

ZAPORIZHZHYA STATE MEDICAL UNIVERSITY

THE DEPARTMENT OF INTERNAL DISEASES № 3

Casebook
in GASTROENTEROLOGY

**(tutorial for practical exercises for 6-year students of
medical faculty)**

2015

«RATIFIED»

By Central methodical advice of
Zaporizhzhya state medical university

Protocol № ____ from _____ 2015

Authors:

1. Dotsenko S.Y. - head of department of internal diseases -3, Zaporizhzhya state medical university, professor, doctor of medical sciences
2. Samura B. B. - associate professor of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences
3. Sychoy R.A. - associate professor of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences
4. Tokarenko I.I. - assistant of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences
5. Kravchenko V.I. - associate professor of department of internal diseases-3 of Zaporizhzhya state medical university, candidate of medical sciences
6. Svistun S.I. - associate professor of department of internal diseases-3 of Zaporizhzhya state medical university, candidate of medical sciences

Практикум “Сборник клинических задач по внутренней медицине (часть III: гастроэнтерология)” (на английском языке) предназначен для самостоятельной подготовки к практическим занятиям по дисциплине внутренние болезни англоговорящим студентам 6-го курса лечебного факультета. В практикум включены клинические задачи, вопросы и ответы к ним, дискуссии по синдромной диагностике в гастроэнтерологической практике.

Reviewers:

- head of the department of Clinical Pharmacology, Pharmacy and Pharmacotherapy with the Course of Cosmetology of Zaporizhzhya state medical university, doctor of medical sciences, professor Kraydashenko O.V.
- professor of the Family Medicine and Therapy Department of FPE of Zaporizhzhya state medical university, doctor of medical sciences Deynega V.G.

Contents

Path I: Gastric dyspepsia	
Path II: Abdominal pain	
Path III: Chronic diarrhea syndrome	
Path IV: Constipation	
Path V: Jaundice	
Path VI: Ascites	
Path VII: Hepatomegaly and portal hypertension.....	
Path VIII: Hepatic encephalopathy.....	
Answers to cases	

PATH I: GASTRIC DYSPEPSIA

CASE 1:

A 32-year-old man presents with a 6-month history of burning epigastric pain between meals and at night. Eating and antacids usually resolves his symptoms. He does not have any other medical problems and does not take any medications. He does not smoke or drink alcohol. Vital signs are normal. The attending physician asks you for the differential diagnosis of dyspepsia.

- > What is the differential diagnosis of dyspepsia?
- > What cause of dyspepsia do his symptoms suggest?
- > Lab studies are normal. He does not have any alarm symptoms. What is the next step?
- > This patient does not have alarm symptoms, does not smoke or drink, and has not recently taken any medications other than antacids. What is the next step?

CASE 2:

The patient is a 32-year-old male who complains of epigastric pain, fullness, bloating, early satiety, and nausea occurring over the last 12 months. He does not have any diarrhea or alarm findings. Physical examination and vital signs are normal. Serology is negative for *H. pylori*. Daily esomeprazole only partially relieves his symptoms. Esophagogastroduodenoscopy (EGD) is normal. Serum electrolytes, liver function tests (LFTs), and complete blood counts (CBC) are all normal.

- > What is the diagnosis?

CASE 3:

A 50-year-old woman presents with a 3-month history of progressively worsening dyspepsia and anorexia. The symptoms were initially provoked by eating food but are now constantly present. She has unintentionally lost 15 lbs in the last 3 months. Physical examination is significant for an enlarged periumbilical lymph node (Sister Mary Joseph node) as well as an enlarged left supraclavicular lymph node (Virchow node). Stool is guaiac-positive.

- > What is the most likely finding on endoscopy?
- > Endoscopy with biopsy confirms the diagnosis of gastric adenocarcinoma. What tests should you order to stage gastric adenocarcinoma?
- > What malignancies can occur in the stomach besides adenocarcinoma?

CASE 4:

A 32-year-old man presents with episodes of burning substernal pain (heartburn), burning epigastric pain (dyspepsia), and regurgitation of acid material into his mouth. The symptoms are worse after a heavy meal and recumbency. He has no other symptoms. He does not take any medications. He smokes a pack of cigarettes every day and drinks a six-pack of beer on the weekends. Vital signs are normal.

- > What is the most likely diagnosis?

- > What are the next steps in management?
- > The patient's symptoms improve with lifestyle measures and daily proton pump inhibitors (PPIs). What is the next step in management?

CASE 5:

A 45-year-old woman presents with a 3-year history of difficulty swallowing (dysphagia) both solids and liquids. She describes the dysphagia as a sensation of food getting stuck substernally a few seconds after she swallows. The dysphagia has gotten worse over the last 12 months, and she reports a 10-lb weight loss this past year. She also complains of substernal burning after meals and occasional regurgitation of food contents. She complains of bad breath (halitosis) despite good oral hygiene. She has taken proton pump inhibitors (PPIs) in the past without any relief.

- > What is the most likely cause of this patient's dysphagia?
- > What is the next step in diagnosis?
- > What are the next diagnostic steps?

CASE 6:

The patient is 45-year-old woman who presents with intermittent dysphagia to solids and liquids over the last year. She has visited the emergency department three times in the same period for chest pain, and she has had a negative cardiac evaluation all three times. She undergoes esophagogastroduodenoscopy (EGD), which does not show any structural abnormalities.

- > What is the next step in management?
- > What therapy is recommended?

CASE 7:

A 50-year-old woman with a history of schizophrenia presents with difficulty swallowing solids but not liquids. She ingested two bottles of drain cleaner 2 months ago. The ingestion required admission to the intensive care unit (ICU). She smokes a pack of cigarettes a day and drinks a six-pack of beer almost every day.

- > What is the most likely cause of her symptoms?
- > What is the next diagnostic step?
- > What treatment is the patient likely to have received immediately after her ingestion?
- > What diagnostic workup is recommended?

CASE 8:

A 67-year-old man attends his general practitioner's (GP's) surgery. He says that he has lost 10 kg in weight over the last 4 months. This has been associated with a decrease in appetite and an increasing problem with vomiting. The vomiting has been productive of food eaten many hours previously. During the last month he has noticed some weakness, particularly in his legs, climbing hills and stairs.

He is a smoker of 20 cigarettes per day and drinks around 10 units of alcohol each week. There is no relevant family history. His past medical history consists of hypertension which was treated for 2 years with beta-blockers. He stopped taking these 4 months ago.

He looks thin and unwell. His pulse is 82/min. His blood pressure is 148/86 mmHg. There are no abnormalities to find on examination of the cardiovascular and respiratory systems. There are no masses to feel in the abdomen and no tenderness, but a succussion splash is present.

		Normal
Sodium	130 mmol/L	135-145 mmol/L
Potassium	3.0 mmol/L	3.5-5.0 mmol/L
Chloride	82 mmol/L	95-105 mmol/L
Bicarbonate	41 mmol/L	25-35 mmol/L
Urea	15.6 mmol/L	2.5-6.7 mmol/L
Creatinine	100 µmol	76-120 µmol
Calcium	2.38 mmol/L	2.12-2.65 mmol/L
Phosphate	1.16 mmol/L	0.8-1.45 mmol/L
Alkaline phosphatase	128 IU/L	30-300 IU/L

Alanine aminotransferase	32 IU/L	5-35 IU/L
Gamma-glutamyl transpeptidase	38 IU/L	11-51 IU/L

Full blood count: normal. Chest X-ray: clear

- > What is the likely explanation for these findings?
- > What is the most likely diagnosis?

PATH II: ABDOMINAL PAIN

CASE 9:

A 66-year-old man is admitted with complaints of progressively severe, constant upper abdominal pain, nausea, and vomiting of 48 hours duration. Recently, he has consumed large quantities of vodka, but has no history of biliary tract disease and is taking no medications.

He is a thin man, wincing and clutching his abdomen. His temperature is 38.0°C (100.4°F); blood pressure, 100/60 mm Hg; pulse, 90 beats per minute; and respirations, 18 per minute. His abdomen is flat and the bowel sounds are hypoactive. There is marked direct tenderness with guarding in the midepigastrium, but no peritoneal signs.

The following laboratory data are gathered: white blood cell count, 10,000 cells/mm³; hematocrit, 50%; serum creatinine, 1.3 mg/dL; total serum bilirubin, 3.4 mg/dL; alkaline phosphatase, 246 IU/L; AST, 209 IU/L; and serum amylase, 741 U/L.

Plain abdominal radiographs reveal the presence of scattered air-fluid levels, predominantly in the small bowel, but no calcification or subdiaphragmatic free air. An abdominal ultrasound examination reveals a dilated, fluid-filled gallbladder, a dilated common bile duct without definite calculi, and a poorly visualized pancreas because of overlying bowel gas.

A nasogastric tube is inserted and placed at low suction, and the patient remains NPO, receiving only IV fluids. Over the ensuing 48 hours, he requires regular doses of meperidine for the control of persistent, severe pain and is noted to have a rise in his bilirubin (8.0 mg/dL), alkaline phosphatase (450 IU/L), and AST (375 IU/L) levels. ERCP, performed on the third hospital day, demonstrates a dilated common bile duct that tapers smoothly in its intrapancreatic portion and contains no stones. The gallbladder is dilated and also contains no stones. No pancreatogram is obtained.

The aforementioned management is continued, and total parenteral nutrition is started. The patient's pain, abdominal tenderness, and liver test abnormalities gradually abate over the subsequent 10 days.

- > Why was an ERCP obtained?
- > What was the cause of the patient's biliary obstruction?

CASE 10:

A 40-year-old, alcoholic man complains of chronic abdominal pain and weight loss. He had consumed two pints of bourbon daily for the last 10 years, until 4 years ago, when he had his first episode of abdominal pain, which was characterized as a sharp, continuous epigastric pain radiating to the back, and associated with nausea and vomiting. He was admitted to the hospital, where his symptoms gradually abated with treatment, consisting of bowel rest and IV fluids for 1 week. His abdominal radiographs at that time revealed calcification in the area of the pancreas. He subsequently reduced his alcohol intake, but required readmission to the hospital on several occasions after the consumption of relatively small quantities of alcohol.

In recent months, the patient has lost 25 lb (11.25 kg), coincident with the passing of persistently loose and occasionally greasy stools. His abdominal pain has become constant, and a macrocytic anemia has developed.

The patient is cachectic, weighing 125 lb (56.25 kg). He has a scaphoid abdomen with normal bowel sounds and mild direct tenderness in the midepigastrium in response to palpation. There is moderate pedal edema.

Relevant laboratory data are: white blood cell count, 4,900 cells/mm³, with 65% segmented cells, 20% lymphocytes, and 10% monocytes; hematocrit, 37%; mean corpuscular volume, 106 Bµm³; prothrombin time, 14 seconds (control, 12 seconds); serum albumin, 2.7 g/dL; serum glucose, normal; serum and electrolytes and liver function tests are otherwise normal; serum vitamin B₁₂, 96 pg/mL (normal, >200 pg/mL); serum folate, normal; and 72-hour fecal fat excretion, 42 g (normal, <15 g).

The patient is started on a regimen of monthly vitamin B₁₂ injections and oral pancreatic enzymes, three capsules with each meal and one capsule with snacks. At first, he fails to gain weight and observes no reduction in the frequency of his bowel movements; his abdominal pain persists at a moderate severity. The dose of enzymes is increased to six capsules with each meal, and he also begins taking cimetidine (300 mg orally four times a day). Over a period of 1 month, his pain subsides considerably and he gains 15 lb (6.75 kg).

- > Is it unusual that the patient had his first attack of pancreatitis pain after 10 years of heavy alcohol consumption, and at that time he already had signs of chronic pancreatitis (pancreatic calcification)?
- > What is the pathophysiologic basis for vitamin B₁₂ deficiency in the setting of chronic pancreatitis?
- > Why did the patient begin to gain weight only after his pancreatic enzyme dose was increased and cimetidine added?
- > Why might the patient's pain have subsided toward the end of the described course?

CASE 11:

A 50-year-old man has had recurrent and at times severe epigastric abdominal pain for the last several years. Antacids have given him symptomatic relief. The most recent episode began 1 week ago and has not responded completely to antacids. The pain now wakes him up at night. He smokes one pack of cigarettes per day, and he takes aspirin several times a week. His family history is unremarkable. Physical examination reveals moderate epigastric tenderness without evidence of a mass. The stool is brown and positive for occult blood.

- > What are this man's risk factors for peptic ulcer disease?
- > What diagnostic tests should you consider?
- > When would you consider treatment for *H. pylori*?

CASE 12:

A 74-year-old woman has a 10-year history of intermittent lower abdominal pain. The pain has been colicky in nature and is associated with a feeling of distension in the left iliac fossa. It is generally relieved by passing flatus or faeces. She tends to be constipated and passes small pieces of faeces. Four years previously she passed some blood with her bowel motion and had a barium enema performed. This is shown in Fig. 12.1. Over the last week her pain has worsened and now she has continuous pain in the left iliac fossa and feels generally unwell. Her appetite has been poor over this same time. She has not had her bowels open over the last 2 days. In her previous medical history she had a hysterectomy for fibroids 20 years ago. There is a family history of ischaemic heart disease and diabetes mellitus. She lives alone and does her own cooking and shopping.

She has a temperature of 38.5°C and is tender with a vague impression of a mass in the left iliac fossa. There is no guarding or rebound tenderness and the bowel sounds are normal. Her pulse is 84/min and blood pressure is 154/88 mmHg. There are no abnormalities to find in the respiratory system.

		Normal
Haemoglobin	11.8 g/dL	11.7-15.7 g/dL
Mean corpuscular volume (MCV)	85 fL	80-99 fL
White cell count	15.6 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	235 X 10 ⁹ /L	150-440 X 10 ⁹ /L
C-reactive protein (CRP)	56 mg/L	<5 mg/L



Figure 12.1 Barium enema.

- > What is the likely diagnosis?
- > What should be the initial management?

CASE 13:

A 31-year-old woman has a 6-year history of abdominal pain and bloating. She has had an irregular bowel habit with periods of increased bowel actions up to four times a day and periods of constipation. Opening her bowels tends to relieve the pain which has been present in both iliac fossae at different times. She had similar problems around the age of 17 years which led to time off school. She thinks that her pains are made worse after eating citrus fruits and after some vegetables and wheat. She has tried to exclude these from her diet with some temporary relief but overall there has been no change in the symptoms over the 6 years. One year previously she was seen in a gastroenterology clinic and had a sigmoidoscopy which was normal. She found the procedure very uncomfortable and developed similar symptoms of abdominal pain during the procedure. She is anxious about the continuing pain but is not keen to have a further endoscopy.

She has a history of occasional episodes of headache which have been diagnosed as migraine and has irregular periods with troublesome period pains but no other relevant medical history. She is a non-smoker who does not drink alcohol. Her paternal grandmother died of carcinoma of the colon aged 64 years. Her parents are alive and well. She works as a secretary.

Examination of the cardiovascular and respiratory systems is normal. She has a palpable, rather tender colon in the left iliac fossa.

		<i>Normal</i>
Haemoglobin	14.7 g/dL	11.7-15.7 g/dL
Mean corpuscular volume (MCV)	84 fL	80-99 fL
White cell count	5.3 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	2 44 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Erythrocyte sedimentation rate (ESR)	8 mm/h	<10 mm/h
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.4 mmol/L	3.5-5.0 mmol/L
Urea	4.2 mmol/L	2.5-6.7 mmol/L
Creatinine	89 µmol/L	70-120 µmol/L
Glucose	4.6 mmol/L	4.0-6.0 mmol/L

- > What is the most likely diagnosis and what investigations should be performed?

CASE 14:

A 56-year-old woman presents to the emergency department complaining of abdominal pain. Twenty-four hours previously she developed a continuous pain in the upper abdomen which has become progressively more severe. The pain radiates into the back. She feels nauseated and alternately hot and

cold. Her past medical history is notable for a duodenal ulcer which was successfully treated with *Helicobacter* eradication therapy 5 years earlier. She smokes 15 cigarettes a day, and shares a bottle of wine each evening with her husband.

The patient looks unwell and dehydrated. She weighs 115 kg. She is febrile, 38.5°C, her pulse is 108/min and blood pressure 124/76 mmHg. Cardiovascular and respiratory system examination is normal. She is tender in the right upper quadrant and epigastrium, with guarding and rebound tenderness. Bowel sounds are sparse.

		<i>Normal</i>
Haemoglobin	14.7 g/dL	11.7-15.7 g/dL
White cell count	19.8 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	239 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Sodium	137 mmol/L	135-145 mmol/L
Potassium	4.8 mmol/L	3.5-5.0 mmol/L
Urea	8.6 mmol/L	2.5-6.7 mmol/L
Creatinine	116 µmol/L	70-120 µmol/L
Bilirubin	19 µmol/L	3-17 µmol/L
Alkaline phosphatase	58IU/L	30-300 IU/L
Alanine aminotransferase (AAT)	67IU/L	5-35 IU/L
Gamma-glutamyl transpeptidase	72 IU/L	11-51 IU/L
C-reactive protein (CRP)	256 mg/L	<5 mg/L

A plain abdominal X-ray is shown in Fig. 14.1.



Figure 14.1 Plain abdominal X-ray.

- > What is the most likely diagnosis?
- > How would you manage this patient?

CASE 15:

A 37-year-old executive returns to your office for follow-up of recurrent upper abdominal pain. He initially presented 6 weeks ago, complaining of an increase in frequency and severity of burning epigastric pain, which he has experienced occasionally for more than 2 years. Now the pain occurs three or four times per week, usually when he has an empty stomach, and it often awakens him at night. The pain usually is relieved within minutes by food or over-the-counter antacids but then recurs within 2 to 3 hours. He admitted that stress at work had recently increased and that because of long working hours, he was drinking more caffeine and eating a lot of take-out foods. His medical history and review of systems were otherwise unremarkable, and, other than the antacids, he takes no medications. His physical examination was normal, including stool guaiac that was negative for occult blood. You advised a change in diet and started him on an H blocker. His symptoms resolved completely with the diet changes and daily use of the medication. Results of laboratory tests performed at his first visit show no anemia, but his serum *Helicobacter pylori* antibody test was positive.

- > What is your diagnosis?
- > What is your next step?

CASE 16:

A 42-year-old Hispanic woman presents to the emergency department complaining of 24 hours of severe, steady epigastric abdominal pain, radiating to her back, with several episodes of nausea and vomiting. She has experienced similar painful episodes in the past, usually in the evening following heavy meals, but the episodes always resolved spontaneously within an hour or two. This time the pain did not improve, so she sought medical attention. She has no medical history and takes no medications. She is married, has three children, and does not drink alcohol or smoke cigarettes.

On examination, she is afebrile, tachycardic with a heart rate of 104 bpm, blood pressure 115/74 mm Hg, and shallow respirations of 22 breaths per minute. She is moving uncomfortably on the stretcher, her skin is warm and diaphoretic, and she has scleral icterus. Her abdomen is soft, mildly distended with marked right upper quadrant and epigastric tenderness to palpation, hypoactive bowel sounds, and no masses or organomegaly appreciated. Her stool is negative for occult blood. Laboratory studies are significant for a total bilirubin (9.2 g/dL) with a direct fraction of 4.8 g/dL, alkaline phosphatase 285 IU/L, aspartate aminotransferase (AST) 78 IU/L, alanine aminotransferase (ALT) 92 IU/L, and elevated amylase level 1249 IU/L. Her leukocyte count is 16,500/mm³ with 82% polymorphonuclear cells and 16% lymphocytes. A plain film of the abdomen shows a nonspecific gas pattern and no pneumoperitoneum.

- > What is the most likely diagnosis?
- > What is the most likely underlying etiology?
- > What is your next diagnostic step?

