Failure (p. 143)
Chronic Liver Failure (p. 149)
HCV/HIV Co-infection (p. 291)
Hepatitis B (p. 145)
Hepatoma (p. 227)

EXTRAHEPATIC MANIFESTATIONS OF HCV

- **HEENT**—uveitis, corneal ulcer, sialadenitis
- **RENAL**—nephritic syndrome (MPGN II), nephrotic syndrome (membranous)

CLINICAL FEATURES (CONT'D)

- **HEMATOLOGIC**—aplastic anemia, lymphoma, cryoglobulinemia, ITP
- **VASCULAR**—necrotizing vasculitis, polyarteritis nodosa
- **RHEUMATOLOGIC**—arthralgias, arthritis, myalgia, sicca
- **NEUROLOGIC**—weakness, peripheral neuropathy
- **ENDOCRINE**—diabetes, antithyroid antibodies
- **DERMATOLOGIC**—psoriasis (20%), pruritus, Raynaud's, porphyria cutaneous tarda, lichen planus, cutaneous necrotizing vasculitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti-HCV IgM and total (sens 92–97%), HCV RNA PCR (qualitative, quantitative), genotyping, βhCG (before treatment), HAV serology, HBV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—US abd

SPECIAL

- **LIVER BIOPSY**—not mandatory before starting treatments
- **FIBROSCAN**—non-invasive assessment of liver fibrosis using ultrasound

PROGNOSTIC ISSUES

GOOD PROGNOSTIC FACTORS—age <40, female, weight <75 kg [165 lbs], low titer, genotype 2/3, mild fibrosis

POOR PROGNOSTIC FACTORS—age of infection ≥40, male, high BMI, alcoholism, HIV co-infection

UNCERTAIN PROGNOSTIC FACTORS—genotype, viral load, route of transmission

MANAGEMENT

TREAT UNDERLYING CAUSE (Note: the treatment paradigm is rapidly evolving. The regimens below are based on AASLD guidelines, and have a response rate of over 90%)

- **GENOTYPE 1 OR 4**—daily fixed-dose combination of ledipasvir/sofosbuvir for 12 weeks; OR paritaprevir/ritonavir/ombitasvir plus dasabuvir and weight-based ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis); OR sofosbuvir plus simeprevir with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

MANAGEMENT (CONT'D)

- **GENOTYPES 2**—sofosbuvir plus ribavirin for 12 weeks; treatment to 16 weeks is recommended in patients with cirrhosis
- **GENOTYPES 3**—sofosbuvir plus ribavirin for 24 weeks
- **GENOTYPE 4 (alternative regimens)**—daily sofosbuvir and ribavirin plus weekly pegylated interferon for 12 weeks; OR daily sofosbuvir plus simeprevir with or without weight-based ribavirin for 12 weeks

ORTHOTOPIC LIVER TRANSPLANT

TREATMENT ISSUES

TREATMENT DECISION—complex decision depending on patient's wishes, risk of progression, chance of response (genotypes 2 and 3 better), and any contraindications to treatment

- **GOOD CANDIDATES**—chronic hepatitis with significant fibrosis, compensated cirrhosis, stable CBC and Cr, good adherence. Elevated ALT is no longer considered a decision factor
- **SPECIAL CIRCUMSTANCES** (regimen modification required and should be done under expert guidance)—acute HCV, HIV/HCV, HBV/HCV previous treatment failures, liver transplant, renal failure, current drug or alcohol use
- **ABSOLUTE CONTRAINDICATION**—decompensated cirrhosis

Please see **Can J Gastroenterol 2012 26:6** at www.hepatology.ca for consensus statement on management of hepatitis C

NOVEL THERAPEUTICS

- **NS3/4A PROTEASE INHIBITORS**—boceprevir (Victrelis), telaprevir (Incivek), and simeprevir (Olysio). The NS3/4A protease is essential for cleaving and processing the HCV-encoded polyprotein
- **NS5B POLYMERASE INHIBITOR**—sofosbuvir (Sovaldi). NS5B is necessary for HCV RNA replication
- **NS5A PHOSPHOPROTEIN INHIBITOR**—ledipasvir (Harvoni in combination with sofosbuvir). NS5A is important for HCV RNA replication, assembly and secretion

MONITORING DURING HCV THERAPY—CBC weekly for 4 weeks, then CBC, AST, ALT, uric acid monthly, TSH and ANA every 3 months, and HCV RNA at 4, 12, and 24 weeks during treatment and 6 months after therapy. For significant anemia and neutropenia, give EPO and GCSF, respectively. Also monitor for depression

Chronic Liver Disease: Cirrhosis

DIFFERENTIAL DIAGNOSIS

INFECTIONS—HBV, HCV, HDV, schistosomiasis, toxoplasmosis
STEATOHEPATITIS—alcohol, non-alcoholic steatohepatitis (NASH)
MEDICATIONS—acetaminophen/paracetamol (chronic use, controversial)
AUTOIMMUNE—autoimmune hepatitis
NEOPLASM—hepatoma, cholangiocarcinoma