CASE 17:

A 61-year-old man comes to the emergency room complaining of 3 days of worsening abdominal pain. The pain is localized to the left lower quadrant of his abdomen. It began as an intermittent crampy pain and now has become steady and moderately severe. He feels nauseated, but he has not vomited. He had a small loose stool at the beginning of this illness, but he has not had any bowel movements since. He has never had symptoms like this before, nor any gastrointestinal (GI) illnesses.

On examination, his temperature is 100.2°F, heart rate 98 bpm, and blood pressure 110/72 mm Hg. He has no pallor or jaundice. His chest is clear, and his heart rhythm is regular without murmurs. His abdomen is mildly distended with hypoactive bowel sounds and marked left lower quadrant tenderness with voluntary guarding. Rectal examination reveals tenderness, and his stool is negative for occult blood.

Laboratory studies are significant for a white blood cell (WBC) count of 800/mm³ with 74% polymorphonuclear leukocytes, 22% lymphocytes, and a normal hemoglobin and hematocrit. A plain film of the abdomen shows no pneumoperitoneum and a nonspecific bowel gas pattern.

- > What is the most likely diagnosis?
- > What is the most appropriate next step?

CASE 18:

A 32-year-old man presents with 4 months of burning epigastric pain between meals relieved by food and antacids. He also reports foul-smelling watery diarrhea and steatorrhea. He does not take nonsteroidal anti-inflammatory drugs (NSAIDs), smoke cigarettes, or drink alcohol. Serology is negative for *H. pylori*. His symptoms persist despite 8 weeks of daily esomeprazole. He then undergoes esophagogastroduodenoscopy (EGD), which shows multiple ulcers, one of which is in the jejunum.

- > What diagnosis should you suspect?
- > What causes Zollinger-Ellison syndrome (ZES)? How can you confirm the diagnosis?
- > How is gastrinoma treated?
- > What is the next step in management?

CASE 19:

The patient is a 70-year-old man with a history of peripheral artery disease and stable angina. He complains of severe upper abdominal cramping approximately 1 hour after meals for the last 6 months. The pain occasionally radiates to his back. The fear of these cramps has caused him to decrease his food

intake considerably, and he has lost 15 lbs in the last 3 months. He has smoked a pack of cigarettes every day for the last 40 years. Esophagogastroduodenoscopy is unremarkable. Serology as well as biopsy does not reveal any evidence of *H. pylori* infection. Serum amylase and lipase are normal. Albumin is low but other liver function tests (LFTs) are normal. There is an upper abdominal bruit. There is no tenderness, guarding, or rebound.

- > What diagnosis should you suspect?
- > How is this condition diagnosed and treated?

CASE 20:

A 53-year-old man presents with 12 hours of nausea, vomiting, and cramping abdominal pain. He had an appendectomy 3 months ago. On physical exam, the abdomen is distended, and there are high-pitched bowel sounds. Abdominal percussion demonstrates a low-pitched drum-like sound (tympany). The rectal vault is empty. There are no abdominal masses. Vital signs are temperature 37°C, pulse 110 bpm, respirations 12/min, and blood pressure 100/70.

- > What diagnosis should you suspect?
- > What are the next steps in diagnosis?
- > How is small bowel obstruction (SBO) treated?
- > The patient's pain, nausea, and abdominal distension improve over the next 24 hours with fluids and NG suction. NG suction is discontinued. Over the next 4 hours, signs and symptoms of SBO recur. What is the next step in management?

CASE 21:

A 53-year man presents with a 12-hour history of cramping abdominal pain. Physical examination is significant for abdominal distension, hyperactive bowel sounds, and an empty rectal vault. Abdominal x-ray is obtained (see Fig. 21-1).



52-11

Figure 21–1. Abdomen x-ray showing cecal volvulus.

- > What is the diagnosis?
- > What is the next step in management?
- > What diagnosis would be more likely if Figure 4-11 was the patient's abdominal film?

CASE 22:

The patient is a 65-year-old man presents with a 6-hour history of severe diffuse cramping abdominal pain, nausea, and vomiting. He has a history of atrial fibrillation and peripheral vascular disease. Abdominal examination is benign. Vital signs are temperature 36.8°C, pulse 115 bpm, respirations 25/min, and blood pressure 110/70.

- > What diagnosis should you suspect?
- > What are the types of acute mesenteric ischemia?
- > What are the next steps in management of patients with suspected mesenteric ischemia?

CASE 23:

A 75-year-old man presents with 3 days of abdominal pain localized to the left lower quadrant (LLQ) and mild nausea. Past medical history is unremarkable. Physical examination is significant for LLQ tenderness. There is a palpable mass in the LLQ. Stool is guaiac-negative. Vital signs are temperature 38.4°C, pulse 90 bpm, respirations 18/min, and blood pressure 120/80. The only significant laboratory finding is a WBC count of 11,500 cells/cubic mm with a left shift.

- > What is most likely cause of the patient's current symptoms?
- > What is the next step in this patient with suspected diverticulitis?

CASE 24:

A 70-year-old man presents with diffuse, cramping left lower quadrant (LLQ) pain. The pain began approximately 24 hours ago. At 16 hours after the onset of pain, he noticed small amounts of bright red blood per rectum (hematochezia) followed by a small amount of bloody diarrhea. Past medical history is significant for peripheral vascular disease and MI 5 years ago. LLQ tenderness is the only abnormal finding on physical examination. Vital signs are normal. The only significant laboratory finding is a WBC count of 11,500 cells/cubic mm with a left shift.

- > What is the most likely diagnosis?
- > What diagnostic tests are indicated?
- > Abdominal plain film is nondiagnostic, but computed tomography (CT) scan shows segmental thickening of bowel wall indicative of acute ischemic colitis. What treatment is indicated?

CASE 25:

A 30-year-old woman presents with episodes of diffuse, cramping, abdominal pain occurring over the last 12 months. The episodes occur about twice a week. The pain is often accompanied by diarrhea, which she defines as frequent loose stools of small to moderate volume. She has noticed mucus in her stool but not blood. The stool is not foul smelling. Sometimes she has constipation rather than diarrhea. During this episode, stool is hard and pellet-shaped. Defecation often improves her abdominal discomfort. She denies anorexia, weight loss, or difficulty swallowing. She does not take any medications. Physical examination and vital signs are normal.

- > What is the most likely diagnosis?
- > What is the next step in management?
- > What are alarm findings that would warrant further diagnostic testing?
- > Laboratory testing is normal. Stool is guaiac-negative. How is IBS treated?

CASE 26:

A 63-year-old man with a history of arterial hypertension and peripheral vascular disease presents for a routine follow-up appointment. He takes hydrochlorothiazide and propranolol. He has a 30-pack/year history of smoking. On physical examination, a pulsatile abdominal mass is palpated just above the level of the umbilicus. Vital signs are normal.

- > What condition should you suspect?
- > What is the next step in management?
- > When is elective surgery warranted for abdominal aortic aneurysm (AAA)?
- > Ultrasound detects a 4.2-cm AAA. What treatment is recommended at this time?
- > When is elective surgery warranted for AAA?

CASE 27:

A 35-year-old woman with a history of polycythemia vera presents with a 2-month history of fatigue and vague discomfort in the right upper quadrant (RUQ). Physical examination is significant for scleral icterus and hepatomegaly. Liver function tests (LFTs) are AST 140 U/L, ALT 120 U/L, GGT 100 U/L, alkaline phosphatase 100 g/dl, total bilirubin 2.4 g/dL, serum albumin 3.0 g/dL, PT 20 seconds. There is no history of alcohol use. Serologies for viral and nonviral causes of liver disease are negative. RUQ ultrasound shows occlusion of the hepatic vein.

- > What is the diagnosis?
- > How is Budd-Chiari syndrome treated?

CASE 28:

A 54-year-old man presents with a 12-month history of severe epigastric pain radiating to the back. The pain occurs in episodes that last for 7 to 8 days and are followed by 1 to 2 pain-free months. Past history is significant for alcoholism and acute pancreatitis. He smokes two packs of cigarettes a day. Physical exam and vital signs are normal. Complete blood count (CBC), serum electrolytes, liver function tests (LFTs), amylase and lipase are all normal.

- > What diagnosis should you suspect?
- > What are the causes of chronic pancreatitis in adults?
- > What is the next diagnostic step?
- > What is the natural history of chronic pancreatitis?
- > How is chronic pancreatitis treated?
- > What is the most likely cause of his symptoms?
- > What are risk factors for pancreatic cancer?
- > What is the next step in management?

CASE 29:

A 60-year-old alcoholic man presents with a 12-hour history of severe epigastric pain radiating to the back, nausea, and vomiting. Pain is somewhat better when he leans forward. He drank a 24-pack of beer 2 days ago. He does not take any medications. Physical exam is significant for abdominal distension, decreased bowel sounds, and epigastric tenderness with guarding. Vital signs are temperature 38.1°C, pulse 110 bpm, respirations 27/min, and blood pressure 130/85.

- > What is the most likely diagnosis?
- > What are the causes of acute pancreatitis in adults?
- > What are the next diagnostic steps?

PATH III: CHRONIC DIARRHEA SYNDROME

CASE 30:

A 23-year-old female presents with a 2-day history of diarrhea, nausea, vomiting, and mild abdominal cramps. She describes her stools as watery and unformed occurring three to four times a day. She does not have any abdominal pain, nausea, vomiting, or blood in her stool. She denies recent travel, sick contacts, antibiotic use, or hospitalization. She is a vegan; she has never had sexual intercourse or used IV drugs. She works at home as a software designer. Physical exam and vitals are normal.

- > What is the differential diagnosis of acute diarrhea?
- > What is the next step in management?

CASE 31:

A 28-year-old man comes to the emergency room complaining of 2 days of abdominal pain and diarrhea. He describes his stools as frequent, with 10 to 12 per day, small volume, sometimes with visible blood and mucus, and preceded by a sudden urge to defecate. The abdominal pain is crampy, diffuse, and moderately severe, and it is not relieved with defecation. In the past 6 to 8 months, he has experienced similar episodes of abdominal pain and loose mucoid stools, but the episodes were milder and resolved within 24 to 48 hours. He has no other medical history and takes no medications. He has neither traveled out of the United States nor had contact with anyone with similar symptoms. He works as an accountant and does not smoke or drink alcohol. No member of his family has gastrointestinal (GI) problems.

On examination, his temperature is 99°F, heart rate 98 bpm, and blood pressure 118/74 mm Hg. He appears uncomfortable, is diaphoretic, and is lying still on the stretcher. His sclerae are anicteric, and his oral mucosa is pink and clear without ulceration. His chest is clear, and his heart rhythm is regular, without murmurs. His abdomen is soft and mildly distended, with hypoactive bowel sounds and minimal diffuse tenderness but no guarding or rebound tenderness.

Laboratory studies are significant for a white blood cell (WBC) count of 15,800/mm³ with 82% polymorphonuclear leukocytes, hemoglobin 10.3 g/dL, and platelet count 754,000/mm³. The HIV (human immunodeficiency virus) assay is negative.

Renal function and liver function tests are normal. A plain film radiograph of the abdomen shows a mildly dilated air-filled colon with a 4.5-cm diameter and no pneumoperitoneum or air/fluid levels.

- > What is the most likely diagnosis?
- > What is your next step?

CASE 32:

A 37-year-old man with documented chronic ulcerative colitis (CUC) was first seen at 19 years because of severe bloody diarrhea and left lower quadrant abdominal pain that necessitated hospitalization. After 10 days of treatment with high-dose prednisone and sulfasalazine his symptoms were controlled, and he has since been managed with these medicines, with the dosages adjusted depending on his disease activity. He has not required corticosteroids except for flare-ups of disease. Subsequent to his initial presentation, after his disease activity had subsided, he underwent colonoscopy for histologic confirmation of the disease and to determine the extent of intestinal involvement; this examination revealed diffuse mucosal inflammation involving the entire colon (pancolitis). The terminal ileum appeared normal. Colonic biopsy specimens revealed a diffuse mucosal inflammatory infiltrate with little involvement of the submucosa, acute and chronic inflammatory cells, and frequent crypt abscesses but no granulomas.

The patient went on to graduate from college and was then hired as a sales representative for a pharmaceutical company. Because his disease has been quiescent and his schedule very busy he has not taken his medications regularly and has rarely seen his physician.

Approximately 2 months ago, he began to feel tired, and intermittent rectal bleeding developed. His physical examination findings are unremarkable, but the fecal occult blood test result is positive. The hemoglobin is 11 g/dL; hematocrit, 33%; and leukocyte count, 7,700 cells/mm³, with a normal differential count.

- > What is your differential diagnosis of his recent symptoms?
- > What tests are necessary to make the correct diagnosis?
- > How should this patient's CUC have been managed over the previous 18 years?

CASE 33:

A 27-year-old woman complains of 11 months of diarrhea, gas, and abdominal cramps. She has five or six loose bowel movements a day, and diarrhea often awakens her from sleep. She also complains of abdominal cramps that are most severe just before a bowel movement, and are then temporarily relieved with the bowel movement. In addition, she feels tired and has lost approximately 8 lb (3.6 kg) without dieting. She has noted a tendency to bruise easily. She drinks four glasses of milk a day.

Her past medical history is positive only for fatigue, for which she saw another physician 11 months ago, before the diarrhea developed. The physician told her that she had an iron-deficiency anemia. Since then, she has taken ferrous sulfate (300 mg four times daily), but still feels fatigued. She takes no other medication.

Physical examination reveals a young woman who appears mildly underweight but is otherwise normal.

Laboratory test results are as follows: white blood cell count, normal; hematocrit, 34%; mean corpuscular volume, 74 B μ m³; serum iron, 50 mg/dL; total iron-binding capacity, 435 mg/dL; stool leukocyte test, negative; stool examination for ova and parasites, negative; serum albumin, 3.2 mg/dL; serum electrolytes, normal; and prothrombin time, 2 seconds greater than control.

While awaiting these laboratory results, you advise the patient to stop ingesting all milk products. The patient reports that this reduces but does not eliminate the diarrhea or gas.

- > What additional history should you obtain from the patient?
- > What might lead you to suspect that malabsorption is the cause of this patient's diarrhea, and why? What test should be performed to confirm this, and why?
- > This patient's fecal fat excretion is measured and found elevated, which proves she has maldigestion or malabsorption.
- > Considering that the patient has either maldigestion or malabsorption, what are the two disorders that may decrease the bile acid pool, two disorders that decrease pancreatic lipase activity, and two disorders that may decrease absorption by small bowel enterocytes?
- > How does the D-xylose test differentiate problems with digestion (e.g., bile salt depletion and

pancreatic lipase deficiency) from problems with absorption? Name one disorder that may produce a false-positive result.

- > The D-xylose test in this patient reveals poor absorption of this sugar, which indicates that the small bowel absorption probably is abnormal.
- > On the basis of the results of the D-xylose test, what test should be performed now?
- > A small bowel biopsy specimen in this patient reveals mucosal villous atrophy and crypt hyperplasia, accompanied by an increased number of plasma cells and lymphocytes in the lamina propria and an increased number of lymphocytes in the epithelium.
- > Although the biopsy findings indicate celiac sprue, what other disorders could produce such a flat mucosa?
- > How can the diagnosis of celiac sprue be confirmed?
- > If the D-xylose test result was abnormal, but the small bowel biopsy findings were normal, a bacterial overgrowth in the proximal small intestine might be suspected. How should this possibility be evaluated?
- > If this patient's D-xylose absorption test result had been normal, what disorder might you suspect and how should you evaluate this possibility?
- > Why did the symptoms in this patient, who had celiac sprue, abate when she stopped drinking milk?

CASE 34:

A 34-year-old woman presents to her general practitioner complaining of a rash. Over the past 2 weeks she has developed multiple tender red swellings on her shins and forearms. The older swellings are darker in colour and seem to be healing from the centre. She feels generally unwell and tired and also has pains in her wrists and ankles. She has not had a recent sore throat. Over the past 2 years she has had recurrent aphthous ulcers in her mouth. She has had no genital ulceration but she has been troubled by intermittent abdominal pain and diarrhoea. She works as a waitress and is unmarried. She smokes about 15 cigarettes per day and drinks alcohol only occasionally. She has had no other previous medical illnesses and there is no relevant family history that she can recall.

She is thin but looks well. There are no aphthous ulcers to see at the time of the examination. Her joints are not inflamed and the range of movement is not restricted or painful. Examining the skin there are multiple tender lesions on the shins and forearms. The lesions are raised and vary from 1 to 3 cm in diameter. The fresher lesions are red and the older ones look like bruises. Physical examination is otherwise normal.

		Normal
Haemoglobin	13.5 g/dL	11.7-15.7 g/dL
White cell count	15.4 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	198 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Erythrocyte sedimentation rate (ESR)	98 mm/h	<10 mm/h
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.3 mmol/L	3.5-5.0 mmol/L
Urea	5.4 mmol/L	2.5-6.7 mmol/L
Creatinine	86 µmol/L	70-120 µmol/L
Glucose	5.8 mmol/L	4.0-6.0 mmol/L

Chest X-ray: normal. Urinalysis: normal.

- > What is the diagnosis?
- > What are the major causes of this condition?

CASE 35:

A 60-year-old woman was hospitalized 5 days ago for treatment of a diabetic foot infection. On the first day in the hospital, clindamycin was initiated. The patient now complains of eight to nine watery stools per day, nausea, vomiting, and abdominal cramps relieved by defecation. On physical examination, skin turgor is decreased. Temperature is 38.6°C. Other vital signs are normal.

- > What diagnostic test is indicated in addition to fecal leukocytes and faecal occult blood?

- > C. difficile cytotoxin assay is positive. How is C. difficile infection treated?

CASE 36:

A 24-year-old Caucasian female presents with a 6-month history of diarrhea. She reports three to four watery stools a day. She has not noticed any blood in her stools. She also reports decreased appetite and a 5-lb weight loss. She sometimes takes Imodium (loperamide), which partially controls her symptoms. She tried a trial of lactose avoidance, which failed to control her symptoms. She has not taken any other medications or been hospitalized in the past year. She does not have any other medical problems. Physical examination and vital signs are normal.

- > What initial workup is indicated for this patient with chronic diarrhea?
- > The only significant laboratory abnormalities are mild iron deficiency anemia and a mildly decreased total protein and albumin. What is the next step in the evaluation?
- > What stool analysis findings are associated with the different categories of diarrhea?
- > Positive findings on stool analysis are osmotic gap 120, steatorrhea, and guaiac-positive stool. Fecal leukocytes are not elevated. Laxative screen is negative. What is the next step in management?
- > What are the next steps in management?
- > What are possible extraintestinal manifestations of celiac sprue?
- > The patient asks about her long-term prognosis. What should you tell her?

PATH IV: CONSTIPATION

CASE 37:

A 51-year-old woman presents to the clinic with constipation. She has only had one or two stools/week for the last 6 weeks. She does not have any other symptoms. She had a negative screening colonoscopy in the past year. She does not take any medications. Physical examination, including anorectal examination, is normal. Vital signs are normal.

- > What is constipation?
- > What are some common secondary causes of constipation?
- > What is the next step in management?
- > Laboratory tests are all negative. What are the next steps in management?
- > What specialized tests are available for patients with constipation?

CASE 38:

A 66-year-old woman, a retired nurse, consults her general practitioner with a 4-month history of tiredness, slight breathlessness on exertion and loss of weight from 71 to 65 kg. Her appetite is unchanged and normal, she has no nausea or vomiting, but over the last 2 months she has had an altered bowel habit with constipation alternating with her usual and normal pattern. She has not seen any blood in her faeces and has had no abdominal pain. There is no relevant past or family history, and she is on no medication. She has smoked 20 cigarettes daily for 48 years and drinks 20-28 units of alcohol a week.

She has slight pallor but otherwise looks well. No lymphadenopathy is detected, and her breasts, thyroid, heart, chest and abdomen, including rectal examination, are all normal. The blood pressure is 148/90 mmHg.

		<i>Normal</i>
Haemoglobin	10.1 g/dL	11.7-15.7 g/dL
Mean corpuscular volume (MCV)	76 fL	80-99 fL
White cell count	4.9 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	277 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Sodium	142 mmol/L	135-145 mmol/L
Potassium	4.4 mmol/L	3.5-5.0 mmol/L
Urea	5.2 mmol/L	2.5-6.7 mmol/L
Creatinine	106	70-120 µmol/L

Urinalysis: no protein, no blood. Blood film shows a microcytic hypochromic picture.

- > What is the likeliest diagnosis?
- > How would you investigate the patient?

PATH V: JAUNDICE

CASE 39:

A 28-year-old man comes to your office complaining of a 5-day history of nausea, vomiting, diffuse abdominal pain, fever to 101°F, and muscle aches. He has lost his appetite, but he is able to tolerate liquids and has no diarrhea. He has no significant medical history or family history, and he has not traveled outside the United States.

He admits to having 12 different lifetime sexual partners, denies illicit drug use, and he drinks alcohol occasionally, but not since this illness began. He takes no medications routinely, but he has been taking acetaminophen, approximately 30 tablets per day for 2 days for fever and body aches since this illness began. On examination, his temperature is 100.8°F, heart rate 98 bpm, and blood pressure 120/74 mm Hg. He appears jaundiced, his chest is clear to auscultation, and his heart rhythm is regular without murmurs. His liver percusses 12 cm, and is smooth and slightly tender to palpation. He has no abdominal distention or peripheral edema. Laboratory values are significant for a normal complete blood count, creatinine 1.1 mg/dL, alanine aminotransferase (ALT) 3440 IU/L, aspartate aminotransferase (AST) 2705 IU/L, total bilirubin 24.5 mg/dL, direct bilirubin 18.2 mg/dL, alkaline phosphatase 349 IU/L, serum albumin 3.0 g/dL, and prothrombin time 14 seconds.

- > What is the most likely diagnosis?
- > What is the most important immediate diagnostic test?

CASE 40:

A 30-year-old man presents to the clinic for a routine physical. On examination, the physician detects scleral icterus and yellow nail beds. Liver function tests (LFTs) are AST 1200 U/L, ALT 1600 U/L, alkaline phosphatase 150 U/L, GGT 70 U/L, serum bilirubin 2.4 g/dL, serum albumin 3.5 g/dL, PT 12 seconds, International Normalized Ratio (INR) 1.0. Hepatitis virus serologies are HCV antibody (–), HBsAg (+), HbcAb IgM (+), and HBsAb (–).

- > What is the diagnosis?
- > What treatment is recommended for this patient with acute infection?

CASE 41:

A 48-year-old woman with a history of asymptomatic gallstones presents with an 8-hour history of right upper quadrant (RUQ) pain. There is jaundice on exam. Murphy's sign is negative. Vital signs are temperature 38.8°C, pulse 120 bpm, respirations 25/min, and blood pressure 125/80. Significant laboratory findings are leukocytosis with a left shift, mildly elevated amylase, and cholestatic liver function tests (LFTs).

- > What is the most likely diagnosis?
- > What are risk factors for cholangitis?
- > What are the next diagnostic steps?
- > How is this condition treated?
- > What is the next step in management?

CASE 42:

A 63-year-old woman is brought in to the surgery by her neighbour who has been worried that she looks increasingly unwell. On direct questioning she says that she has felt increasingly tired for around 2 years. She has been off her food but is unclear whether she has lost any weight. She was diagnosed with hypothyroidism 8 years ago and has been on thyroxine replacement but has not had her blood tests checked for a few years. Her other complaints are of itching for 2-3 months, but she has not noticed any rash. She says that her mouth has been dry and, on direct questioning, thinks her eyes have also felt dry.

There has been no disturbance of her bowels or urine although she thinks that her urine has been rather 'strong' lately. She is 14 years postmenopausal. There is a family history of thyroid disease and of diabetes. She does not smoke, and drinks two glasses of sherry every weekend. She has never drunk

more than this regularly. She has taken occasional paracetamol for headaches but has been on no regular medication other than thyroxine and some vitamin tablets she buys from the chemist.

Her sclerae look a little yellow and she has xanthelasmata around the eyes. There are some excoriated marks from scratching over her back and upper arms. The pulse is 74/min and regular, blood pressure is 128/76 mmHg. No abnormalities are found in the cardiovascular or respiratory system. In the abdomen, the liver is not palpable but the spleen is felt cm under the left costal margin. It is not tender.

		Normal
Sodium	142 mmol/L	135-145 mmol/L
Potassium	4.2 mmol/L	3.5-5.0 mmol/L
Urea	5.6 mmol/L	2.5-6.7 mmol/L
Creatinine	84 µmol/L	70-120 µmol/L
Calcium	2.24 mmol/L	2.12-2.65 mmol/L
Phosphate	1.09 mmol/L	0.8-1.45 mmol/L
Total bilirubin	84 mmol/L	3-17 mmol/L
Alkaline phosphatase	494 IU/L	30-300 IU/L
Alanine aminotransferase	63 IU/L	5-35 IU/L
Gamma-glutamyl transpeptidase	568 IU/L	11-51 IU/L
Thyroid stimulating hormone	1.2 mU/L	0.3-6.0 mU/L
Cholesterol	7.8 mmol/L	<5.5 mmol/L
Fasting glucose	4.7 mmol/L	4.0-6.0 mmol/L

- > What is your interpretation of these findings?
- > What is the likely diagnosis and how might this be confirmed?

CASE 44:

A 70-year-old woman has been complaining of upper abdominal pain which has increased over the last 3 days. It has been a general ache in the upper abdomen and there have been some more severe waves of pain. She has vomited three times in the last 24 h. On two or three occasions in the past 5 years she has had a more severe pain in the right upper abdomen. This has sometimes been associated with feeling as if she had a fever and she was treated with antibiotics on one occasion. Her appetite is generally good but she has been off her food over the last week. She has not lost any weight. There have been no urinary or bowel problems but she does say that her urine may have been darker than usual for a few days and she thinks the problem may be a urinary infection.

In her previous medical history she has had hypothyroidism and is on replacement thyroxine. She has annual blood tests to check on the dose; the last test was 3 months ago. She has had some episodes of chest pain on exercise once or twice a week for 6 months and has been given atenolol 50 mg daily and a glyceryl trinitrate spray to use sublingually as needed.

Her sclerae are yellow. Her pulse is 56/min and regular. Her blood pressure is 122/80 mmHg. There are no abnormalities in the cardiovascular system or respiratory system. She is tender in the right upper abdomen and there is marked pain when feeling for the liver during inspiration. No masses are palpable in the abdomen. She is clinically euthyroid.

		Normal
Sodium	139 mmol/L	135-145 mmol/L
Potassium	4.1 mmol/L	3.5-5.0 mmol/L
Urea	6.4 mmol/L	2.5-6.7 mmol/L
Creatinine	110 µmol/L	70-120 µmol/L
Calcium	2.44 mmol/L	2.12-2.65 mmol/L
Phosphate	1.19 mmol/L	0.8-1.45 mmol/L
Total bilirubin	83 mmol/L	3-17 mmol/L
Alkaline phosphatase	840 IU/L	30-300 IU/L
Alanine aminotransferase	57 IU/L	5-35 IU/L
Gamma-glutamyl transpeptidase	434 IU/L	11-51 IU/L

- > How do you interpret these findings?

- > What is the appropriate management?

CASE 45:

A 58-year-old woman consults her general practitioner with a 2-month history of intermittent dull central epigastric pain. It has no clear relationship to eating and no radiation. Her appetite is normal, she has no nausea or vomiting and she has not lost weight. Her bowel habit is normal and unchanged. There is no relevant past or family history. She has never smoked, and drinks alcohol very rarely. She has worked all her life as an infant school teacher. Physical examination at this time was completely normal, with a blood pressure of 128/72 mmHg. Investigations showed normal full blood count, urea, creatinine and electrolytes, and liver function tests.

An H2 antagonist was prescribed and follow-up advised if her symptoms did not resolve. There was slight relief at first, but after 1 month the pain became more frequent and severe, and the patient noticed that it was relieved by sitting forward. It had also begun to radiate through to the back. Despite the progressive symptoms she and her husband went on a 2-week holiday to Scandinavia which had been booked long before. During the second week her husband remarked that her eyes had become slightly yellow, and a few days later she noticed that her urine had become dark and her stools pale. On return from holiday she was referred to a gastroenterologist.

She was found to have yellow sclerae with a slight yellow tinge to the skin. There was no lymphadenopathy and her back was normal. As before her heart, chest and abdomen were normal.

		Normal
Haemoglobin	15.3 g/dL	11.7-15.7 g/dL
White cell count	6.2 X 10 ⁹ /L	3.5-11.0 X 10 ⁹ /L
Platelets	280 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Sodium	140 mmol/L	135-145 mmol/L
Potassium	4.8 mmol/L	3.5-5.0 mmol/L
Urea	6.5 mmol/L	2.5-6.7 mmol/L
Creatinine	111 µmol/L	70-120 µmol/L
Calcium	2.44 mmol/L	2.12-2.65 mmol/L
Phosphate	1.19 mmol/L	0.8-1.45 mmol/L
Total bilirubin	97 mmol/L	3-17 mmol/L
Alkaline phosphatase	1007 IU/L	30-300 IU/L
Alanine aminotransferase	38 IU/L	5-35 IU/L
Gamma-glutamyl transpeptidase	499 IU/L	11-51 IU/L

- > What is the likely diagnosis?

CASE 46:

A 57-year-old man comes to the office complaining of malaise for several weeks. He says that he has not been feeling well for some time, with fatigue, depressed mood, loss of appetite, and a 20-lb unintentional weight loss. In addition, he has been bothered by generalized itching of his skin and has tried moisturizing lotions and creams without improvement. He denies fevers, abdominal pain, nausea, vomiting, or diarrhea. He does think his stools have been lighter in color recently. He has no other medical history and takes no medications except for a multivitamin. He drinks alcohol occasionally and smokes cigars.

On examination, he is afebrile, with heart rate 68 bpm and blood pressure 128/74 mm Hg. He has a flat affect and a somewhat disheveled appearance. He has noticeable icterus of his sclera and skin. His chest is clear, and his heart rhythm is regular without murmurs. His abdomen is soft and nontender with active bowel sounds, a liver span of 10 cm, and no splenomegaly or masses. His skin has a few excoriations on his arms and back, but no rashes or telangiectasias.

Blood is obtained for laboratory analysis; the results are available the next day. His serum albumin is 3.1 g/dL, alkaline phosphatase 588 IU/L, total bilirubin 8.5 mg/dL, direct bilirubin 6 mg/dL, alanine aminotransferase (ALT) 175 IU/L, and aspartate aminotransferase (AST) 140 IU/L. His hemoglobin level is 13.5 g/dL. Prothrombin time (PT) is 15 seconds, and partial thromboplastin time (PTT) is 32

- > What is the most likely diagnosis?
- > What is the next step?

CASE 47:

A physician detects scleral icterus in a 40-year-old woman with a history of type 1 diabetes. Liver function tests (LFTs) are AST 270, ALT 290, GGT 40 U/L, alkaline phosphatase 45 U/L, total bilirubin 2.2 mg/dL. Viral serologies are negative. Iron studies are normal. Elevated amino transaminases persist for 6 months. SPEP reveals polyclonal increase in serum globulins more than twice the upper limit of normal (hypergammaglobulinemia).

- > What is the most likely diagnosis?
- > What is the next step in management?
- > How should you treat this patient with anti-nuclear antibodies (ANA)?
- > What is the next step in management?

PATH VI: ASCITES

CASE 48:

A 49-year-old woman presents to the emergency room complaining of a 4-week history of progressive abdominal swelling and discomfort. She has no other gastrointestinal symptoms, and she has a normal appetite and normal bowel habits. Her medical history is significant only for three pregnancies, one of which was complicated by excessive blood loss, requiring a blood transfusion. She is happily married for 20 years, exercises, does not smoke, and drinks only occasionally. On pointed questioning, however, she does admit that she was “wild” in her youth, and she had snorted cocaine once or twice at parties many years ago. She does not use drugs now. She was HIV negative at the time of the birth of her last child.

On examination, her temperature is 100.3°F, heart rate 88 bpm, and blood pressure 94/60 mm Hg. She is thin, her complexion is sallow, her sclerae are icteric, her chest is clear, and her heart rhythm is regular with no murmur. Her abdomen is distended, with mild diffuse tenderness, hypoactive bowel sounds, shifting dullness to percussion, and a fluid wave. She has no peripheral edema. Laboratory studies are normal except for Na 129 mEq/L, albumin 2.8 mg/dL, total bilirubin 4 mg/dL, prothrombin time 15 seconds, hemoglobin 12 g/dL with mean cell volume (MCV) 102 fL, and platelet count 78,000/mm³.

- > What is the most likely diagnosis?
- > What is your next step?

CASE 49:

A 60-year-old man is brought to the hospital by his wife because he has not been acting his usual self. For the last 3 days, he has not been sleeping at night and has been napping during the day. There is no history of recent trauma, taking new medications, or suicidal ideation. He has been taking diazepam, 5 mg nightly, for insomnia. Risk factors for chronic liver disease, according to his wife, include the consumption of two beers nightly for 35 years and a blood transfusion for the treatment of a bleeding peptic ulcer 25 years ago, at which time he underwent an ulcer surgery.

On physical examination, he appears sleepy but arousable. The vital signs are normal. Several large spider angiomas are present on the torso. There is no scleral icterus. The parotid glands are enlarged bilaterally, and wasting of the temporal muscles is noted. The heart and lung examination findings are normal. His abdomen is slightly distended, and shifting dullness and a midline scar are present. The liver is not palpable below the right costal margin but is palpable 10 cm below the xiphoid process; it is firm and percussed to a span of 8 cm in the right midclavicular line. The spleen is palpable. The abdomen is not tender to palpation or percussion. The testes are small. The rectum is found to contain hard, brown stool, which is positive for occult blood. There is mild edema of the legs and moderate muscle wasting. Asterixis is present. The cranial nerves and deep tendon reflexes are intact. The patient is somewhat uncooperative but his muscular strength is not focally diminished; his plantar reflexes (Babinski's sign) are normal.

Laboratory data are as follows: peripheral blood white cell count, 2,500 cells/mm³; hemoglobin, 10 g/dL; hematocrit, 33%; platelet count, 125,000/mm³; serum AST, 100 IU/L (normal, <30 IU/L); ALT, 80 IU/L (normal, <45 IU/L); total bilirubin, 1.2 mg/dL; alkaline phosphatase, 150 IU/L (normal, <130 IU/L); total protein, 8.0 g/dL; albumin, 3.1 g/dL; and prothrombin time, 13 seconds (control, 11 seconds).

- > What features help you to diagnose chronic versus acute liver disease in this patient?
- > Does any particular factor help you determine the cause of this man's liver disease?
- > What reversible factors could be contributing to this man's presumed portosystemic encephalopathy (PSE)?
- > When, if ever, should this man's ascites be sampled? If it should, how and where should it be sampled?
- > What are three possible explanations for the occult blood in his stool?
- > What is the serum/ascites albumin gradient, and of what value is it?
- > Would you start diuretic therapy now? Why or why not?
- > Why are his testes small?
- > Why are his parotid glands enlarged?
- > Is this man at increased risk for hepatocellular carcinoma?
- > How would you exclude hepatocellular carcinoma?
- > What is included in your differential diagnosis of this man's chronic liver disease?
- > Why is hepatitis A not in your differential diagnosis?

The results of additional tests are available within 4 hours of admission. The ascites is sampled from a left lower quadrant paracentesis, yielding a clear yellow fluid with a white blood cell count of 380 cells/mm³, 2% polymorphonuclear leukocytes, an albumin concentration of 0.5 g/dL, and a total protein level of 1 g/dL. No organisms are seen on Gram's-stained specimens.

- > Do the findings from the additional tests on the ascitic fluid support the diagnosis of portal hypertension-associated ascites? Why or why not?
- > With these data in mind, what treatment would you offer this patient now, and why?
- > What areas of the patient's history should you examine at greater length, and why?
- > Would you offer this patient a liver biopsy and, if so, when?

CASE 50:

A 45-year-old man presents to the clinic with a 3-week history of abdominal swelling. He has a history of alcoholic cirrhosis. He drinks five to six 12-oz beers every day. The patient has jaundice, spider nevi, and palmar erythema. The abdomen is distended, and palpation demonstrates flank dullness that shifts when the patient rotates. Both feet are swollen (peripheral edema). Heart and lung exam are normal. There is no elevated jugular vein distension. Vital signs are normal. LFTs are AST 180 U/L, ALT 85 U/L, GGT 42 U/L, alkaline phosphatase 85 U/L, total bilirubin 2.6 g/dL, PT 20 seconds, serum albumin 3.1 g/dL.

- > What is the most likely cause of this patient's abdominal swelling?
- > What causes ascites in patients with cirrhosis?
- > What is the next step in management?
- > Ultrasound confirms the presence of ascites. What is the next step in management?
- > What do these values tell you regarding the cause of ascites and the presence or absence of ascitic fluid infection?
- > What is the next step in management?
- > What is the most likely cause of his symptoms?
- > How is hepatorenal syndrome treated?

PATH VII: HEPATOMEGALY AND PORTAL HYPERTENSION

CASE 51:

A 45-year-old man with a history of cirrhosis due to hepatitis C presents to the emergency department with acute onset of hematemesis. Vital signs are temperature 37.1°C, pulse 115 bpm, respirations 20/min, and blood pressure 90/60. Oxygen saturation is 99% on room air. He receives normal saline, octreotide, and ciprofloxacin. NG aspirate yields 2 L of coffee grounds. Hematocrit is 28%, INR is 1.7, platelets are 100,000/μL. Aspartate aminotransferase and alanine aminotransferase are elevated. He receives PRBCs and fresh-frozen plasma. Vital signs are now stable.

- > What is the most likely finding on endoscopy?
- > Esophagogastroduodenoscopy (EGD) detects an actively bleeding esophageal varix. What is the next step?

> The patient continues to bleed copiously despite octreotide and endoscopic sclerotherapy of the bleeding varix. What are the next steps in management?

CASE 52:

A 30-year-old woman decides to donate blood. Screening liver function tests (LFTs) are as follows: aspartate amino transaminase (AST) 180, alanine amino transaminase (ALT) 170, γ -glutamyl transpeptidase (GGT) 40 U/L, serum alkaline phosphatase 45 U/L, total bilirubin 1.7 mg/dL. Complete blood count (CBC) is normal. She is completely asymptomatic. There is no family history of liver disease. She does not take any medications or herbal supplements. She occasionally drinks alcohol on social occasions. She denies illegal drug use. Physical exam and vital signs are normal. Body mass index (BMI) is 27.

- > What are the causes of mildly elevated amino transaminases (AST and ALT <250 U/L)?
- > What is the next step in management of this asymptomatic patient with elevated amino transaminases?
- > What is the next step in management?

CASE 53:

A 30-year-old man presents to the clinic with a 7-day history of fatigue, anorexia, pruritis, and dark-colored urine. He also reports light gray stools. He recently returned from a trip to Mexico. He has not taken any medications recently. Physical exam is significant for yellow discoloration of nail beds and scleral icterus (jaundice). Temperature is 38.4°C. Other vital signs are normal. Liver function tests (LFTs) are AST 1200 U/L, ALT 1600 U/L, alkaline phosphatase 150 U/L, GGT 70 U/L, serum bilirubin 2.4 g/dL, serum albumin 3.5 g/dL, PT 25 seconds.