DIFFERENTIAL DIAGNOSIS (CONT'D)

METABOLIC—hemochromatosis, Wilson's, α1-antitrypsin deficiency, glycogen storage disease
BILIARY CIRRHOSIS—primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis (stones, strictures)
CARDIAC CIRRHOSIS—chronic right-sided heart failure

PATHOPHYSIOLOGY

CHILD–PUGH CLASSIFICATION OF LIVER CIRRHOSIS

Points	Encephalopathy	Ascites	Albumin	Total bili	INR
1	0	None	>35 g/L [>3.5 g/dL]	<34 μM [<2 mg/dL]	<1.7
2	1–2	Slight	28–35 g/L [2.8–3.5 g/dL]	34–51 μM [2–3 mg/dL]	1.7–2.3
3	3–4	Mod	<28 g/L [<2.8 g/dL]	>51 μM [>3 mg/dL]	>2.3

PATHOPHYSIOLOGY (CONT'D)

The Child–Pugh score is calculated as either encephalopathy plus ascites plus INR, or albumin plus bilirubin plus INR. Patients with score >7 or any clinical signs of decompensation (variceal bleeding, ascites, encephalopathy) should be considered for liver transplantation. Alternative calculation is a total score of all five parameters, grade A = 5–6, grade B = 7–9, grade C = 10–15

MODEL FOR END-STAGE LIVER DISEASE (MELD) SCORE—originally designed to predict survival in patients with portal hypertension undergoing elective TIPS procedure, now used as a tool for organ allocation in patients with chronic liver disease. The MELD score ranges from 6 to 40, with higher values indicating a worse prognosis

- **ORIGINAL MELD** = $9.57 \times \log_e$(Cr in mg/dL) + $3.78 \times \log_e$(total bilirubin in mg/dL) + $11.2 \times \log_e$(INR) + 6.43
- **UNITED NETWORK OF ORGAN SHARING MELD (UNOS-MELD)** = same formula but fixed lower limit of 1 for all variables and fixed upper limit of 4 mg/dL for Cr. Furthermore, Cr set at 4 for patients on renal replacement therapy
- **MELD-Na** = UNOS-MELD − Na − [0.025 × MELD × (140 − Na)] + 140

For web-based calculator, please see www.mayoclinic.org/meld/

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, hereditary disorders), medication history (acetaminophen/paracetamol, other hepatotoxins)

PHYSICAL

- **STIGMATA OF CHRONIC LIVER DISEASE**—leukonychia, Terry's nails, clubbing, Dupuytren's contractures, palmar erythema, asterixis, scleral icterus, altered mental status, parotid enlargement, fetor hepaticus, spider angiomas, gynecomastia, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, peripheral edema, petechiae
- **CLUES TO ETIOLOGY**—obesity (fatty liver), excoriations (PBC), tattoos/needle tracks (hepatitis), bronze skin (hemochromatosis), Kayser–Fleischer rings (Wilson's disease)

DISTINGUISHING LIVER FROM RIGHT KIDNEY

1. The liver has no palpable upper border and extends more laterally and medially
2. The liver is not usually ballotable, but the kidney is because of its retroperitoneal position

CLINICAL FEATURES (CONT'D)

3. The percussion note is dull over the liver but is usually tympanic over the kidney
4. A friction rub may occasionally be heard over the liver, but never over the kidney because it is too posterior
5. The liver has a shaper edge while kidney is usually more rounded

DISTINGUISHING FEATURES BETWEEN PORTAL HYPERTENSION AND VENA CAVA OBSTRUCTION

- **PORTAL HYPERTENSION**—caput medusa veins drain away from umbilicus. Stigmata of liver disease
- **IVC OBSTRUCTION**—veins prominent in the abdomen and drain up toward the superior vena cava system. No evidence of liver disease
- **SVC OBSTRUCTION**—veins prominent in the chest and drain down toward the inferior vena cava system. No evidence of liver disease

RATIONAL CLINICAL EXAMINATION SERIES: PHYSICAL EXAMINATION OF THE LIVER

INSPECTION—bulging mass over right costal margin (low sens)

PALPATION—move fingers 2 cm [0.79 in.] up at each exhalation. Palpable liver suggests hepatomegaly (LR+ 2.0, LR 0.41)

PERCUSSION—locate upper border along midclavicular line. Locate lower border with palpation, scratch test, or percussion. Liver span >12 cm (>4.7 in.) suggests hepatomegaly. Scratch test not recommended to assess liver span

AUSCULTATION—friction rubs (tumors, infection), venous hums (portal hypertension), arterial bruit (tumors, alcohol hepatitis)