- > What is the most likely diagnosis?
- > What is the diagnosis?
- > What treatment is recommended?
- > Is any therapy recommended to prevent HAV in close personal contacts?

CASE 54:

A 40-year-old man presents to the clinic with a 2-month history of fatigue and weakness. He has had diabetes for the last 2 years. His uncle died of liver disease in his 50s. Physical exam is significant for jaundice, spider nevi, palmar erythema, and skin hyperpigmentation. Liver function tests (LFTs) are ALT 300 U/L, AST 280 U/L, serum bilirubin 2.4 mg/dL, alkaline phosphatase 99 g/dL, serum albumin 2.8 g/dL, PT 18 seconds.

- > What is the most likely cause of cirrhosis?
- > What diagnostic tests are indicated?
- > How is hereditary hemochromatosis treated?

CASE 55:

A 20-year-old woman presents to the clinic for a medical evaluation required for entry into the US Air Force. The physician detects scleral icterus and yellow nail beds. AST is 180 U/L, ALT is 90 U/L, alkaline phosphatase is 90 U/L, GGT is 32 U/L, serum albumin is 4 g/dl, and PT is 14 seconds. Viral hepatitis serologies are all negative. Iron studies are normal. Ceruloplasmin is 13 mg/dL. Her father and a paternal aunt died of liver disease in their 40s.

- > What is the diagnosis?
- > What are the next diagnostic steps?
- > How is Wilson's disease treated?

PATH VIII: HEPATIC ENCEPHALOPATHY

CASE 56:

The patient is a 50-year-old man with a history of cirrhosis secondary to HCV infection. He has a history of ascites that is well controlled with dietary sodium restriction, spironolactone, and furosemide. Over the last couple of months he has had difficulty sleeping. His wife brings him to the clinic for a

follow-up appointment. She complains that he seems increasingly confused. Physical exam is significant for muscle wasting, spider nevi, and caput medusae. His breath smells musty (fotor hepaticus). His hands flap when his arm is held outstretched with the palm dorsiflexed (asterixis). Liver function tests (LFTs) are AST 90 U/L, ALT 90 U/L, GGT 30 U/L, alkaline phosphatase 60 g/dL, total bilirubin 1.6 g/dL, PT 22 seconds, serum albumin 3.2 g/dL, serum potassium is 3.2 mEq/L.

- > What is the most likely cause of his symptoms?
- > What causes hepatic encephalopathy in patients with cirrhosis?
- > What is the next step in management?
- > How is hepatic encephalopathy treated?

CASE 57:

A man of 45 consults his general practitioner with a 6-month history of reduced appetite and weight loss, from 78 to 71 kg. During the last 3 months he has had intermittent nausea, especially in the mornings, and in the last 3 months the morning nausea has been accompanied by vomiting on several occasions. For 1 month he has noted swelling of his ankles. Despite his weight loss he has recently noticed his trousers getting tighter. He has had no abdominal pain. He has no relevant past history and knows no family history as he was adopted. He takes no medication. From the age of 18 he has smoked 6 cigarettes daily and drunk 15-20 units of alcohol per week. He has been a chef all his working life, without exception in fashionable restaurants. He now lives alone as his wife left him 1 year ago.

He has plethoric features. There is pitting oedema of his ankles. He appears to have lost weight from his limbs, but not his trunk. He has nine spider naevi on his upper trunk. His pulse is normal and the rate is 92/min. His jugular venous pressure (JVP) is not raised and his blood pressure is 146/84 mmHg.

The cardiovascular and respiratory systems are normal. The abdomen is distended. He has no palpable masses but there is shifting dullness and a fluid thrill.

		Normal
Haemoglobin	12.6 g/dL	13.3-17.7 g/dL
Mean corpuscular volume (MCV)	107 fL	80-99 fL
White cell count	10.2 X 10 ⁹ /L	3.9-10.6 X 10 ⁹ /L
Platelets	321 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Sodium	131 mmol/L	135-145 mmol/L
Potassium	4.2 mmol/L	3.5-5.0 mmol/L
Urea	2.2 mmol/L	2.5-6.7 mmol/L
Creatinine	101 µmol/L	70-120 µmol/L
Calcium	2.44 mmol/L	2.12-2.65 mmol/L
Phosphate	1.2 mmol/L	0.8-1.45 mmol/L
Total protein	48 g/L	60-80 g/L
Albumin	26 g/L	35-50 g/L
Bilirubin	25 mmol/L	3-17 mmol/L
Alanine transaminase	276 IU/L	5-35 IU/L
Gamma-glutamyl transaminase	873 IU/L	11-51 IU/L
Alkaline phosphatase	351 IU/L	30-300 IU/L

Urinalysis: no protein; no blood

- > What is the diagnosis?
- > How would you manage this patient?

ANSWERS TO CASES

ANSWERS TO CASE 1:

What is the differential diagnosis of dyspepsia?

The most common cause of dyspepsia is functional dyspepsia, followed by peptic ulcer disease (PUD). Other important causes of dyspepsia are:

- Gastric: gastric cancer and gastritis
- Biliary: cholelithiasis and cholecystitis
- Pancreatic: chronic pancreatitis and pancreatic pseudocyst
- Intestinal: malabsorption, mesenteric ischemia, and irritable bowel syndrome (IBS)

History and physical do not reliably distinguish functional dyspepsia from PUD.

What cause of dyspepsia do his symptoms suggest?

Burning epigastric pain related to meals suggests that the patient may have PUD. The term “peptic” is a misnomer because peptic ulcers can be duodenal or gastric. This patient's symptoms are typical for duodenal ulcers, which cause pain between meals and improve with food and antacids. Gastric ulcers tend to cause symptoms immediately after meals and are not relieved by food or antacids.

- duodenal ulcers are more common in blood type O and have low malignant potential.
- gastric ulcers are more common in blood type A and high malignant potential.

What causes PUD?

• *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common causes of PUD.

- Zollinger-Ellison syndrome (ZES) is rare cause of PUD.
- Smoking may increase the risk of PUD.

Contrary to popular belief, diet and alcohol are not risk factors for PUD.

Lab studies are normal. He does not have any alarm symptoms. What is the next step?

Find out whether the patient smokes cigarettes, drinks alcohol, or takes NSAIDs, and have him discontinue them.

This patient does not have alarm symptoms, does not smoke or drink, and has not recently taken any medications other than antacids. What is the next step?

The next step in management is serology to test for *H. pylori* infection (see Fig. 1-1). If serology is positive, initiate *H. pylori* eradication therapy. There are many regimens to eradicate *H. pylori*. One such regimen is amoxicillin + clarithromycin + proton pump inhibitor (PPI) for 10 to 14 days. Between 4 and 6 weeks after the patient completes treatment for *H. pylori*, confirm eradication with urea breath test or stool antigen test.

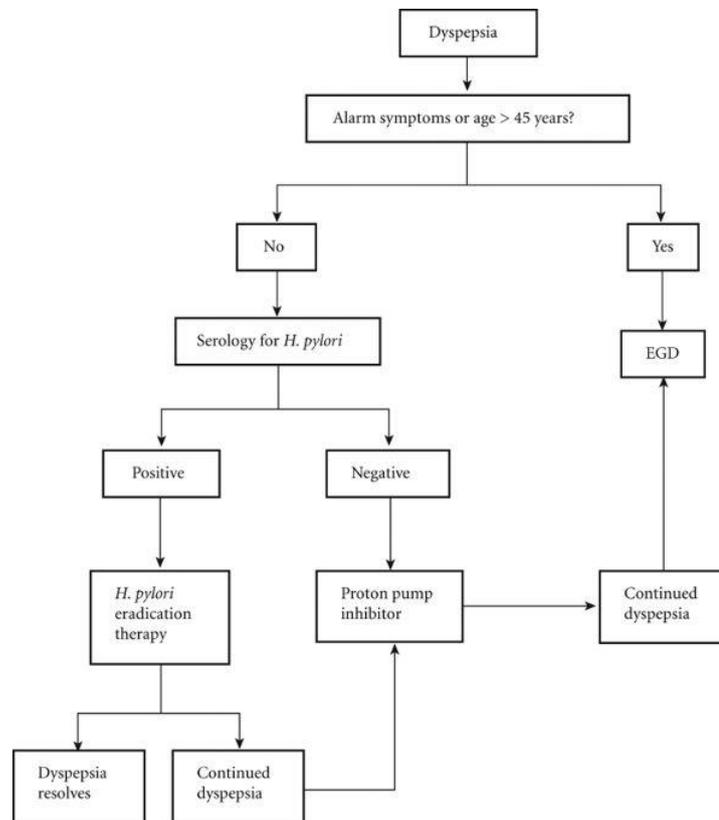


Figure 1–1. Workup of dyspepsia

CASE DISCUSSION

What is dyspepsia?

The term “dyspepsia” refers to chronic and recurrent upper abdominal discomfort. There are three patterns of discomfort:

- Ulcer or acid-like dyspepsia: burning epigastric pain that is affected by food and may improve with acid-suppressing medications and antacids.
- Gastroesophageal reflux-like dyspepsia: burning epigastric pain accompanied by heartburn (burning substernal chest pain) and regurgitation; work-up and management differs from other patterns of dyspepsia.
- Functional dyspepsia (non-ulcer dyspepsia): epigastric fullness, bloating, early satiety, and nausea.

- Acute abdominal pain: Pain progressively increases over hours to days.

- Chronic abdominal pain: Pain has not changed for months to years.

- Subacute abdominal pain: Pain is neither acute nor chronic.

How is dyspepsia managed in patients <45 years of age?

First, determine whether the patient has alarm findings for gastric cancer. Obtain esophagogastroduodenoscopy (EGD) if the patient has any of the following alarm findings:

- Jaundice: Check liver function tests (LFTs).
- Anemia or gastrointestinal bleeding: Check complete blood count (CBC) and fecal occult blood test (FOBT).
- Protracted vomiting: Check serum electrolytes.
- Progressive dysphagia or odynophagia
- Unintentional weight loss
- Palpable mass or lymphadenopathy

Age >45 years: EGD is indicated in all patients with dyspepsia to rule out cancer.

If initial serology is negative for *H. pylori*, initiate a trial of proton pump inhibitors (PPIs).

***H. pylori* serology is positive. The patient completes a 14-day course of amoxicillin, clarithromycin, and omeprazole. Stool antigen test confirms eradication of *H. pylori*. The patient remains symptomatic. What is the next step in management?**

Initiate a trial of PPIs. If symptoms persist despite 8 weeks of PPIs or recur rapidly after PPI cessation, perform EGD.

The patient responds well to PPIs. Two years later, he presents to the emergency department with a 2-hour history of severe, diffuse abdominal pain. He has been taking ibuprofen for the last 2 weeks. On physical exam, his abdomen is tender with involuntary guarding (rigid abdomen) and rebound tenderness. Vital signs are temperature 37°C, pulse 110 beats per minute (bpm), respirations 20/min, and blood pressure 110/70. What is the most likely cause of his symptoms?

Suspect chemical peritonitis due to ulcer perforation in any patient with a history of PUD who presents signs of a diffuse acute abdomen. Recent NSAID use is the likely cause of perforation in this patient. Perforated peptic ulcer is an emergency because secondary bacterial infection of the peritoneum can lead to septic shock.

Acute abdomen (peritonitis): acute onset of severe abdominal pain and rebound tenderness; suggests inflammation of an abdominal organ(s) and peritoneum. Many causes of acute abdomen require emergent surgical management.

The most common laboratory findings in patients with perforated peptic ulcers are leukocytosis and a mildly elevated serum amylase.

What is the next step in diagnosis?

Obtain upright or decubitus abdominal radiographs. Free air under the diaphragm is diagnostic of a perforated ulcer (see Fig. 1-2). If abdominal radiograph is normal but clinical suspicion of perforation is high, obtain abdominal computed tomography (CT) scan. If abdominal x-ray or CT scan is positive, evaluate the severity of bleeding with upper gastrointestinal (GI) series (fluoroscopy images obtained after contrast ingestion). Use Gastrografin contrast initially because barium can cause peritonitis if it extravasates into the peritoneum.

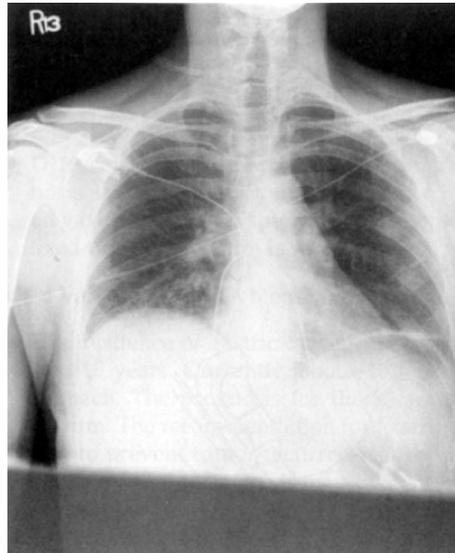


Figure 1–2. Abdominal X-ray showing free air under the diaphragm.

Abdominal radiographs show free air under the diaphragm, which confirms the diagnosis of a perforated peptic ulcer. There is no leakage identified on upper gastrointestinal (GI) series. What are the next steps in management?

Medical management is often sufficient for stable patients who present within 12 hours of symptom onset and do not have any leakage documented on upper GI series (i.e., no brisk bleeding). Medical management of perforated peptic ulcer is as follows:

- Fluids and electrolytes: correct any hypotension with IV normal saline; correct electrolyte imbalances.
- IV PPIs or H2-blockers
- NG suction
- Antibiotics: cover anaerobes, enteric Gram-negative rods, and oral flora with a combination of ampicillin, metronidazole, and a third-generation cephalosporin (or fluoroquinolone).
- Reassess: Monitor the patient closely in the ICU for deterioration, increased abdominal pain, tenderness, rigidity, or signs of shock (e.g., hypotension, increased pulse or increased temperature); any deterioration is an indication for emergent surgery.

The patient recovers with medical management. Two years later, he presents with a 4-week history of nausea, early satiety, and epigastric fullness after meals. Over the last 7 days, he also

reports persistent vomiting after meals. The emesis contains partially digested food contents. He has lost 10 lbs over the past month. Physical examination is significant for a succussion splash over the epigastric area. Vital signs are normal except for a pulse of 110 bpm. Serum potassium is low and bicarbonate is high. What is the most likely complication?

The clinical presentation is consistent with gastric outlet obstruction. Outlet obstruction causes epigastric fullness, nausea, and vomiting after meals, which results in weight loss, dehydration, metabolic alkalosis, and hypokalemia. A succussion splash is sometimes heard over the epigastric area.

What is the next step in management?

Confirm the diagnosis by measuring the quantity of residual gastric contents aspirated during NG suction. A residual volume of 250 to 300 mL establishes the diagnosis. If the residual volume is lower, confirm gastric outlet obstruction with a saline load test.

Saline load test: Administer 750 mL of normal saline into the stomach. Perform NG aspiration 30 minutes later. Retention of ≥ 400 mL indicates a positive test.

270 mL of foul-smelling gastric contents are aspirated, which confirms the diagnosis. What are the next steps in management?

- Medical management: Initial management is similar to perforated peptic ulcer (fluids and electrolytes, IV PPIs or H2-blockers, antibiotics, and NG suction to decompress bowel).
- Evaluate nutritional status: After performing initial steps, obtain serum albumin (marker of nutritional status); consider supplemental nutrition if albumin is low.
- EGD: After 24 to 72 hours of medical management, obtain EGD to define the extent of the obstruction and biopsy to rule out gastric cancer.
- Endoscopic dilation: If the obstruction does not improve after 5 to 7 days, consider endoscopic dilation.
- Surgery: If obstruction persists despite dilation, consider surgery.

Complications of PUD (mnemonic: “POP Blood”): Perforation, Obstruction, Penetration (ulcer penetrates into other organs like pancreas and causes inflammation of that organ), and Bleeding (slow or rapid).

ANSWERS TO CASE 2:

What is the diagnosis?

Patients with dyspepsia in the absence of any identifiable structural cause are classified as having functional dyspepsia, a diagnosis of exclusion. Symptoms must be present for at least 3 months to make this diagnosis. No drug consistently improves symptoms. The recommended strategy for patients with functional dyspepsia is acknowledgement that their symptoms are real and reassurance that the disorder is not life threatening.

ANSWERS TO CASE 3:

What is the most likely finding on endoscopy?

Unintentional weight loss is an alarm symptom for gastric cancer in patients with dyspepsia. The likelihood of gastric cancer is very high in this patient with other suspicious signs including constant symptoms, gastrointestinal (GI) bleeding, an enlarged periumbilical lymph node, and an enlarged left supraclavicular lymph node (Table 3-1).

Table 3–1. Physical signs of gastric adenocarcinoma

Physical signs of lymphatic spread	1. Sister Mary Joseph node: enlarged periumbilical lymph node 2. Virchow node: enlarged left supraclavicular lymph node
Physical signs of peritoneal spread	1. Krukenberg tumor: enlarging ovarian mass 2. Blumer's shelf: mass in rectal cul-de-sac 3. Ascites: due to peritoneal carcinomatosis
Physical signs of intestinal spread	1. Gastrocolic fistula: feces in emesis or undigested material in stool

Paraneoplastic signs (not specific for gastric cancer)	<ol style="list-style-type: none"> 1. Leser-Trelat sign: diffuse seborrheic keratoses 2. Acanthosis nigricans: hyperpigmented, velvety patches on skin folds 3. Trousseau syndrome: migrating thrombophlebitis
---------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Early gastric cancer is usually asymptomatic, so most patients already have advanced disease at the time of diagnosis.

Endoscopy with biopsy confirms the diagnosis of gastric adenocarcinoma. What tests should you order to stage gastric adenocarcinoma?

Order abdominal and chest computed tomography (CT) scans to detect distant metastases. If CT scan detects liver lesions, consider laparoscopic biopsy to verify whether or not they are metastatic lesions. Many centers use EUS to define tumor size and nodal involvement.

Gastric adenocarcinoma morphologies:

- Superficially spreading: Early gastric cancer is confined to mucosa or submucosa. Prognosis is excellent.

- Linitis plastica: Diffuse, full thickness extension leads to a rigid, atonic “leather bottle” appearance. Prognosis is dismal.

- Polypoid
- Ulcerating

What are the risk factors for gastric adenocarcinoma?

Established risk factors for gastric adenocarcinoma are:

- Diet with high N-nitroso and salt intake and low vitamin C and β -carotene intake
- Chronic gastritis due to H. pylori infection and pernicious anemia
- Surgery: Partial gastric resection increases risk of cancer after approximately 15 years.
- Smoking
- Blood type A

The association between gastric ulcer and gastric cancer is controversial. The current recommendation is to biopsy any gastric ulcer to detect early gastric cancer.

Chronic H. pylori infection is implicated in 35% to 90% of gastric cancers but <1% of patients with chronic H. pylori infection develop gastric cancer.

What malignancies can occur in the stomach besides adenocarcinoma?

- Gastric lymphoma is the second most common gastric malignancy after adenocarcinoma. Most gastric lymphomas are non-Hodgkins B-cell lymphomas. More than half arise from mucosa-associated lymphoid tissue. Clinical presentation and esophagogastroduodenoscopy (EGD) appearance are similar to adenocarcinoma, so biopsy is necessary to distinguish between the two. After diagnosis, stage using abdominal CT, chest CT, and EUS.