APPROACH—"if clinical suspicion low, start with palpation. If positive, percuss liver span. If negative, hepatomegaly is unlikely. If clinical suspicion is high, palpate and percuss. Overall, negative findings cannot rule out abnormal liver, and positive findings cannot rule in liver disease"

JAMA 1994 271:23
The Rational Clinical Examination. McGraw-Hill, 2009

RIEDEL'S LOBE—an extension of the right lobe of the liver down below the costal margin along the anterior axillary line. It is often mistaken for a pathological enlargement of the liver or gallbladder. It is a normal anatomical variant

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV serology, HBsAg, HBsAb, HBcIgM, HBcIgG, HCV serology, quantitiative immunoglobulins
- **IMAGING**—US abd (with Doppler), CT abd

SPECIAL

- **LABS**—ANA, anti-smooth muscle antibodies (anti-actin antibodies), anti-liver-kidney-microsomal (LKM) antibody, AMA, ferritin, ceruloplasmin, α1-antitrypsin, AFP, antitransglutaminase
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**
- **FIBROSCAN**

MANAGEMENT

TREAT UNDERLYING CAUSE—consideration for liver transplantation

SYMPTOM CONTROL—for variceal bleed prophylaxis, consider band ligation and non-selective β-blocker if moderate/large varices or Child–Pugh B/C (*nadolol* 40–80 mg PO daily, *propranolol* 20 mg PO BID, or *carvedilol* 6.25 mg PO daily-BID) and titrate to target heart rate of 55–60/min. Perform initial screen for esophageal varices with endoscopy → repeat endoscopy in 3 years if no varices; repeat in 1–2 years if small varices; endoscopic treatment (banding/glue) if moderate/large varices. For active variceal bleed after failed endoscopic therapy, consider TIPS. See UPPER GI BLEED (p. 131), HEPATIC ENCEPHALOPATHY (p. 152), and ASCITES (p. 153) for details

HEPATOMA SCREENING—for all patients with cirrhosis, and those with HBV and hepatocellular carcinoma risk factors, repeat AFP and abdominal US every 6 months for surveillance

SPECIFIC ENTITIES

CAUSES OF HEPATOMEGALY

- **PSEUDOHEPATOMEGALY**—obstructive lung disease (emphysema), subdiaphragmatic collection
- **CONGESTIVE**—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic vein obstruction
- **INFILTRATION**—malignancy, amyloidosis, hemochromatosis, fatty liver
- **REACTIVE**—hepatitis

WILSON'S DISEASE

- **ETIOLOGY**—copper excretion defect
- **DIAGNOSIS**—Kayser–Fleischer ring, low serum ceruloplasmin, 24-h urine for copper

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**dietary restriction** (avoid shellfish, organs, chocolate, nuts, and mushrooms), **chelating agent** (D-penicillamine or trientine), and zinc. For severe liver failure, consider orthotopic liver transplantation

AUTOIMMUNE HEPATITIS

- **SUBTYPES**—**I** (classic, female predominance, extrahepatic disease, ANA >1/160, anti-smooth muscle antibody >1/40, ↑ IgG, steroid responsive), **II** (anti-liver-kidney-microsomal [LKM] antibody, less steroid responsive), **III** (anti-SLA)
- **DIAGNOSIS**—quantitative immunoglobulins (↑ IgG), ANA, anti-smooth muscle antibody, anti-LKM antibody, liver biopsy
- **TREATMENTS**—steroids, azathioprine, or mycophenolate mofetil. For fulminant hepatitis or cirrhosis, consider liver transplantation

HEPATIC HYDROTHORAX

- **PATHOPHYSIOLOGY**—low oncotic pressure, congenital diaphragmatic defect, ascitic fluid moves to pleural space due to pressure gradient → transudative pleural effusion → decreased lung volumes → V/Q mismatch → hypoxemia
- **DIAGNOSIS**—diagnostic paracentesis/thoracentesis. US abd to assess liver and ascites. CT chest and abd to rule out other lesions. Intraperitoneal injection of ^{99}mTc-labeled serum albumin may be helpful to confirm diagnosis
- **TREATMENTS**—O_2, salt restriction, diuretics, therapeutic paracentesis, may need thoracentesis, TIPS. Avoid chest tube if possible (high risk of SBP and hepatorenal syndrome)

HEPATOPULMONARY SYNDROME

- **PATHOPHYSIOLOGY**—portal hypertension → ↓ metabolism of vasodilating substance, or ↓ production of vasoconstricting substance → pulmonary capillary dilatation → diffusion–perfusion imbalance → hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cyanosis, clubbing and spider nevi
- **DIAGNOSIS**—contrast echocardiogram/bubble study (presence of microbubbles in the left atrium 3–6 cardiac cycles after intravenous injection of normal saline suggests dilated pulmonary capillaries), lung perfusion scan, pulmonary angiogram (if severe hypoxemia)
- **TREATMENTS**—O_2, liver transplant