- Gastric carcinoid is a rare gastric malignancy. Pernicious anemia and multiple endocrine neoplasia type 1 are risk factors. Early carcinoids are typically asymptomatic. Carcinoids that metastasize to the liver may release excessive serotonin, leading to carcinoid syndrome. Symptoms of carcinoid syndrome are blushing, tricuspid, or pulmonary stenosis; diarrhea; and bronchospasm. Carcinoids can occur anywhere in the GI tract, so endoscopy is not sufficient to rule out the diagnosis if the patient has symptoms of carcinoid syndrome. Diagnose carcinoid by documenting elevated urinary 5-HIAA (end-product of serotonin metabolism). If results are equivocal, obtain whole-blood serotonin levels.

- Stromal tumors: Two thirds of GI stromal tumors occur in the stomach. Leiomyomas are benign stromal tumors, and leiomyosarcomas are malignant stromal tumors.

- Appendix: This is the most common location of carcinoids (low metastasis rate).
- Ileum: Ileal carcinoids have the highest rate of metastasis.

Approximately 75% of stage 1 mucosa-associated lymphoid tissue lymphomas regress completely with H. pylori eradication.

ANSWERS TO CASE 4:

What is the most likely diagnosis?

Dyspepsia in the presence of heartburn and regurgitation are characteristic of gastro-oesophageal reflux disease (GERD).

Water brash: hypersalivation in response to reflux (uncommon).

What are the next steps in management?

The history is typical for uncomplicated GERD. There are two options in such patients:

- Step-up approach: Start with lifestyle measures and antacids as needed. If symptoms persist, add an over-the-counter H₂-blocker or proton pump inhibitor (PPI) to the regimen. Increase the dosage over the next few weeks until symptoms are controlled.

- Step-down approach: Start with lifestyle measures, antacids as needed, and a potent dose of H₂-blocker or PPI. Taper down the dose until the lowest dose that controls symptoms is reached.

Perform esophagogastroduodenoscopy (EGD) only if symptoms persist despite therapy or the patient has any of the alarm findings for gastric cancer described earlier.

The patient's symptoms improve with lifestyle measures and daily PPIs. What is the next step in management?

Discontinue acid-suppressing medications after 8 weeks of successful empiric therapy. If the patient's symptoms do not recur for at least 3 months off medications, the patient can take the acid-suppressing drugs intermittently on an as-needed basis. Otherwise, restart the previously effective regimen.

- H₂-blockers: Generic name ends with –tidine (e.g., ranitidine).
- PPIs: Generic name ends with –prazole (e.g., pantoprazole).

CASE DISCUSSION

What is the pathophysiology of GERD?

Heartburn and dyspepsia result from esophagitis due to excessive gastric acid in the esophagus. The pathophysiology involves a combination of decreased LES tone (which causes excessive reflux of gastric contents into the esophagus) and esophageal dysmotility (which leads to decreased clearance of gastric contents from the esophagus).

Nonerosive GERD: Most patients with uncomplicated GERD do not have overt esophagitis. Symptoms result from hypersensitivity to physiological amounts of gastric acid.

What lifestyle measures are recommended to decrease symptoms of GERD?

Remember lifestyle measures with the mnemonic “WASTED”:

- Weight loss: Obesity is a risk factor for GERD.
- Alcohol avoidance
- Salivation: Use chewing gum and lozenges to increase saliva (neutralizes gastric acid).
- Tobacco: Avoid cigarettes because they increase stress on the sphincter.
- Elevate the head of the bed.
- Diet: Avoid fatty foods, chocolate, and peppermint.

The patient's symptoms recur in 2 weeks. He restarts the previous regimen. Over the next few years, he requires continually increasing frequency and dosages of PPIs to relieve symptoms. What are the complications of long-standing GERD?

Inflammation and repair can lead to:

- Peptic stricture: Suspect peptic stricture if the patient develops esophageal dysphagia to solid foods. Diagnose with barium swallow and/or EGD. Treat with dilation.

- Barrett's esophagus: Chronic GERD can cause replacement of the normal stratified squamous epithelium with columnar epithelium. Although asymptomatic, this metaplastic change greatly increases the risk of esophageal adenocarcinoma. Consider screening endoscopy for all patients with longstanding GERD (see Fig. 4-1).

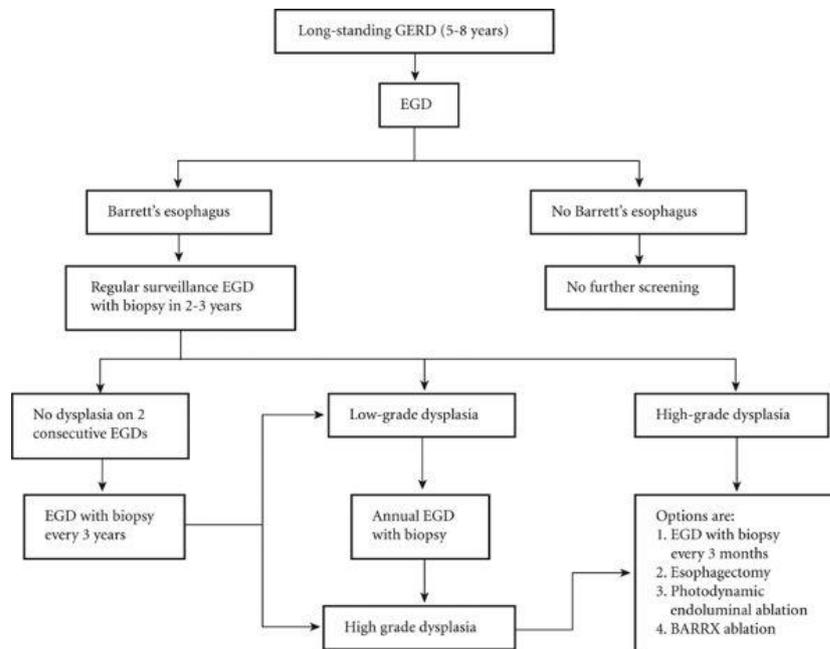


Figure 4–1. American College of Gastroenterology recommendations for surveillance endoscopy in patients with Barrett's esophagus.

Reflux of gastric contents into the tracheobronchial tree and lungs can lead to:

- Asthma, chronic cough.
- Aspiration pneumonia: If GERD is the suspected cause, obtain cytologic aspirates using bronchoscopy. The characteristic finding is lipid-laden macrophages.
- Laryngitis: Suspect laryngitis when a patient with long-standing GERD complains of chronic hoarseness, cough, frequent throat clearing, or sore throat in the absence of infection. Rule out structural causes with a laryngoscope. Treat with a high dose PPI for 12 weeks. If the patient does not respond, evaluate for a pulmonary or allergic cause.
- Laryngeal cancer: SCC may occur in patients with chronic GERD-induced laryngitis. The major risk factors however, are smoking and alcohol.

Complications of long-term PPI use: osteoporosis, pneumonia, Clostridium difficile infection, and gastric polyps.

Adding a promotility agent to the acid-suppressing regimen may improve symptoms for some patients with GERD. However, side effects limit their widespread use. Examples are bethanechol, metoclopramide, domperidone, and cisapride (not available in the United States unless gastrointestinal (GI) physician enrolls patient in the compassionate drug program).

The patient undergoes screening endoscopy. There is no columnar metaplasia or dysplasia. The endoscopy report does mention that the patient has a sliding hiatal hernia. What is the significance of this finding?

Type 1 (sliding hiatal hernia) accounts for 95% of hiatal hernias. A wide diaphragm ring allows the gastric cardia (gastroesophageal junction) to herniate upward, which predisposes to GERD. No specific therapy is necessary except control of GERD.

What treatment option exists for patients with refractory symptoms?

Consider antireflux surgery for the following patients with GERD:

- Persistent esophagitis: Heartburn, regurgitation, or dyspepsia persist despite maximal medical therapy.
- Persistent complications: Complications persist despite maximal medical therapy.
- Paraesophageal hiatal hernia (types II, III, and IV): Gastroesophageal junction remains in place, but other parts of stomach herniate through diaphragm ring. Type II requires surgery even if asymptomatic. Types III and IV require surgery if symptomatic.

Preoperative evaluation: Perform manometry (to rule out other causes) and esophageal pH monitoring. Surgery does not benefit patients with visceral hyperalgesia (pH monitoring documents that symptoms occur despite adequate acid control).

BRAVO pH monitor: Implant capsule in esophagus. Capsule collects pH data and transmits data wirelessly to a pager-sized receiver worn by patient.

What surgical procedure is typically performed for refractory GERD?

The most commonly performed surgery for GERD is laparoscopic fundoplication (stomach fundus is sutured around the cardia, and the diaphragm defect is closed).

ANSWERS TO CASE 5:

What is the most likely cause of this patient's dysphagia?

This patient's symptoms suggest that an esophageal cause is responsible for her symptoms. Dysphagia with both solids and liquids indicates an esophageal motility disorder. Heartburn, regurgitation, halitosis, and weight loss are characteristic symptoms of achalasia (see Fig. 5-1).

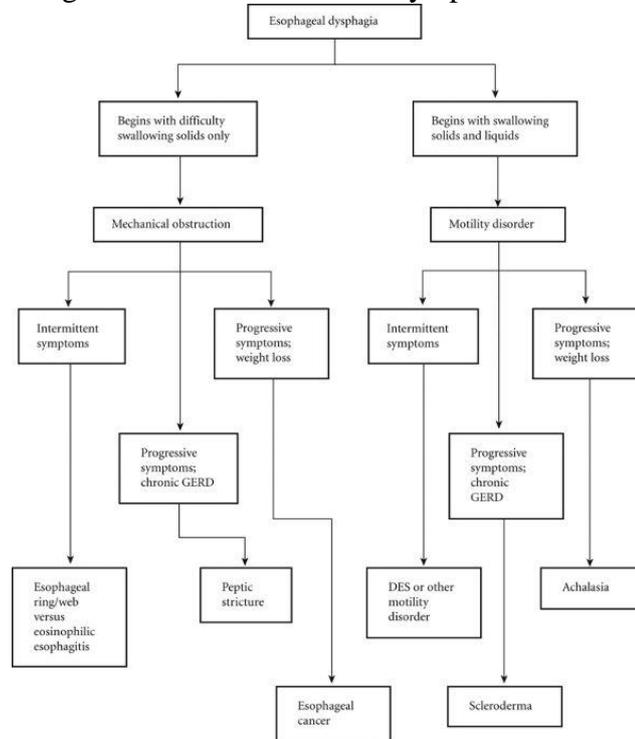


Figure 5–1 Causes of esophageal dysphagia.

What is the next step in diagnosis?

Order a barium swallow (see Fig. 5-2). The classic finding in achalasia is a dilated esophagus that terminates in a beak-like narrowing caused by the persistently contracted lower esophageal sphincter (LES) (see Fig. 5-3). If the barium swallow is positive, confirm the diagnosis with esophageal manometry. Manometry findings of achalasia are increased resting LES pressure, incomplete LES relaxation after swallowing, and aperistalsis in the lower esophagus (Table 5-1).

Table 5–1 Manometry findings in specific esophageal motility disorders

Disorder	Peristalsis Frequency	Peristalsis Amplitude/Duration	LES
Normal	≥80% of contractions are peristaltic	Mean amplitude 40–160 mm Hg	Resting pressure 10–35 mm Hg above intragastric pressure
Achalasia	Aperistalsis in distal esophagus	Aperistalsis in distal esophagus	Increased resting LES pressure, incomplete relaxation
DES	>30% of distal esophageal contractions are aperistaltic	Frequent multip peaked contraction waves with increased amplitude in distal esophagus	Normal
Nutcracker esophagus	Normal	>30% of distal esophageal contractions with increased amplitude and duration	Normal

Isolated hypertensive LES	Normal	Normal	Increased resting LES pressure
---------------------------	--------	--------	--------------------------------

Abbreviations: LES, lower esophageal sphincter; DES, diffuse esophageal spasm.

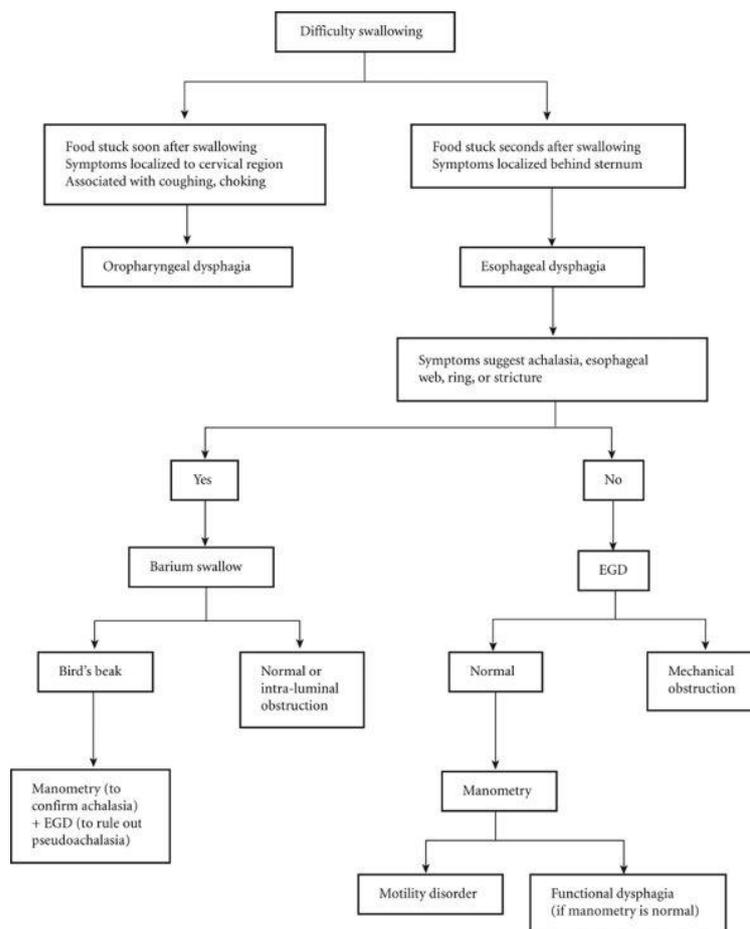


Figure 5–2. Diagnostic approach to dysphagia.



Figure 5–3. Barium swallow: achalasia.

Pseudoachalasia: Other conditions can cause abnormalities identical to achalasia. Most common among these are malignancies and Chagas' disease. Perform upper endoscopy in all patients with achalasia to rule out malignancy.

Upper endoscope: Also called an esophagogastroduodenoscope (EGD), this scope has a light and a camera at the tip and is used to visualize the esophagus, stomach, and duodenum.

What are the next diagnostic steps?

- Posterior-to-anterior and lateral chest radiograph (CXR): This initial test in suspected esophageal rupture often detects subcutaneous or mediastinal emphysema. CXR may be negative for up to 1 hour after rupture.

- Contrast esophagography should be obtained if x-rays are positive or negative. In case of positive x-rays, this test confirms the diagnosis. In case of negative x-rays, the test can decrease likelihood of a

false-negative x-ray. Use a water-soluble contrast agent (Gastrografin) first because extravasation of a large amount of barium contrast into the mediastinum can cause severe inflammation (mediastinitis). Gastrografin is very sensitive at detecting large perforations, but barium is more sensitive for small perforations. Consider barium to rule out a small perforation if Gastrografin esophagography is negative.

- CT scan should be used if esophagography is negative because contrast esophagography can miss 10% of ruptures. Some centers obtain a CT scan before esophagography.

How is esophageal perforation managed?

- Medical management comprises no oral intake (nothing per oral (NPO)), total parenteral nutrition, intravenous (IV) broad-spectrum antibiotics, and drainage of fluid collections. This method is indicated only in the subset of patients who are hemodynamically stable and do not have any intrapleural or intraperitoneal contrast extravasation; in addition, the rupture must be diagnosed within 24 hours of the event.

- Surgery is indicated for all other patients.

This patient with signs of mediastinal emphysema will probably have contrast extravasation and require surgical repair.

CASE DISCUSSION

What are the causes of dysphagia?

- Oropharyngeal dysphagia presents with a sensation of “food getting stuck” immediately after swallowing. Patients often report coughing or choking after a meal. Symptoms are localized to the cervical region. Causes include oropharyngeal tumor, zenker diverticulum, myasthenia gravis, inflammatory myopathies, and thyrotoxicosis.

- Esophageal dysphagia presents with a sensation of “food getting stuck” a few seconds after swallowing. Symptoms are localized to the suprasternal notch or substernal region. Dysphagia that begins with difficulty swallowing both solids and liquids suggests a motility disorder (achalasia, diffuse esophageal spasm (DES), nutcracker esophagus, or isolated lower esophageal sphincter (LES) hypertension). Dysphagia that begins with difficulty swallowing solids but not liquids suggests mechanical obstruction (esophageal web, ring, stricture, or tumor).

- Functional dysphagia has no identified cause after a complete diagnostic evaluation.

- Dysphagia = difficulty swallowing

- Odynophagia = painful swallowing

- Globus sensation = feeling of “lump in throat” even between meals in the absence of dysphagia or odynophagia

What is the pathophysiology of achalasia?

Achalasia is an idiopathic degeneration of myenteric plexus neurons in the distal esophagus. Neurons that cause smooth muscle relaxation are preferentially affected, while those that lead to smooth muscle contraction are spared. As a result, the LES does not adequately relax, and the distal esophagus loses its normal peristaltic function.

Barium swallow and esophageal manometry confirm the diagnosis of achalasia. There is no evidence of malignancy on endoscopy. How is achalasia treated?

Unfortunately, there is no way to halt neuron degeneration in achalasia. Current therapies all aim to decrease LES pressure.

- Good surgical candidates: On the basis of patient preference and the availability of physicians with the necessary expertise, perform either pneumatic balloon dilation of the LES or modified Heller myotomy (a surgical procedure that weakens the LES by cutting the muscle fibers). At least half the patients who undergo pneumatic dilation will require another treatment in 5 years. Most patients who undergo Heller myotomy develop gastroesophageal reflux disease (GERD).

- Poor surgical candidates: These patients can take nitrates and/or calcium channel blockers before meals. If pharmacotherapy fails to control their symptoms, consider injecting botulinum into the LES during endoscopy. Botulinum poisons excitatory acetylcholine-producing neurons.

Patients with achalasia have an increased risk of esophageal squamous cell carcinoma (SCC), but surveillance EGD is not recommended because it is not cost-effective.

The patient undergoes pneumatic dilation. Shortly after the procedure, she complains of dyspnea and severe pain in the chest and epigastrium that increases with inspiration and swallowing. Auscultation of the chest reveals a crunching sound (Hamman's crunch). What complication should you suspect?

The most serious complication of pneumatic dilation is esophageal rupture. Suspect an intrathoracic esophageal rupture if a patient develops dyspnea, chest pain, epigastric pain, or back pain that increases with inspiration and swallowing. Common presenting signs are tachycardia, tachypnea, and Hamman's crunch (indicates mediastinal emphysema due to leakage of air from the esophagus to the mediastinum).

Cervical perforation causes neck pain, hoarseness, sternocleidomastoid muscle tenderness, and cervical subcutaneous emphysema (smooth bulging of the skin overlying the neck that crackles on palpation).

ANSWERS TO CASE 6:

What is the next step in management?

Intermittent dysphagia to both solids and liquids suggests that this patient may have a motility disorder such as DES, nutcracker esophagus, or hypertensive lower esophageal sphincter (LES). Esophageal motility disorders commonly cause chest pain with negative cardiac and endoscopic findings. The next step in management is esophageal manometry.

More than 30% of distal esophageal contractions on esophageal manometry are nonperistaltic. There are frequent contraction waves with multiple peaks and increased amplitude. Peristaltic contractions are interspersed between waves. LES response is normal. What is the diagnosis?

The manometry findings are diagnostic of diffuse esophageal spasm (DES) (see Table 5-1).

The classic barium swallow radiograph in DES is a “corkscrew pattern” (see Fig. 6-1). This finding is neither sensitive nor specific.

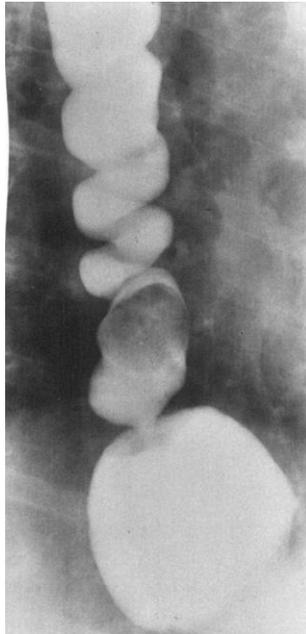


Figure 6–1. Barium swallow: diffuse esophageal spasm (corkscrew pattern).

What therapy is recommended?

Many potential therapies may benefit patients with DES, but the ideal therapy and often their mechanism of effect is unknown. Calcium channel blockers and tricyclic antidepressants are generally the initial therapy for DES, nutcracker esophagus, and hypertensive LES. Second-line options are botulinum injection, phosphodiesterase inhibitors, nitrates, and peppermint.

ANSWERS TO CASE 7:

What is the most likely cause of her symptoms?

Ingestion of alkaline agents such as battery fluids, drain cleaners, and other household cleaning products leads to caustic esophageal injury. More than 70% of patients with injuries severe enough to necessitate intensive care unit (ICU) admission develop dysphagia weeks to months later as a result of esophageal stricture.

Alkali ingestions damage the esophagus more than acid ingestions. Acid ingestions damage the stomach more than alkali ingestions.

What is the next diagnostic step?

Perform either barium swallow or esophagogastroduodenoscopy (EGD) in patients with suspected stricture. The utility of barium swallow prior to EGD is an area of debate. Consider barium swallow as the initial test for dysphagia when symptoms suggest:

- Achalasia: In older studies, barium swallow was more sensitive.
- Esophageal stricture, web, or ring: EGD may miss subtle narrowing.
- Zenker diverticulum: EGD may be hazardous.

What treatment is the patient likely to have received immediately after her ingestion?

Patients with acute caustic ingestions usually require EGD to assess the degree of injury. If there is only mild mucosal edema and superficial ulcers, the patient can consume a liquid diet and advance to regular foods in 24 to 48 hours. This patient probably had more severe injuries (deep ulcers or necrosis). Such patients maintain fasting and are admitted to the ICU to monitor for life-threatening complications.

The following are contraindicated immediately after a caustic ingestion:

- Emetics: Emesis re-exposes esophagus to caustic agent.
- Neutralizing agents: Neutralization causes thermal injury.
- Nasogastric (NS) intubation: Induces retching and emesis.

What diagnostic workup is recommended?

- Establish the diagnosis using endoscopy with biopsy. If the biopsy is positive, obtain abdominal and chest CT scans to search for distant metastases. If computed tomography (CT) detects metastases, the patient has stage 4 disease and the work-up is complete. If CT scans are negative, measure size and invasion of the tumor using endoscopic ultrasound.
- EUS: An ultrasound probe attached to the tip of an upper endoscope or colonoscope helps visualize extraintestinal structures such as pancreas, liver, and lymph nodes. A needle passed through a channel on the endoscope can pierce the stomach or intestine to biopsy any abnormal extraintestinal lesions (fine-needle aspiration).

CASE DISCUSSION

What are other important causes of esophageal stricture?

- Proximal and mid-esophageal strictures: Common causes are caustic ingestions, “pill-induced” stricture (e.g., alendronate, iron, nonsteroidal anti-inflammatory drugs (NSAIDs)), trauma, and malignancy. Eosinophilic esophagitis is an uncommon but frequently tested condition.
- Distal esophageal strictures: Most common cause is chronic gastro-oesophageal reflux disease (GERD) and Barrett's esophagus. Collagen vascular diseases are another common cause.

Barium swallow shows an area of intraluminal narrowing. EGD confirms the finding of an esophageal stricture. What is the usual treatment for this complication?

Treat dysphagia due to esophageal stricture with esophageal dilation.

What are important acute life-threatening complications of caustic ingestion?

- Esophageal perforation and mediastinitis present with severe retrosternal or back pain; treatment is emergent surgery.
- Gastric perforation and peritonitis present with abdominal tenderness, rebound, and rigidity; treatment is emergent surgery.
- Respiratory distress and shock.

The dysphagia resolves with two esophageal dilation treatments. The patient returns 20 years later with a 3-month history of progressive dysphagia. Initially, she had trouble swallowing only solids, but now she has difficulty with liquids as well. She does not have much of an appetite, and she has lost 25 lbs in the last 3 months. What is the suspected diagnosis?

Progressive dysphagia and weight loss are extremely suspicious for esophageal cancer. Caustic alkali injury to the esophagus greatly increases the risk of Squamous cell carcinoma (SCC) of the esophagus 15 to 20 years after the original injury. Major risk factors for SCC in the United States are smoking, alcohol, and achalasia. In other countries, ingestion of betel nuts, extremely hot tea, and nitrosamines are responsible for a significant proportion of esophageal SCC.

Perform surveillance endoscopy every 1 to 3 years beginning 15 to 20 years after caustic injury to screen for esophageal cancer.

What is the overall prognosis for patients with SCC of the esophagus?

Overall 5-year survival is only 15% because patients tend to present at later stages. Potentially curative esophagectomy is an option for patients at stage I and stage IIa. For most patients, however, the primary goal of treatment is palliation of pain and dysphagia.

Symptoms, work-up, and prognosis of esophageal adenocarcinoma and SCC are similar.

ANSWERS TO CASE 8:

What is the likely explanation for these findings?

The clinical picture suggests obstruction to outflow from the stomach. This would be compatible with vomiting of residual food some time after eating and the succussion splash from the retained fluid and food in the stomach. The biochemical results fit with this diagnosis. There is a rise in urea but not creatinine, suggesting a degree of dehydration. Sodium, chloride and hydrogen ions are lost in the vomited stomach contents. Loss of hydrochloric acid produces a metabolic alkalosis. In compensation, hydrogen ions are retained by exchange for potassium in the kidney and across the cell membranes, so leading to hypokalaemia, and carbonic acid dissociates to hydrogen ions and bicarbonate. The hypokalaemia indicates a considerable loss of total body potassium, which is mostly in the skeletal muscle, and explains the patient's recent weakness.

What is the most likely diagnosis?

The most likely cause would be a carcinoma of the stomach involving the pyloric antrum and producing obstruction to outflow. A chronic gastric ulcer in this area could produce the same picture from associated scarring, and gastroscopy and biopsy would be necessary to be sure of the diagnosis.

Gastroscopy may be difficult because of retained food in the stomach. In this case, after this was washed out a tumour was visible at the pylorus causing almost complete obstruction of the outflow tract of the stomach. The next step would be a computed tomography (CT) scan of the abdomen to look for metastases in the liver and any suggestion of local spread of the tumour outside the stomach. If there is no evidence of extension or spread, or even to relieve obstruction, laparotomy and resection should be considered. Otherwise chemotherapy and surgical palliation are treatment options.

Clinical pearls

- > Vomiting food eaten a long time previously suggests gastric outlet obstruction.
- > Mild-to-moderate dehydration tends to increase urea more than creatinine.
- > Prolonged vomiting causes a typical picture of hypochloreaemic metabolic alkalosis. Carcinoma of the stomach can present without abdominal pain or anaemia.

ANSWERS TO CASE 9:

Why was an ERCP obtained?

The patient's laboratory data included abnormal liver test results consistent with cholestasis, and common bile duct dilation was seen on the ultrasound examination. These findings and the failure of his symptoms to subside during the early hospital course raised concern about a gallstone at the ampulla of Vater and gallstone pancreatitis. Performing an emergency ERCP, with papillotomy when ampullary or common bile duct stones are found, has been advocated within 24 hours in patients who have acute biliary pancreatitis.

What was the cause of the patient's biliary obstruction?

Compression of the intrapancreatic common bile duct by an inflamed pancreas is the cause of the biliary obstruction in this patient. This is shown by the absence of gallstones on the ERCP study and the patient's gradual improvement with conservative management of acute pancreatitis.

Discussion

- What are the common and uncommon causes of acute pancreatitis?

The common causes of acute pancreatitis are alcohol (60%), gallstones (25% to 30%), and idiopathic causes. Table 9-1 lists uncommon causes.

Table 9-1. Common and uncommon causes of acute pancreatitis

- Postoperative causes
- After endoscopic retrograde cholangiopancreatography
- Trauma

- Metabolic causes (hypertriglyceridemia, hyperparathyroidism, renal failure, and acute fatty liver of pregnancy)
 - Hereditary causes
 - Infections (mumps, Mycoplasma, coxsackie virus, and echovirus)
 - Vasculitides (systemic lupus erythematosus, thrombotic thrombocytopenic purpura, Henoch-Schonlein purpura, necrotizing angitis)
 - Ampulla of Vater obstruction (Crohn's diseases, duodenal diverticula, penetrating duodenal ulcer, pancreas divisum, and scorpion venom)
 - Drugs
 - Azathioprine/6-mercaptopurine
 - Thiazide diuretics
 - Estrogens
 - Furosemide
 - Sulfonamides (sulfasalazine, trimethoprim/sulfamethoxazole)
 - Tetracycline
 - Methyldopa
 - Sulindac
 - Valproate
 - Pentamidine
 - Didanosine
 - Oral 5-aminosalicylate (olsalazine and mesalamine)
 - Octreotide
-

What pathogenetic mechanism is hypothesized to be common to these causes of acute pancreatitis, and how does it explain the clinical features of the disease?

Autodigestion is the pathogenetic mechanism common to all the causes of acute pancreatitis. Etiologic factors are believed to lead to the premature activation of pancreatic proenzymes within the gland. Destruction of the pancreas by the activated enzymes leads to local injury (edema, necrosis, and hemorrhage). In addition, the activation and release of proinflammatory cytokines, vasoactive peptides, and enzymes leads to the systemic effects that often accompany pancreatic injury (shock, disseminated intravascular coagulation, adult respiratory distress syndrome, renal failure, hyperglycemia, and hypocalcemia).

What symptoms and signs typify acute pancreatitis?

Pain is a characteristic symptom of acute pancreatitis and is located in the midepigastic and periumbilical regions. Commonly, it radiates to the back and is more constant and sustained than the pain associated with other abdominal processes. It is often more intense in the supine position and ameliorated by sitting forward. Patients may exhibit marked abdominal tenderness and guarding.

Nausea and vomiting are other symptoms. In this setting, the abdomen may be distended from the accumulation of intraabdominal and fluid, paralytic ileus, and chemical peritonitis. The bowel sounds may be diminished.

Hypotension may be present in as many as half of the patients; it results from vasodilation, myocardial depressant factor, and the loss of plasma and blood into the retroperitoneum.

Less common, but important, findings include periumbilical (Cullen's sign) or flank ecchymoses (Grey Turner's sign).

What difficulties may be encountered in confirming the diagnosis of acute pancreatitis through the measurement of amylase levels, and how might the diagnostic accuracy be improved?

Although the serum amylase level usually rises within 12 hours of the onset of pain and remains elevated for 3 to 5 days, a normal serum amylase value does not exclude pancreatitis. Spuriously normal serum amylase levels may result from the rapid clearance of amylase into the urine, and may be seen with hypertriglyceridemia and in late-stage (burned out) chronic pancreatitis. The magnitude of the amylase elevation in serum or urine does not correlate with the severity of pancreatitis. In addition, hyperamylasemia is not a specific finding for pancreatitis because it may occur in a variety of pancreatic and nonpancreatic diseases. There are salivary as well as pancreatic-type isoamylases, and salivary amylase accounts for 60% to 65% of the total amylase content. Salivary hyperamylasemia can occur in the settings of diabetic ketoacidosis, alcoholism, and malignancy (especially with hepatic metastasis).

Macroamylasemia occurs without any relationship to pancreatitis and results in elevated serum (but not urine) amylase levels.

Attempts at improving the sensitivity, and especially the specificity, of the laboratory-based diagnosis of pancreatitis have included measurement of the renal amylase clearance and the ratio of renal amylase clearance to creatinine clearance (C_{am}/C_{cr}). However, the specificity of the C_{am}/C_{cr} is questionable because it may be elevated in the settings of diabetic ketoacidosis, burns, renal failure, chronic hemodialysis, pancreatic neoplasms, and alcoholic liver disease. Measurement of the pancreatic isoamylase levels has also been tried. This may provide information that changes the clinical diagnosis in 20% to 40% of patients with hyperamylasemia. Measurement of the serum lipase level is slightly less sensitive for the diagnosis of pancreatitis than that of the serum amylase level, but the lipase concentration remains elevated longer and is more specific than the amylase value.

What clinical and laboratory indices can be used to assess the prognosis in a case of acute pancreatitis?

A set of the early risk factors, known as Ranson's criteria, has been used to predict the potential complications and mortality in a patient with acute pancreatitis (see Tables 4.4/4.5).

The mortality rate associated with these signs has been determined as follows: two or fewer signs, 1%; three or four signs, 16%; five or six signs, 40%; and more than six signs, 100%.

Table 4-5 Ranson's

-
- At admission
 - Age, older than 55 y
 - White blood cell count, >16,000/mm³
 - Blood glucose, > 200 mg/dL
 - Serum lactate dehydrogenase, <350 IU/L
 - Aspartate aminotransferase, > 250 IU/L
 - During initial 48 hr
 - Hematocrit decrease, > 10%
 - Blood urea nitrogen rise, > 5 mg/dL
 - Serum calcium, <8 mg/dL
 - Arterial partial pressure of oxygen (Po₂), <60 mm Hg
 - Base deficit, >4 mEq/L
 - Estimated fluid sequestration, > 6 L
-

Measurement of trypsinogen activation peptide in urine may distinguish mild from severe pancreatitis, but the test is not generally available.

What events signal the development of local complications of acute pancreatitis, and how are they best evaluated?

Local and infectious complications of acute pancreatitis account for 80% of the mortality associated with the disease; therefore, detection of these complications is crucial in minimizing the likelihood of a fatal outcome. A pancreatic pseudocyst should be suspected in the setting of persistent pain and hyperamylasemia, and may be manifested as a palpable mass in the upper abdomen. Pancreatic necrosis or phlegmon, and pancreatic abscess are often difficult to distinguish because they both commonly cause prolonged abdominal pain and tenderness, fever, leukocytosis, and a palpable mass.

A computed tomography (CT) scan with oral and IV contrast enhancement is the best method for imaging these complications. Extraluminal gas may be seen on the studies and can be used to distinguish pancreatic necrosis from pancreatic abscess. However, it is CT-guided percutaneous needle aspiration that usually allows for the early diagnosis of pancreatic infection and abscess, which require either percutaneous or surgical drainage.

What are the mainstays of treatment of acute pancreatitis, and what is the rationale for their use?

By eliminating oral intake (NPO), the neural and hormonal stimuli to pancreatic exocrine secretion may be minimized, thereby limiting the cycle of pancreatic autodigestion and inflammation. Eliminating food intake reduces the vagal stimulation of pancreatic secretion and reduces the delivery of acid, fatty acids, and amino acids to the duodenum, which would elicit release of secretin and cholecystokinin. Parenteral nutrition is often administered, but enteral nutrition through a tube placed in the jejunum is preferred because of its lower cost and fewer complications. Nasogastric suction is usually not advocated, but it may be useful in those patients experiencing nausea and vomiting resulting from paralytic ileus.

Adequate replacement of fluid and electrolyte losses (especially calcium) stemming from the retroperitoneal inflammation and exudation is essential. Hypocalcemia is believed to result from a combination of factors: hypoalbuminemia, the sequestration of calcium in areas of fat necrosis, and an inadequate parathormone response. Analgesic administration is usually required to control the pain, which is often intense and prolonged.

What cardinal feature distinguishes chronic pancreatitis from acute pancreatitis?

The permanent destruction of the pancreatic gland is a cardinal feature of chronic pancreatitis. Pathologically, there is atrophy of the acini, a loss of islet cells, fibrosis, and plugging of irregular pancreatic ducts by protein. The protein plugs may be calcified and, on radiographic studies, 30% of patients exhibit pancreatic calcification. The clinical sequelae of glandular destruction include exocrine and endocrine insufficiency, manifested by steatorrhea and diabetes mellitus, respectively (the former occurring only when there is a more than 90% reduction in exocrine function). Abdominal pain is not uniformly seen and may be intermittent, constant, or absent. Because of the acinar destruction, the serum amylase levels may be only mildly elevated or normal.

How does the etiology of chronic pancreatitis differ from that of acute pancreatitis?

In western countries, most (approximately 90%) cases of chronic pancreatitis are attributable to alcoholism. Other possible causes include metabolic disorders such as hypercalcemia of any cause (perhaps hyperparathyroidism), hyperlipidemia, and congenital or hereditary conditions (pancreas divisum, cystic fibrosis, and hereditary pancreatitis).

What are the mainstays of treatment of chronic pancreatitis?

Acute relapses of chronic pancreatitis may require management identical to that for acute pancreatitis, and may be accompanied by pseudocyst formation and pancreatic ascites. Exocrine insufficiency resulting in steatorrhea and weight loss is treated with oral pancreatic enzyme replacement, whereas endocrine insufficiency (diabetes mellitus) requires insulin therapy. Management of the chronic pain has been problematic, and patients frequently become addicted to narcotic analgesics. The oral administration of high doses of pancreatic enzymes may reduce the pain. Surgical intervention (ganglionectomy, partial and total pancreatectomy, and pancreatic duct drainage operations) confers inconsistent benefits and is fraught with long-term morbidity.

ANSWERS TO CASE 10:

Is it unusual that the patient had his first attack of pancreatitis pain after 10 years of heavy alcohol consumption, and at that time he already had signs of chronic pancreatitis (pancreatic calcification)?

No. It is believed that most people must consume at least 50 g of alcohol daily on a prolonged basis before chronic pancreatitis develops, and most have been drinking excessively for 5 to 20 years before their first attack. Alcohol-induced pancreatitis is probably chronic, even at the time of the first attack. Pancreatic calcifications are seen in 25% to 50% of the patients and are particularly common in alcoholics who have chronic pancreatitis.

What is the pathophysiologic basis for vitamin B₁₂ deficiency in the setting of chronic pancreatitis?

The vitamin B₁₂ deficiency stems from the exocrine insufficiency. Pancreatic proteases are necessary to cleave R protein from vitamin B₁₂ in the proximal intestine, so that the latter may be absorbed as a complex with intrinsic factor (in the terminal ileum). Approximately 50% of patients with advanced pancreatitis have vitamin B₁₂ deficiency due to exocrine insufficiency.

Why did the patient begin to gain weight only after his pancreatic enzyme dose was increased and cimetidine added?

Pancreatic enzymes can be inactivated by gastric acid, and this inactivation can be reduced by the administration of antacids or histamine 2 (H₂) receptor antagonists. In addition, evidence suggests that certain enzyme capsules are more effective at delivering active enzyme to the small intestine than others.

Why might the patient's pain have subsided toward the end of the described course?

Sustained pain relief in patients with chronic pancreatitis often occurs after several years and only with marked progression of the pancreatic exocrine insufficiency, rather than being a result of therapeutic intervention. However, this patient's pain seemed to subside rather quickly with the institution of high doses of pancreatic enzyme therapy. The suppression of pancreatic exocrine secretion has been

accomplished in patients who received intraduodenal perfusions of pancreatic extract, and the pain of chronic pancreatitis has been shown to respond to treatment with orally administered pancreatic enzymes in some patients.

ANSWERS TO CASE 11:

What are this man's risk factors for peptic ulcer disease?

His smoking and nonsteroidal anti-inflammatory drug (NSAID) ingestion are both risk factors for peptic ulcer disease.