SPECIFIC ENTITIES (CONT'D)

PORTOPULMONARY HYPERTENSION

- **PATHOPHYSIOLOGY**—portal hypertension → unknown substance reaches pulmonary vasculature causing vasoconstriction → findings similar to primary pulmonary hypertension
- **DIAGNOSIS**—echocardiogram, right heart catheterization
- **TREATMENTS**—O_2, diuretics, sildenafil, prostaglandins, calcium channel blockers, liver transplant

HEPATORENAL SYNDROME

- **PATHOPHYSIOLOGY**—liver failure → dilated systemic circulation → ↑ renin–aldosterone system with ↑ cardiac output but not enough to counter splanchnic vasodilatation → pre-renal failure. Type I is more serious, defined as >50% reduction of CrCl to ≤20 mL/min in ≤2 weeks or >2× increase in creatinine to >220 µmol/L [>2.2 mg/dL]. Patients are usually oligouric or anuric. Type II includes patients not meeting criteria for type I and is characterized by ascites resistant to diuretics
- **DIAGNOSIS**—a clinical diagnosis of exclusion; rule-out other etiologies of acute kidney injury (including pre-renal causes, ATN, infection, and GI bleed). Typically, urine Na <10 mM (<10 mEq/L), bland U/A, oliguria, and minimal improvement in renal function after volume expansion with IV albumin (1 g/kg/d and up to 100 g/d × 2 days)
- **TREATMENTS**—stop diuretics, fluid (usually no response), albumin, vasoconstrictors (midodrine, octreotide, norepinephrine), TIPS, renal replacement therapy, liver transplant

FLOOD SYNDROME (SPONTANEOUS UMBILICAL HERNIA RUPTURE)

- **PATHOPHYSIOLOGY**—liver failure → portal hypertension → ascites → umbilical hernia (up to 20%) → spontaneous rupture (rare)
- **PROGNOSIS**—50% mortality with supportive care, 10–20% mortality with urgent surgical repair

Related Topics
Acute Hepatic Failure (p. 143)
Ascites (p. 153)
Encephalopathy (p. 152)
Hemochromatosis (p. 482)
Hepatitis B (p. 145)
Hepatitis C (p. 147)
Jaundice (p. 155)

Hepatic Encephalopathy NEJM 1997 337:7

DIFFERENTIAL DIAGNOSIS

DRUGS
- **ALCOHOL**—acute intoxication, withdrawal, Wernicke–Korsakoff
- **PSYCHOACTIVE**—benzodiazepines, cocaine, heroine, ecstasy
- **OTHERS**—salicylates

INFECTIOUS—spontaneous bacterial peritonitis, pneumonia, UTI, meningitis, encephalitis, abscess

METABOLIC
- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism, hypoxemia, CO_2 narcosis
- **ELECTROLYTES**—ketoacidosis, hyponatremia, hypomagnesemia, hypercalcemia, glucose (hypo, hyper)

STRUCTURAL
- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar
- **TUMOR**
- **EPILEPSY**

NEUROPSYCHIATRIC

PATHOPHYSIOLOGY

GRADING OF HEPATIC ENCEPHALOPATHY
- **1**—reversed sleep cycle, mild confusion, tremor, incoordination
- **2**—lethargy or irritability, disoriented to time, asterixis, ataxia
- **3**—somnolence or agitation, disoriented to place, asterixis, hyperreflexia, positive Babinski
- **4**—coma, decerebrate

PRECIPITANTS OF HEPATIC ENCEPHALOPATHY
- ↑ **NH_4** —↑ protein intake, constipation, GI bleed, transfusion, infection (spontaneous bacterial peritonitis), azotemia, hypokalemia
- ↑ **DIFFUSION ACROSS BLOOD–BRAIN BARRIER**—alkalosis
- ↓ **METABOLISM**—dehydration, hypotension, hypoxemia, anemia, portosystemic shunt, hepatoma, progressive liver damage

CLINICAL FEATURES

HISTORY—characterize confusion (onset, duration, fluctuation), infectious symptoms, neurological symptoms, precipitants (diet, hydration, constipation, GI bleed, infection), past medical history (liver disease, alcohol and illicit drug use), medication history (sedatives, narcotics, missed lactulose)

PHYSICAL—vitals, signs of chronic liver disease, rectal examination (if suspect GI bleed), neurological examination, check for asterixis

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH_4 (poorly correlated with degree of encephalopathy), Ca, Mg, PO_4, osmolality, CK, troponin (as part of delirium workup), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S, sputum Gram stain/C&S
- **IMAGING**—US abd, CT abd
- **ASCITIC FLUID ANALYSIS**—cell count and diff, C&S to rule out SBP

SPECIAL
- **CT HEAD**—delirium workup
- **ABG**—if critically ill
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**
- **EEG**—symmetric, high voltage, slow wave pattern

MANAGEMENT

ACUTE HEPATIC ENCEPHALOPATHY
- **WORKUP FOR SEPSIS**
- **SYMPTOM CONTROL**—correct hypokalemia, if present. ***Lactulose*** 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider lactulose 300 mL (mixed with 700 mL of H_2O or NS) PR via rectal balloon catheter QID until awake. Consider sedation (*haloperidol* 1–2 mg PO/IV/SC q6h and q1h PRN) and ventilation, *mannitol* 1 g/kg 20% solution, acetylcysteine, epoprostenol
- **TREAT UNDERLYING CAUSE**—liver transplant

CHRONIC HEPATIC ENCEPHALOPATHY
- **SYMPTOM CONTROL**—protein restriction no longer routinely recommended. ***Lactulose*** 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day. **Prophylaxis** with ***metronidazole*** 800 mg PO daily (associated peripheral neuropathy), ***neomycin*** 500–2000 mg PO TID (associated ototoxicity and nephrotoxicity), or ***rifaximin*** 550 mg PO BID (in high-risk patients with ≥2 episodes of hepatic encephalopathy in last 6 months). **Others** (*H. pylori* treatment, ornithine aspartate, branched amino acids)
- **TREAT UNDERLYING CAUSE**—liver transplant

Related Topic
Delirium (p. 432)

Ascites

NEJM 2004 350:16

DIFFERENTIAL DIAGNOSIS

↑ HYDROSTATIC PRESSURE

- **CARDIAC**—right heart failure, tricuspid regurgitation, constrictive pericarditis
- **HEPATIC**—**presinusoidal** (portal vein thrombosis, schistosomiasis), **sinusoidal** (cirrhosis), **postsinusoidal** (Budd–Chiari, veno-occlusive)

↓ ONCOTIC PRESSURE—malnutrition, liver disease, nephrotic syndrome, protein-losing enteropathy

DIFFERENTIAL DIAGNOSIS (CONT'D)

↑ CAPILLARY PERMEABILITY/LYMPHATIC OBSTRUCTION

- **INFECTIONS**—spontaneous bacterial peritonitis
- **MALIGNANCY**—ovarian, peritoneal metastasis
- **PANCREATITIS**

OTHERS—hypothyroidism

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ASCITES?

	Sens	Spc	LR+	LR–
History				
↑ abdominal girth	87%	77%	4.1	0.17
Recent weight gain	67%	79%	3.2	0.42
Ankle swelling	93%	68%	2.8	0.10
Hepatitis	67%	79%	3.2	0.42
Heart failure	47%	73%	2.0	0.73
Alcoholism	60%	58%	1.4	0.69
Hx of carcinoma	13%	85%	0.91	1.01
Physical				
Fluid wave	62%	90%	5.3	0.6
Shifting dullness	77%	72%	2.1	0.4
Flank dullness	84%	59%	1.7	0.4
Bulging flanks	81%	59%	1.8	0.5

APPROACH—the most useful finding for making a diagnosis of ascites is a positive fluid wave. The most useful findings to rule out ascites are a negative history of ankle swelling or increased abdominal girth. Puddle sign and auscultatory percussion not recommended

JAMA 1992 267:19

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, amylase, lipase, TSH, urinalysis
- **IMAGING**—US abd, CT abd
- **PARACENTESIS**—cell count + diff, Gram stain, C&S, AFB, albumin, LDH, glucose, amylase, triglyceride, cytology

SPECIAL

- **LAPAROSCOPY WITH PERITONEAL BIOPSY**

DIAGNOSTIC ISSUES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE BACTERIAL PERITONITIS OR PORTAL HYPERTENSION? HOW DO I PERFORM A PARACENTESIS AND ANALYZE THE RESULTS?

PARACENTESIS TECHNIQUE—two studies showed that testing for coagulation prior to paracentesis was probably unnecessary; one study showed that a 15-gauge, 3.25-in. needle-cannula was associated with less multiple

DIAGNOSTIC ISSUES (CONT'D)

peritoneal punctures and termination due to poor fluid return as compared to a 14-gauge needle in therapeutic paracentesis; one study showed immediate as compared to delayed inoculation of culture bottles improved diagnostic yield (100% vs. 77%); nine studies examined therapeutic paracentesis with or without albumin or nonalbumin plasma expanders and found no consistent effect on morbidity or mortality