What diagnostic tests should you consider?

If the patient were younger than 40 years, had only mild and intermittent symptoms, and had no evidence of systemic disease or risk factors for malignancy, a trial of empiric anti-ulcer therapy without prior diagnostic tests would be acceptable. Otherwise, either esophagogastroduodenoscopy (EGD) or a double-contrast upper gastrointestinal (GI) radiographic series is recommended. When there is a possibility of malignancy and if biopsy specimens are needed, EGD is considered superior to radiography for the purpose of diagnosis. Because the man described is older than 40 years, smokes cigarettes, has occult blood in the stool, and is having increasingly severe pain, a diagnostic workup (preferably EGD) rather than empiric therapy is recommended.

When would you consider treatment for *H. pylori*?

Eradication of *H. pylori* is usually advocated when associated with duodenal ulcer, and results in a dramatic reduction in ulcer recurrence. Infection can be demonstrated by endoscopic biopsy, serology, or radioisotope breath test findings. A multiple-drug regimen is required for reliable eradication of the organisms. A commonly used combination has been that of a bismuth-containing compound, tetracycline, metronidazole, and either a proton pump inhibitor or H₂ receptor antagonist. Better patient compliance and equal efficacy have been reported with combinations of clarithromycin, amoxicillin, bismuth, and a proton pump inhibitor or H₂ receptor antagonist.

Discussion

What are the major risk factors for the development of peptic ulcers?

The major risk factors for the development of peptic ulcer disease are cigarette smoking, the ingestion of nonsteroidal antiinflammatory drugs (NSAIDs), and a family history of peptic ulcer. Peptic ulcers are thought to form when the effects of gastric acid and pepsin overwhelm the protective mucosal barrier. Diseases such as the Zollinger-Ellison syndrome increase the secretion of gastric acid. Other factors promote the breakdown of the mucosal barrier.

Ulcers are twice as likely to develop in cigarette smokers than in nonsmokers. In addition, ulcers heal more slowly and are more likely to recur in smokers. The mechanism responsible for cigarette smoke's ulcerogenic effect is not completely understood. NSAIDs disrupt the mucus-bicarbonate barrier, allowing acid to damage the underlying mucosa. The GI complications of NSAIDs are a major cause of upper GI bleeding and perforation, particularly in elderly women, and are responsible for a two- to threefold increased mortality risk in long-term users of NSAIDs. The combined use of NSAIDs and corticosteroids appears to increase the risk even further.

People who have first-degree relatives with peptic ulcers have three times the risk of acquiring ulcers compared with the general population. The risk is even higher for the identical twin of a patient with ulcer disease.

Infection of the gastric mucosa by *Helicobacter pylori* is strongly associated with lower rates of duodenal ulcer healing and with higher rates of ulcer recurrence. The exact manner in which *H. pylori* infection promotes ulcers is not known.

No conclusive evidence links dietary substances, including ethanol, caffeine, and spicy foods, with the development of peptic ulcers. Similarly, although a critically ill hospitalized patient may have stress ulcers, environmental stressors at home or at work have not been conclusively linked with the development of peptic ulcers.

Is dietary adherence to bland meals and milk an accepted treatment of peptic ulcer disease? If not, what should the treatment be?

No. Before the advent of modern pharmacologic therapy, the treatment of ulcer disease with frequent bland meals and milk was widely accepted. Unfortunately, such treatment actually increases the

production of gastric acid and does not accelerate ulcer healing.

H₂ receptor antagonists, of which cimetidine was the first agent released for use, are widely accepted as safe and effective for the treatment of peptic ulcers. These agents directly inhibit histamine-stimulated gastric acid secretion and indirectly inhibit the histamine-potentiated, gastrin-stimulated acid secretion. When given in sufficient doses, the various H₂ receptor antagonists act equally well, with duodenal ulcer healing rates of 75% after 4 weeks, and 85% to 95% after 8 weeks of therapy. The selection of a particular agent should be determined by the patient's ability to comply with the dosing regimen, as well as the cost per dose.

Proton pump inhibitors, such as omeprazole, and esomeprazole, are concentrated in the highly acidic environment of the parietal cell secretory canaliculi. When activated by protonation, these agents covalently bind to H⁺/K⁺ AT-Pase, thereby causing irreversible inhibition of the enzyme and a 90% to 99% suppression of gastric acid production within 24 hours. At doses of 20 to 40 mg per day, omeprazole achieves more rapid pain relief and faster healing of peptic ulcers than do standard doses of H₂ receptor antagonists. Proton pump inhibitors are the treatment of choice for patients with nonsurgically correctable Zollinger-Ellison syndrome. These agents have displayed an excellent short-term safety profile, and, with increasing use, their long-term risk seems less than initially feared.

Sucralfate is an aluminum salt of sulfated sucrose. When placed in an acidic environment, it binds tenaciously to ulcers and promotes healing. It has no effect on acid secretion and has minimal acid-neutralizing effects. The entire mechanism of sucralfate's beneficial actions has not been determined. Sucralfate appears to be as effective as H₂ receptor antagonists in promoting the healing of acute peptic ulcers. Its systemic absorption is minimal, although its long-term effects on aluminum deposition are unknown. Its primary side effect is dose-related constipation.

Antacids are also effective in promoting the healing of gastric and duodenal ulcers. Frequent dosing is usually required to achieve effectiveness equal to that of H₂ receptor antagonists. Such a dosing schedule often results in poor patient compliance, not to mention the side effect of diarrhea associated with the use of magnesium-containing antacids.

There is no evidence to support the use of these agents in various combinations for the primary treatment of peptic ulcers. Combination therapy with antibiotics, acid-suppressive medications, and bismuth compounds is effective in healing duodenal ulcers associated with *H. pylori* infection, and in preventing the recurrence of such ulcers.

ANSWERS TO CASE 12:

What is the likely diagnosis?

This woman has diverticulitis. Colonic diverticula are small outpouchings which are most commonly found in the left colon. They are very common in the elderly Western population probably due to a deficiency in dietary fibre. Symptomatic diverticular disease has many of the features of irritable bowel syndrome. Inflammation in a diverticulum is termed diverticulitis. In severe cases, perforation, paracolic abscess formation or septicaemia may develop. Other potential complications include bowel obstruction, formation of a fistula into rectum or vagina, and haemorrhage.

The barium enema from 4 years ago shows evidence of diverticular disease with outpouchings of the mucosa in the sigmoid colon. This would be consistent with the long-standing history of abdominal pain of colonic type and tendency to constipation. The recent problems with increased pain, tenderness, fever, raised white cell count and CRP and a mass in the left iliac fossa would be compatible with an acute exacerbation of her diverticular disease. In her case there is no evidence of peritonitis which would signal a possible perforation of one of the diverticula.

What should be the initial management?

The differential diagnosis, with the suggestion of a mass and change in bowel habit, would be carcinoma of the colon and Crohn's disease. In the absence of evidence of perforation with leak of bowel contents into the peritoneum (no peritonitis) or obstruction (normal bowel sounds, no general distension), treatment should be based on the presumptive diagnosis of diverticulitis. A colonoscopy should be performed at a later date to exclude the possibility of a colonic neoplasm.

A computed tomography (CT) scan of the abdomen will delineate the mass and suggest whether there is evidence of local abscess formation. Treatment should include broad-spectrum antibiotics, intravenous fluids and rest. Further investigations are indicated, including electrolytes, urea and creatinine,

glucose, liver function tests and blood cultures. Repeated severe episodes, bleeding or obstruction may necessitate surgery.

Clinical pearls

- > Diverticular disease is a common finding in the elderly Western population and may be asymptomatic or cause irritable bowel syndrome-type symptoms.
- > Diverticular disease is a common condition; its presence can distract the unwary doctor from pursuing a co-incident condition.
- > Diverticulitis needs to be treated with antibiotics to reduce the chance of complications such as perforation or fistula formation occurring.

ANSWERS TO CASE 13:

What is the most likely diagnosis and what investigations should be performed?

The pattern of the pain, the absence of physical signs, normal investigations and reproduction of the pain during sigmoidoscopy all make it likely that this is irritable bowel syndrome (IBS). This is a very common condition accounting for a large number of referrals to gastroenterology clinics. IBS is often episodic, with variable periods of relapse and remission. Periods of frequent defaecation alternate with periods of relative constipation. Relapses are often associated with periods of stress. In IBS it is common to have a history of other conditions such as migraine and menstrual irregularity. Under the age of 40 years with a history of 6 years of similar problems, it would be reasonable to accept the diagnosis and reassure the patient. However, the family history of carcinoma of the colon raises the possibility of a condition such as familial polyposis coli. The family history, the circumstances of the grandmother's death and the patient's feelings about this should be explored further. Anxiety about the family history might contribute to the patient's own symptoms or her presentation at this time. If there are living family members with polyposis coli, DNA probing may be used to identify family members at high risk. If any doubt remains in this woman it would be sensible to proceed to a barium enema or a colonoscopy to rule out any significant problems.

The diagnosis of IBS relies on the exclusion of other significant conditions such as inflammatory bowel disease, diverticular disease or large-bowel malignancy. In patients under the age of 40 years it is usually reasonable to do this on the basis of the history, examination and a normal full blood count and ESR. In older patients, sigmoidoscopy and barium enema or colonoscopy should be performed. A plan of investigation and management should be clearly established. The symptoms tend to be persistent and are not helped by repeated normal investigations looking for an underlying cause. Symptoms may be helped by antispasmodic drugs or tricyclic antidepressants. Some patients will benefit from the consumption of a high-fibre diet.

Clinical pearls

- > Irritable bowel syndrome is a common disorder and difficult to treat.
- > Explanation of the condition to the patient is an important part of the management.
- > Sigmoidoscopy with air insufflation often reproduces the symptoms of IBS.

ANSWERS TO CASE 14:

What is the most likely diagnosis?

This woman has acute cholecystitis. Cholecystitis is most common in obese, middle-aged women, and classically is triggered by eating a fatty meal. Cholecystitis is usually caused by a gallstone impacting in the cystic duct. Continued secretion by the gallbladder leads to increased pressure and inflammation of the gallbladder wall. Bacterial infection is usually by Gram-negative organisms and anaerobes. Ischaemia in the distended gallbladder can lead to perforation causing either generalized peritonitis or formation of a localized abscess. Alternatively the stone can spontaneously disimpact and the symptoms spontaneously improve. Gallstones can get stuck in the common bile duct leading to cholangitis or pancreatitis. Rarely, gallstones can perforate through the inflamed gallbladder wall into the small intestine and cause intestinal obstruction (gallstone ileus). The typical symptom is of sudden-onset right upper quadrant abdominal pain which radiates into the back. In uncomplicated cases the pain improves within 24 h. Fever suggests a bacterial infection. Jaundice usually occurs if there is a stone in the common bile duct. There is usually guarding and rebound tenderness in the right upper quadrant

(Murphy's sign).

In this patient the leucocytosis and raised CRP are consistent with acute cholecystitis. If the serum bilirubin and liver enzymes are very deranged, acute cholangitis due to a stone in the common bile duct should be suspected. The abdominal X-ray is normal; the majority of gallstones are radiolucent and do not show on plain films.

The major differential diagnoses of acute cholecystitis include perforated peptic ulcer, acute pancreatitis, acute hepatitis, subphrenic abscess, retrocaecal appendicitis and perforated carcinoma or diverticulum of the hepatic flexure of the colon. Myocardial infarction or right lower lobe pneumonia may also mimic cholecystitis.

How would you manage this patient?

This patient should be admitted under the surgical team. Serum amylase should be measured to rule out pancreatitis. Blood cultures should be taken. Chest X-ray should be performed to exclude pneumonia, and erect abdominal X-ray to rule out air under the diaphragm which occurs with a perforated peptic ulcer. An abdominal ultrasound will show inflammation of the gallbladder wall. The patient should be kept nil by mouth, given intravenous fluids and commenced on intravenous cephalosporins and metronidazole. The patient should be examined regularly for signs of generalized peritonitis or cholangitis. If the symptoms settle down the patient is normally discharged to be readmitted in a few weeks once the inflammation has settled down to have a cholecystectomy.

Clinical pearls

- > Acute cholecystitis typically causes right upper quadrant pain and a positive Murphy's sign.
- > Potential complications include septicaemia and peritonitis.

ANSWERS TO CASE 15:

A 37-year-old man presents with complaints of chronic and recurrent upper abdominal pain with characteristics suggestive of duodenal ulcer: the pain is burning, occurs when the stomach is empty, and is relieved within minutes by food or antacids. He does not have evidence of gastrointestinal bleeding or anemia. He does not take nonsteroidal anti-inflammatory drugs, which might cause ulcer formation, but he does have serologic evidence of *H.pylori* infection.

- > Most likely diagnosis: Peptic ulcer disease (PUD)
- > Next step: Antibiotic therapy for *H.pylori* infection

Considerations

In this patient, the symptoms are suggestive of duodenal ulcer. He does not have "alarm symptoms," such as weight loss, bleeding, or anemia, and his young age and chronicity of symptoms make gastric malignancy an unlikely cause for his symptoms. *Helicobacter pylori* commonly is associated with PUD and requires treatment for cure of the ulcer and prevention of recurrence. This patient's symptoms are also consistent with nonulcer dyspepsia.

APPROACH TO PEPTIC ULCER DISEASE

Definitions

DYSPEPSIA: Pain or discomfort centered in the upper abdomen (mainly in or around the midline), which can be associated with fullness, early satiety, bloating, or nausea. Dyspepsia can be intermittent or continuous, and it may or may not be related to meals.

FUNCTIONAL (NONULCER) DYSPEPSIA: Symptoms as described for dyspepsia, persisting for at least 12 weeks but without evidence of ulcer on endoscopy.

HELICOBACTER PYLORI: A gram-negative microaerophilic bacillus that resides within the mucus layer of the gastric mucosa and causes persistent gastric infection and chronic inflammation. It produces a urease enzyme that splits urea, raising local pH and allowing it to survive in the acidic environment.

PEPTIC ULCER DISEASE (PUD): Presence of gastric or duodenal ulcers as demonstrated by endoscopy or by upper gastrointestinal barium study.

Clinical approach

Upper abdominal pain is one of the most common complaints encountered in primary care practice. Many patients have benign functional disorders (ie, no specific pathology can be identified after diagnostic testing), but others have potentially more serious conditions such as PUD or gastric cancer. Historical clues, knowledge of the epidemiology of diseases, and some simple laboratory assessments

can help to separate benign from serious causes of pain. However, endoscopy is often necessary to confirm the diagnosis.

Dyspepsia refers to upper abdominal pain or discomfort that can be caused by PUD, but it also can be produced by a number of other gastrointestinal disorders. Gastroesophageal reflux typically produces “heartburn,” or burning epigastric or mid chest pain, usually occurring after meals and worsening with recumbency. Biliary colic caused by gallstones typically has acute onset of severe pain located in the right upper quadrant or epigastrium, usually is precipitated by meals, especially fatty foods, lasts 30 to 60 minutes with spontaneous resolution, and is more common in women. Irritable bowel syndrome is a diagnosis of exclusion but is suggested by chronic dysmotility symptoms, (bloating, cramping) often relieved with defecation, without weight loss or bleeding. If these causes are excluded by history or other investigations, it is still difficult to clinically distinguish by symptoms the patients with PUD and those without ulcers, termed *nonulcer dyspepsia*.

The classic symptoms of duodenal ulcers are caused by the presence of acid without food or other buffers. Symptoms are typically produced after the stomach is emptied but food-stimulated acid production still persists, typically 2 to 5 hours after a meal. They may awaken patients at night, when circadian rhythms increase acid production. The pain is typically relieved within minutes by neutralization of acid by food or antacids (eg, calcium carbonate, aluminum-magnesium hydroxide). Gastric ulcers, by contrast, are more variable in their presentation. Food may actually worsen symptoms in patients with gastric ulcer, or pain might not be relieved by antacids. In fact, many patients with PUD have no symptoms at all. Gastric cancers may present with dysphagia if they are located in the cardiac region of the stomach, with persistent vomiting if they block the pyloric channel, or with early satiety by their mass effect or infiltration of the stomach wall. They may present with pain symptoms as a result of ulcer formation.

Because the incidence of gastric cancer increases with age, patients older than 45 years who present with new-onset dyspepsia should generally undergo endoscopy. In addition, patients with alarm symptoms (eg, weight loss, recurrent vomiting, dysphagia, evidence of bleeding, or anemia) should be referred for prompt endoscopy. Finally, endoscopy should be recommended for patients whose symptoms have failed to respond to empiric therapy. When endoscopy is undertaken, besides visualization of the ulcer, biopsy samples can be taken to exclude the possibility of malignancy as the cause of a gastric ulcer, and biopsy specimens can be obtained for urease testing or microscopic examination to prove current *H pylori* infection.

In younger patients with no alarm features, an acceptable strategy is to perform a noninvasive *H pylori* antibody test to determine if the patient is infected. *Helicobacter pylori* is more common in older patients, in lower socioeconomic groups, in institutionalized patients, and in developing countries. It has been established as the causative agent in the majority of duodenal and gastric ulcers, and it is associated with the development of gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. The two most common tests are the urea breath test, which provides evidence of current active infection, and *H pylori* antibody tests, which provide evidence of prior infection but will remain positive for life, even after successful treatment. Because chronic infection with *H pylori* is found in 90% to 95% of duodenal ulcers and in 80% of patients with gastric ulcers not related to nonsteroidal anti-inflammatory drug (NSAID) use, a suggested strategy is to test for infection and, if present, to treat it with an antibiotic regimen such as clarithromycin and amoxicillin, as well as acid suppression with a proton pump inhibitor. The reason for treating infection with antibiotics is that eradication of the infection will largely prevent recurrence. Whether treatment of *H pylori* infection reduces or eliminates dyspeptic symptoms in the absence of ulcers (nonulcer dyspepsia) is uncertain. Similarly, whether treatment of asymptomatic patients found to be *H pylori* positive is beneficial is unclear. In *H pylori*-positive patients with dyspepsia, antibiotic treatment may be considered, but a follow-up visit is recommended within 4 to 8 weeks. If symptoms persist or alarm features develop, then prompt upper endoscopy is indicated.

In addition to *H pylori*, the other major cause of duodenal and gastric ulcers is the use of NSAIDs. They promote ulcer formation by inhibiting gastroduodenal prostaglandin synthesis, resulting in reduced secretion of mucus and bicarbonate and decreased mucosal blood flow. In other words, they impair local defenses against acid damage. The risk of ulcer formation caused by NSAID use is dose dependent and can occur within days after treatment is initiated. If ulceration occurs, the NSAID should be discontinued if possible, and acid-suppression therapy with an H₂-receptor antagonist or proton pump inhibitor should

be initiated.

A rare cause of ulcer is the Zollinger-Ellison syndrome, a condition in which a gastrin-producing tumor (usually pancreatic) causes acid hypersecretion, peptic ulceration, and often diarrhea. This condition should be suspected if ulcer disease occurs and the patient is *H. pylori* negative and does not use NSAIDs. To diagnose this condition, one should measure serum gastrin levels, which are markedly elevated (>1000 pg/mL), and then try to localize the tumor with an imaging study.

Hemorrhage is the most common severe complication of PUD and can present with hematemesis or melena. Free perforation into the abdominal cavity may occur in association with hemorrhage, with sudden onset of pain and development of peritonitis. If the perforation occurs adjacent to the pancreas, it may induce pancreatitis. Some patients with chronic ulcers later develop gastric outlet obstruction, with persistent vomiting and weight loss but no abdominal distention. Perforation and obstruction are indications for surgical intervention.

Comprehension Questions

1. A 42-year-old overweight but otherwise healthy woman presents with sudden onset of right upper abdominal colicky pain 45 minutes after a meal of fried chicken. The pain is associated with nausea and vomiting, and any attempt to eat since has caused increased pain. Which of the following is the most likely cause?