FEATURES SUGGESTIVE OF SPONTANEOUS BACTERIAL PERITONITIS

	LR+	LR–
Ascitic fluid WBC/PMN		
Ascitic fluid WBC >1000 cells/μL	9.1	0.25
Ascitic fluid WBC >500 cells/μL	5.9	0.21
Ascitic fluid WBC >250 cells/μL	0.9	1.1
Ascitic fluid PMN >500 cells/μL	10.6	0.16
Ascitic fluid PMN >250 cells/μL	6.4	0.20
Ascitic fluid pH and blood ascitic pH gradient		
Ascitic fluid pH <7.31	4.1	0.47
Ascitic fluid pH <7.32	4.8	0.65
Ascitic fluid pH ≤7.31	5.8	0.43
Ascitic fluid pH <7.35	9.0	0.31
Ascitic fluid pH <7.40	2.5	0.23
Blood ascitic fluid pH gradient >0.11	4.6	0.47
Blood ascitic fluid pH gradient >0.10	7.1	0.30
Blood ascitic fluid pH gradient ≥0.10	11.3	0.12

FEATURES SUGGESTIVE OF PORTAL HYPERTENSION

	LR+	LR–
Serum ascites albumin gradient (SAAG)		
Serum-ascites albumin gradient ≥11 g/L (≥1.1 g/dL)	4.6	0.06

APPROACH—"ascitic fluid should be inoculated into blood culture bottles at the bedside. Spontaneous bacterial peritonitis is more likely at predescribed parameters of ascitic WBC count (>1000 cells/μL), PMN count (>250 cells/μL) or blood–ascitic fluid pH (<7.35), and portal hypertension is less likely below a predescribed serum-ascites albumin gradient (<11 g/L [<1.1 g/dL])"

JAMA 2008 299:10

DIAGNOSTIC ISSUES (CONT'D)

PARACENTESIS PROCEDURE—**NEJM 2006 355:E21**

SERUM-ASCITES ALBUMIN GRADIENT (SAAG)

- **PORTAL HYPERTENSION OR CONGESTIVE HEART FAILURE**—(serum albumin – ascites albumin) ≥11 g/L [≥1.1 g/dL]. To distinguish between portal hypertension and HF, consider checking for ascitic fluid total protein level (generally >25 g/L [>2.5 g/dL] in cardiac ascites due to normal leaky hepatic sinusoid, while portal hypertension is associated with "capillarized" sinusoids that are less leaky)
- **INFLAMMATORY**—(serum albumin – ascites albumin) <11 g/L [<1.1 g/dL]

MANAGEMENT

SYMPTOM CONTROL—**Na restriction** (88 mmol/day or 2 g/day. Check urine Na for compliance, i.e. <77 mmol/day). **Fluid restriction** (<1.5 L/day only if Na <120 mmol/L). **Diuretics** (*spironolactone* 100–400 mg PO daily and *furosemide* 40–160 mg PO daily, stepwise increase). **Paracentesis. Albumin** (if >5 L ascitic fluid removed, then replace with albumin. In general, give 100 mL of 25% albumin for every 3 L of ascites removed over 5 L), TIPS, liver transplant

TREAT UNDERLYING CAUSE—stop alcohol consumption

SPECIFIC ENTITIES

DIFFERENTIAL DIAGNOSIS OF ANASARCA—renal (nephrotic syndrome), cardiac (HF, tricuspid regurgitation, constrictive pericarditis), liver (cirrhosis), thyroid (hypothyroidism), malignancy (venous/lymphatic obstruction)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- **PATHOPHYSIOLOGY**—overgrowth of bacteria in bowel (usually *E. coli*) → bacterial translocation (migration) across bowel wall → infect ascites. Usually in patients with cirrhosis and large volume ascites with low ascites protein. Symptoms may be subtle as the visceral peritoneum is separated from the parietal peritoneum. Important to differentiate SBP from perforated bowel causing peritonitis
- **CLINICAL FEATURES**—may be asymptomatic if detected early. Common signs and symptoms include fever, abdominal pain and tenderness (diffuse, continuous), diarrhea, confusion, or renal deterioration. Sepsis with hypotension and paralytic ileus may develop later

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—paracentesis (ascitic fluid PMN ≥250 cells/μL, fluid protein <10 g/L [<1.0 g/dL], Gram stain, C&S), blood cultures, urine cultures. (Note that in peritonitis secondary to perforated viscous, the ascitic fluid protein is usually >10 g/L [>1.0 g/dL], glucose <2.8 mmol/L [<51 mg/dL], and LDH > upper limit of normal, and polymicrobial)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—*cefotaxime* 2 g IV q8h (preferred) or *ceftriaxone* 2 g IV q24h × 5–10 days, *albumin* 1.5 g/kg IV within 6 h of detection, then 1 g/kg IV on day 3 (reduces mortality and incidence of hepato-renal syndrome). **Secondary prophylaxis** include *ciprofloxacin* 750 mg PO weekly, *norfloxacin* 400 mg PO daily, or *trimethoprim–sulfamethoxazole* DS 1 tab PO daily

Jaundice

DIFFERENTIAL DIAGNOSIS OF JAUNDICE/ HYPERBILIRUBINEMIA

PRE-HEPATIC (hemolysis)
- **RBC MEMBRANE**—spherocytosis, elliptocytosis
- **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
- **RBC HEMOGLOBIN**—sickle cell
- **BLOOD**—toxins, drugs (fludarabine), infections (malaria), immune
- **VASCULAR**—mechanical valve, vasculitis, HUS/TTP/DIC, HELLP, severe hypertension
- **INEFFECTIVE ERYTHROPOIESIS**—megaloblastic anemia

HEPATIC
- ↓ **UPTAKE**—Gilbert's, drugs (rifampin, contrast)
- ↓ **CONJUGATION**—Gilbert's, Crigler–Najjar I/II, hepatocellular diseases, drugs (chloramphenicol)
- ↓ **EXCRETION** (cholestasis)—Dubin–Johnson, Rotor, benign recurrent cholestasis, cholestasis of pregnancy, drug-induced cholestasis, PBC, PSC, TPN
- **MIXED**—hepatocellular disease, sepsis

POST-HEPATIC
- **GALLSTONES**
- **CANCER**—pancreas, bile ducts, ampulla
- **BILIARY STRUCTURES**—post-cholecystectomy, PSC, biliary atresia

PATHOPHYSIOLOGY

CHOLESTASIS—any condition in which bile excretion from the liver is blocked, which can occur either in the intrahepatic bile ducts (hepatic causes) or in the extrahepatic bile ducts (post-hepatic causes)

CLINICAL FEATURES

HISTORY—characterize jaundice (duration, previous episodes), abdominal pain, abdominal mass, stool color, urine color, pruritus, weight loss, past medical history (liver disease, hepatitis risk factors, IBD/PSC, hereditary disorders), medications

PHYSICAL—signs of chronic liver disease, liver and spleen examination

JAUNDICE—becomes clinically evident at levels of bilirubin >70 μmol/L [>41 mg/dL]

DARK URINE—suggests conjugated hyperbilirubinemia

PALE STOOL/PRURITUS—suggests cholestasis (bile cannot be secreted into the biliary system)

PAIN—painful jaundice suggests acute obstruction (by stones, masses); investigate with US abd/ERCP/MRCP/EUS. Painless jaundice suggests pancreatic cancer, infiltration, PSC, PBC, and drugs; investigate with imaging + biopsy

INVESTIGATIONS

BASIC
- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin (conjugated and unconjugated), INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, anti-HCV, ANA, antismooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), ferritin, ceruloplasmin, α1-antitrypsin, AFP, LDH, haptoglobin, peripheral smear, reticulocyte counts
- **IMAGING**—US, CT abd

SPECIAL
- **ENDOSCOPIC US**
- **MRCP**
- **ERCP**
- **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

PRIMARY BILIARY CIRRHOSIS (PBC)

- **PATHOPHYSIOLOGY**—autoimmune destruction of intrahepatic bile ducts → cholestasis → inflammation and necrosis → cirrhosis
- **CLINICAL FEATURES**—pruritus, fatigue, RUQ pain, xanthelasmas, sicca syndrome, hyperlipidemia. Females >> males. With disease progression, symptoms of liver failure may be seen. Decreased bone mineral density
- **DIAGNOSIS**—antimitochondrial antibody (sens 95%), ANA (40%), ↑ bilirubin, ↑ ALP, ↓ C4, ↑ IgM, hyperlipidemia (cholesterol, rather than TG, is what classically becomes elevated). Liver biopsy can be helpful for staging but is not essential for diagnosis. Consider DEXA scan
- **TREATMENTS**—*ursodeoxycholic acid (ursodiol)* 13–15 mg/kg/day PO in 2–4 divided doses with food. Ursodeoxycholic acid has been shown to improve liver enzymes, slow disease progression (for stages I and II), delay time to transplant but does not treat pruritus. For pruritus, consider cholestyramine, rifampin, and naltrexone. Consider treating hyperlipidemia (despite hypercholesterolemia, risk of atherosclerotic death not increased). Prevent osteoporosis with calcium and vitamin D. Also provide supplement with fat-soluble vitamins (KADE), which are not well absorbed in cholestasis. Consider liver transplant if rising bilirubin, liver decompensation, refractory pruritus, or severe bone disease

NEJM 2007 357:15

PRIMARY SCLEROSING CHOLANGITIS (PSC)

- **PATHOPHYSIOLOGY**—cholangitis → fibrosis with intra-and extrahepatic duct strictures → cirrhosis; 75% associated with ulcerative colitis, 10% with cholangiocarcinoma
- **DIAGNOSIS**—MRCP, ERCP (beading, strictures), biopsy
- **TREATMENTS**—liver transplant

Acute Pancreatitis NEJM 1994 330:17

CAUSES

★BAD HITS★
BILIARY STONES
ALCOHOL
DRUGS—thiazides, furosemide, sulfonamide, tetracycline, calcium, estrogen, vinca alkaloids, antiretrovirals (didanosine, pentamidine)
HYPER—hypercalcemia, hyperlipidemia (V, I, IV)
INFECTIOUS—*E. coli*, HIV, CMV, mumps, ascariasis
IDIOPATHIC
INHERITED—familial
TRAUMA—blunt
SURGERY—ERCP (± sphincterotomy, 5% risk), sphincter of Oddi dysfunction

PATHOPHYSIOLOGY

COMPLICATIONS OF ACUTE PANCREATITIS
★SCAR★
Sepsis
Calcium (hypocalcemia)
Abdominal (necrotizing pancreatitis ± hemorrhage, pancreatic pseudocyst ± hemorrhage [10–20%], pancreatic abscess, splenic vein thrombosis, fistula, cholangitis
Respiratory failure (ARDS) and aspiration pneumonia
Renal failure

CLINICAL FEATURES

HISTORY—abdominal pain, nausea and vomiting, fever, anorexia, past medical history (previous pancreatitis, recent ERCP, biliary stones, alcohol use, HIV), medication history (diuretics, antibiotics)
PHYSICAL—vitals, volume status, abdominal examination, Cullen's sign (periumbilical ecchymoses suggestive of hemoperitoneum), Grey Turner's sign (ecchymoses of the flanks suggestive of retroperitoneal hemorrhage), Fox's sign (ecchymoses parallel and inferior to inguinal ligament along upper thighs suggesting retroperitoneal hemorrhage), Bryant's sign (blue scrotum suggesting retroperitoneal hemorrhage)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, LDH, lipase, amylase, Ca, albumin, fasting lipid profile
- **IMAGING**—US abd, CT abd (+ contrast for necrotic pancreatitis)
- **ERCP**—both diagnostic and therapeutic to relieve obstruction

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIFFERENTIAL DIAGNOSIS FOR LIPASE ELEVATION—acute pancreatitis, pancreatic cancer, pancreatic duct obstruction, perforated peptic ulcer, bowel infarction, intestinal obstruction, renal failure

RANSON'S CRITERIA

- **ON ADMISSION**—age >55, WBC $>16 \times 10^9$/L, glucose >11.1 mmol/L [>200 mg/dL], AST >250 U/L, LDH >350 U/L
- **48 H**—hematocrit ↓ >10%, urea ↑ >1.78 mmol/L [>5 mg/dL], base deficit >4 mEq/L, Ca <2 mmol/L [<8 mg/dL], sequestration of fluid >6 L
- **PROGNOSIS**—0–2 = 2% mortality, 3–4 = 15%, 5–6 = 50%, 7–8 = 100%

MANAGEMENT

ACUTE—ABC, O_2, **IV hydration**. NPO, NG if severe N&V or obstruction. ***Morphine*** 2.5–5 mg SC q4h PRN and 1–2 mg IV q1h PRN (for theoretical concern of morphine-causing sphincter of Oddi spasm, some consider using Demerol instead). **Antiemetics** (*dimenhydrinate* 50 mg 2IM/IV q4h, *metoclopramide* 10 mg IV q4h).

MANAGEMENT (CONT'D)

Consider broad-spectrum **antibiotics** (*meropenem* 1 g IV q8h or *imipenem* 500 mg IV q6h) if infected necrosis suspected

NUTRITION SUPPORT—enteral or parenteral. Early aggressive nutrition may not be warranted

TREAT UNDERLYING CAUSE—**gallstone pancreatitis** (ERCP and biliary sphincterotomy within 72 h, cholecystectomy). **Necrotizing pancreatitis** (ICU admission, surgical debridement)

SPECIFIC ENTITIES

ASCENDING CHOLANGITIS

- **PATHOPHYSIOLOGY**—biliary calculi (choledocholithiasis), post-ERCP, tumors, primary sclerosing cholangitis, or benign stricture → biliary obstruction and stasis → bacterial colonization and infection (*E. coli*, *Klebsiella, Enterobacter*, *Enterococcus*, anaerobes) → liver failure, sepsis
- **CLINICAL FEATURES**—Charcot's triad consists of fever, right upper quadrant pain, and jaundice. Reynold's pentad is associated with the addition of hypotension and confusion
- **DIAGNOSIS**—↑ bilirubin, ALP, and potentially AST and ALT. Blood cultures essential. US abd to check for common bile duct dilatation and stones, ERCP (diagnostic and therapeutic)
- **TREATMENTS**—**antibiotics** (*meropenem* 1 g IV q8h, *imipenem* 500 mg IV q6h, or ampicillin plus gentamicin). **Facilitate biliary drainage** (urgent ERCP with sphincterotomy for infection source control, stone extraction, stent insertion, percutaneous transhepatic cholangiogram [PTC] with stent drainage, and surgical decompression as last resort)