- A. Gastric ulcer
- B. Cholelithiasis
- C. Duodenal ulcer
- D. Acute hepatitis

2. Which of the following is the most accurate statement regarding *H. pylori* infection?

- A. It is more common in developed than underdeveloped countries.
- B. It is associated with the development of colon cancer.
- C. It is believed to be the cause of nonulcer dyspepsia.
- D. The route of transmission is believed to be sexually transmitted.
- E. It is believed to be a common cause of both duodenal and gastric ulcers.

3. A 45-year-old man was brought to the emergency room after vomiting bright red blood. He has a blood pressure of 88/46 mm Hg and heart rate of 120 bpm. Which of the following is the best next step?

- A. Intravenous fluid resuscitation and preparation for a transfusion
- B. Administration of a proton pump inhibitor
- C. Guaiac test of the stool
- D. Treatment for *H. pylori*

4. Which one of the following patients should be promptly referred for endoscopy?

- A. A 65-year-old man with new onset of epigastric pain and weight loss
- B. A 32-year-old patient whose symptoms are not relieved with ranitidine
- C. A 29-year-old *H. pylori*-positive patient with dyspeptic symptoms
- D. A 49-year-old woman with intermittent right upper quadrant pain following meals

Answers

1. B. Right upper abdominal pain of acute onset that occurs after ingestion of a fatty meal and is associated with nausea and vomiting is most suggestive of biliary colic as a result of gallstones. Duodenal ulcer pain is likely to be diminished with food, and gastric ulcer pain is not likely to have acute severe onset. Acute hepatitis is more likely to produce dull ache and tenderness.

2. E. Although *H. pylori* is clearly linked to gastric and duodenal ulcers and probably to gastric carcinoma and lymphoma, whether it is more common in patients with nonulcer dyspepsia and whether treatment in those patients reduces symptoms are unclear. It is more common in underdeveloped or developing countries.

3. A. This patient is hemodynamically unstable with hypotension and tachycardia as a consequence of the acute blood loss. Volume resuscitation, immediately with crystalloid or colloid solution, followed by blood transfusion, if necessary, is the initial step to prevent irreversible shock and death. Later, after stabilization, acid suppression and *H. pylori* treatment might be useful to heal an ulcer, if one is present.

4. A. Patient in answer A has “red flag” symptoms: he is older than 45 years and has new onset symptoms. Patient in answer B may benefit from the reassurance of a negative endoscopic examination. Patient in answer C, however, may benefit from treatment of her *H. pylori* first. Some studies indicate this approach may be cost-saving overall. This patient could be sent for an endoscopic examination if she

does not improve following the therapy.

Clinical Pearls

▶ The most common causes of duodenal and gastric ulcers are *Helicobacter pylori* infection and use of nonsteroidal anti-inflammatory drugs.

▶ *Helicobacter pylori* is associated with duodenal and gastric ulcers, chronic active gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. It is not definitively associated with nonulcer dyspepsia.

▶ Treatment of peptic ulcers requires acid suppression with an H2 blocker or proton- pump inhibitor to heal the ulcer, as well as antibiotic therapy of *Helicobacter pylori* infection, if present, to prevent recurrence.

▶ Patients with dyspepsia who have "red flag" symptoms (new dyspepsia after age 45 years, weight loss, dysphagia, evidence of bleeding or anemia) should be referred for an early endoscopic examination.

▶ Other patients (patients with dyspepsia who does not have "red flag" symptoms) may be tested for *Helicobacter pylori* and treated first. Antibody tests show evidence of infection but remain positive for life, even after successful treatment. Urea breath tests are evidence of current infection.

▶ Common treatment regimens for *Helicobacter pylori* infection include a 14-day course of a proton-pump inhibitor in high doses (e.g., lansoprazole 30 mg twice daily or omeprazole 20 mg twice daily) along with antibiotic therapy, usually clarithromycin and amoxicillin.

ANSWERS TO CASE 16:

A 42-year-old woman with a prior history consistent with symptomatic cholelithiasis now presents with epigastric pain and nausea for 24 hours, much longer than would be expected with uncomplicated biliary colic. Her symptoms are consistent with acute pancreatitis. She also has hyperbilirubinemia and an elevated alkaline phosphatase level, suggesting obstruction of the common bile duct caused by a gallstone, which is the likely cause of her pancreatitis.

Most likely diagnosis: Acute pancreatitis.

Most likely etiology: Choledocholithiasis (common bile duct stone).

Next diagnostic step: Right upper quadrant abdominal ultrasonography.

Considerations

This 42-year-old woman complained of episodes of mild right upper quadrant abdominal pain with heavy meals in the past. These prior episodes were shortlived. This is very consistent with biliary colic. However, this episode is different in severity and location of pain (now radiating straight to her back and accompanied by nausea and vomiting). The elevated amylase level confirms the clinical impression of acute pancreatitis. She likely has acute pancreatitis caused by a stone in the common bile duct. Biliary obstruction is suggested by the elevated bilirubin level. She is moderately ill but is hemodynamically stable and has only one prognostic feature to predict mortality—her elevated white blood cell (WBC) count (Table 16-1). She likely can be managed on a hospital ward without the need for intensive care.

Table 16-1. Ranson criteria for severity of pancreatitis

Initial	Within 48 hours of admission
<ul style="list-style-type: none"> . Age >55 years . WBC >16,000/mm³ . Serum glucose >200 . Serum lactate dehydrogenase (LDH) >350 IU/L . AST >250 IU/L 	<ul style="list-style-type: none"> . Hematocrit drop >10 points . Blood urea nitrogen (BUN) rise >5 mg/dL after intravenous hydration . Arterial Po₂ <60 mm Hg . Serum calcium <8 mg/dL . Base deficit >4 mEq/L . Estimated fluid sequestration of >6 L

APPROACH TO ACUTE PANCREATITIS

Definitions

ACUTE PANCREATITIS: An inflammatory process in which pancreatic enzymes are activated and cause autodigestion of the gland.

PANCREATIC PSEUDOCYST: Cystic space within the pancreas not lined by epithelial cells, often associated with chronic pancreatitis.

Clinical approach

Acute pancreatitis can be caused by many processes, but in the United States, alcohol use is the most common cause, and episodes are often precipitated by binge drinking. The next most common cause is biliary tract disease, usually due to passage of a gallstone into the common bile duct. Hypertriglyceridemia is another common cause and occurs when serum triglyceride levels are more than 1000 mg/dL, as is seen in patients with familial dyslipidemias or diabetes (etiologies are given in Table 16-2). When patients appear to have “idiopathic” pancreatitis, that is, no gallstones are seen on ultrasonography and no other predisposing factor can be found, biliary tract disease is still the most likely cause—either biliary sludge (microlithiasis) or sphincter of Oddi dysfunction.

Table 16-2. Causes of acute pancreatitis

- Biliary tract disease (eg, gallstones)
 - Alcohol use
 - Drugs (eg, the antiretroviral didanosine [ddl], pentamidine, thiazides, furosemide, sulfonamides, azathioprine, L-asparaginase)
 - Surgical manipulation of the gland or ERCP
 - Hypertriglyceridemia/hypercalcemia
 - Infections such as mumps or cytomegalovirus
 - Trauma such as blunt abdominal trauma
-

Abdominal pain is the cardinal symptom of pancreatitis and often is severe, typically in the upper abdomen with radiation to the back. The pain often is relieved by sitting up and bending forward, and is exacerbated by food. Patients commonly experience nausea and vomiting that is precipitated by oral intake. They may have low-grade fever (if temperature is $>101^{\circ}\text{F}$, one should suspect infection) and often are volume depleted because of the vomiting, inability to tolerate oral intake, and because the inflammatory process may cause third spacing with sequestration of large volumes of fluid in the peritoneal cavity.

The most common test used to diagnose pancreatitis is an elevated serum amylase level. It is released from the inflamed pancreas within hours of the attack and remains elevated for 3 to 4 days. Amylase undergoes renal clearance, and after serum levels decline, its level remains elevated in the urine. Amylase is not specific to the pancreas, however, and can be elevated as a consequence of many other abdominal processes, such as gastrointestinal ischemia with infarction or perforation; even just the vomiting associated with pancreatitis can cause elevated amylase of salivary origin. Elevated serum lipase level, also seen in acute pancreatitis, is more specific than is amylase to pancreatic origin and remains elevated longer than does amylase. When the diagnosis is uncertain or when complications of pancreatitis are suspected, computed tomographic (CT) imaging of the abdomen is highly sensitive for showing the inflammatory changes in patients with moderate to severe pancreatitis.

Treatment of pancreatitis is mainly supportive and includes “pancreatic rest,” that is, withholding food or liquids by mouth until symptoms subside and adequate narcotic analgesia, usually with meperidine. Intravenous fluids are necessary for maintenance and to replace any deficits. In patients with severe pancreatitis who sequester large volumes of fluid in their abdomen as pancreatic ascites, sometimes prodigious amounts of parenteral fluid replacement are necessary to maintain intravascular volume. Patients with adynamic ileus and abdominal distention or protracted vomiting may benefit from nasogastric suction. When pain has largely subsided and the patient has bowel sounds, oral clear liquids can be started and the diet advanced as tolerated.

The large majority of patients with acute pancreatitis will recover spontaneously and have a relatively uncomplicated course. Several criteria have been developed in an attempt to identify the 15% to 25% of patients who will have a more complicated course. These include the Ranson (United States) and Glasgow/Imrie (United Kingdom) criteria, as well as the APACHE (Acute Physiology and Chronic Health Evaluation) II scoring system. When three or more of the following criteria are present, a severe course complicated by pancreatic necrosis can be predicted by Ranson criteria (Table 14-1). The most common cause of early death in patients with pancreatitis is hypovolemic shock, which is multifactorial: third spacing and sequestration of large fluid volumes in the abdomen, as well as increased capillary permeability. Others develop pulmonary edema, which may be noncardiogenic as a consequence of acute

respiratory distress syndrome (ARDS), or cardiogenic as a consequence of myocardial dysfunction.

Pancreatic complications include a phlegmon, which is a solid mass of inflamed pancreas, often with patchy areas of necrosis. Sometimes, extensive areas of pancreatic necrosis develop within a phlegmon. Either necrosis or a phlegmon can become secondarily infected, resulting in pancreatic abscess. Abscesses typically develop 2 to 3 weeks after the onset of illness and should be suspected if there is fever or leukocytosis. If pancreatic abscesses are not drained, mortality approaches 100%. Pancreatic necrosis and abscess are the leading causes of death in patients after the first week of illness. A pancreatic pseudocyst is a cystic collection of inflammatory fluid and pancreatic secretions, which unlike true cysts do not have an epithelial lining. Most pancreatic pseudocysts resolve spontaneously within 6 weeks, especially if they are smaller than 6 cm. However, if they are causing pain, are large or expanding, or become infected, they usually require drainage. Any of these local complications of pancreatitis should be suspected if persistent pain, fever, abdominal mass, or persistent hyperamylasemia occurs.

Gallstones

Gallstones usually form as a consequence of precipitation of cholesterol microcrystals in bile. They are very common, occurring in 10% to 20% of patients older than 65 years. Patients often are asymptomatic. When discovered incidentally, they can be followed without intervention, as only 10% of patients will develop any symptoms related to their stones within 10 years. When patients do develop symptoms because of a stone in the cystic duct or Hartmann pouch, the typical attack of biliary colic usually has a sudden onset, often precipitated by a large or fatty meal, with severe steady pain in the right upper quadrant or epigastrium, lasting between 1 and 4 hours. They may have mild elevations of the alkaline phosphatase level and slight hyperbilirubinemia, but elevations of the bilirubin level over 3 g/dL suggest a common duct stone. The first diagnostic test in a patient with suspected gallstones usually is an ultrasonogram. The test is noninvasive and very sensitive for detecting stones in the gallbladder as well as intrahepatic or extrahepatic biliary duct dilation.

One of the most common complications of gallstones is acute cholecystitis, which occurs when a stone becomes impacted in the cystic duct, and edema and inflammation develop behind the obstruction. This is apparent ultrasonographically as gallbladder wall thickening and pericholecystic fluid, and is characterized clinically as a persistent right upper quadrant abdominal pain, with fever and leukocytosis. Cultures of bile in the gallbladder often yield enteric flora such as *Escherichia coli* and *Klebsiella*. If the diagnosis is in question, nuclear scintigraphy with a hepatobiliary iminodiacetic acid (HIDA) scan may be performed. The positive test shows visualization of the liver by the isotope, but nonvisualization of the gallbladder may indicate an obstructed cystic duct. Treatment of acute cholecystitis usually involves making the patient NPO (nil per os), intravenous fluids and antibiotics, and early cholecystectomy within 48 to 72 hours.

Another complication of gallstones is cholangitis, which occurs when there is intermittent obstruction of the common bile duct, allowing reflux of bacteria up the biliary tree, followed by development of purulent infection behind the obstruction. If the patient is septic, the condition requires urgent decompression of the biliary tree, either surgically or by endoscopic retrograde cholangiography (ERCP), to remove the stones endoscopically after performing a papillotomy, which allows the other stones to pass.

Comprehension Questions

1. A 43-year-old man who is an alcoholic is admitted to the hospital with acute pancreatitis. He is given intravenous hydration and is placed NPO. Which of the following findings is a poor prognostic sign?

- A. His age
- B. Initial serum glucose level of 60 mg/dL
- C. Blood urea nitrogen (BUN) level rises 7 mg/dL over 48 hours
- D. Hematocrit drops 3%
- E. Amylase level of 1000 IU/L

2. A 37-year-old woman is noted to have gallstones on ultrasonography. She is placed on a low-fat diet. After 3 months she is noted to have severe right upper quadrant pain, fever to 102°F, and nausea. Which of the following is the most likely diagnosis?

- A. Acute cholangitis
- B. Acute cholecystitis

- c. Acute pancreatitis
- d. Acute perforation of the gallbladder

3. A 45-year-old man was admitted for acute pancreatitis, thought to be a result of blunt abdominal trauma. After 3 months he still has epigastric pain but is able to eat solid food. His amylase level is elevated at 260 IU/L. Which of the following is the most likely diagnosis?

- A. Recurrent pancreatitis
- B. Diverticulitis
- C. Peptic ulcer disease
- D. Pancreatic pseudocyst

Answers

1. C. When the BUN rises by 5 mg/dL after 48 hours despite IV hydration, it is a poor prognostic sign. Notably, the amylase level does not correlate to the severity of the disease. An elevated serum glucose would be a poor prognostic factor. A drop of hematocrit of at least 10% is a significant poor prognostic criteria.

2. B. Acute cholecystitis is one of the most common complications of gallstones. This patient with fever, right upper quadrant pain, and a history of gallstones likely has acute cholecystitis.

3. D. A pancreatic pseudocyst has a clinical presentation of abdominal pain and mass and persistent hyperamylasemia in a patient with prior pancreatitis.

Clinical Pearls

- ▶ The most common causes of acute pancreatitis in the United States are alcohol consumption, gallstones, and hypertriglyceridemia.

- ▶ Acute pancreatitis usually is managed with pancreatic rest, intravenous hydration, and analgesia, often with narcotics.

- ▶ Patients with pancreatitis who have zero to two of the Ranson criteria are expected to have a mild course; those with three or more criteria can have significant mortality.

- ▶ Pancreatic complications (phlegmon, necrosis, abscess, pseudocyst) should be suspected if persistent pain, fever, abdominal mass, or persistent hyperamylasemia occurs.

- ▶ Patients with asymptomatic gallstones do not require treatment; they can be observed and treated if symptoms develop. Cholecystectomy is performed for patients with symptoms of biliary colic or for those with complications.

- ▶ Acute cholecystitis is best treated with antibiotics and then cholecystectomy, generally within 48 to 72 hours.

ANSWERS TO CASE 17:

A 61-year-old man has 3 days of new-onset, worsening, left lower quadrant abdominal pain. He feels nauseated, and he has not had any bowel movements since the illness began. His temperature is 100.2°F and he has no pallor or jaundice. His abdomen is mildly distended with hypoactive bowel sounds and marked left lower quadrant tenderness with voluntary guarding. Rectal examination reveals tenderness, and his stool is negative for occult blood. The WBC count is 11,800/mm³ with 74% polymorphonuclear cells, 22% lymphocytes, and a normal hemoglobin and hematocrit. A plain film of the abdomen shows no acute changes.

- > Most likely diagnosis: Acute sigmoid diverticulitis.

- > Most appropriate next step: Admit to the hospital for intravenous antibiotics and monitoring.

Computed tomographic (CT) scan of the abdomen will be very useful to confirm the diagnosis and to exclude pericolic abscess or other complications, such as fistula formation.

Considerations

This is an older patient with new-onset, progressively severe, lower abdominal pain. It is on the left side, suggesting diverticulitis as a diagnosis. The pattern of the pain suggests a bowel process because he has had nausea, no bowel movement, and pain that initially was crampy and intermittent but now is steady. The low-grade temperature is consistent with acute sigmoid diverticulitis, which is likely to improve with antibiotic therapy. Because the clinical presentation is similar, it is important to evaluate the patient for colon cancer with perforation, once all signs of inflammation have subsided. The abdominal film reveals no free air under the diaphragm. Ischemic colitis is another diagnostic

consideration in an older patient, but it usually is associated with signs of bleeding, whereas diverticulitis is not.

APPROACH TO SUSPECTED DIVERTICULITIS

Definitions

COLONIC DIVERTICULUM: Herniation of the mucosa and submucosa through a weakness of the muscle lining of the colon.

DIVERTICULITIS: Inflammation of the colonic diverticulum, typically on the left colon, such as the sigmoid.

DIVERTICULOSIS: Presence of diverticular disease in the colon with uninflamed diverticula.

Clinical approach

Diverticulosis is extremely common, affecting 50% to 80% of people older than 80 years. Diverticula are, in fact, *pseudodiverticula* through a weakness in the muscle lining, typically at areas of vascular penetration to the smooth muscle. Therefore, their walls do not contain the muscle layers surrounding the colon. They are typically 5 to 10 mm in diameter and occur mainly in the distal colon in Western societies. The development of diverticula has been linked to insufficient dietary fiber leading to alteration in colonic transit time and increased resting colonic intraluminal pressure. The majority of patients will remain asymptomatic. However, some patients will have chronic symptoms resembling those of irritable bowel syndrome (nonspecific lower abdominal pain aggravated by eating with relief upon defecation, bloating, and constipation or diarrhea). They may even present with acute symptoms that could be confused with acute diverticulitis, but without evidence of inflammation upon further workup. This entity has been named “painful diverticular disease without diverticulitis.” Complications of diverticulosis include acute diverticulitis, hemorrhage, and obstruction.

Diverticular hemorrhage, one of the most common causes of lower gastrointestinal (GI) bleeding in patients older than 40 years, typically presents as painless passage of bright red blood. Generally, the hemorrhage is abrupt in onset and abrupt in resolution. The diagnosis may be established by finding diverticula on endoscopy without other pathology. Most diverticular hemorrhages are self-limited, and treatment is supportive, with intravenous fluid or blood replacement as needed. Treatment of diverticulosis consists of dietary measures with increased fiber. Avoidance of foods with small seeds (eg, strawberries) is traditionally advised, although data supporting this recommendation are scant. For patients with recurrent or chronic bleeding, resection of the affected colonic segment may be indicated.

Acute diverticulitis is the most common complication of diverticulosis, developing in approximately 20% of all patients with diverticula. Patients often present with acute abdominal pain and signs of peritoneal irritation localizing to the left lower quadrant and often thought of presenting like “leftsided appendicitis.” Inspissated stool particles (fecaliths) appear to obstruct the diverticular neck, setting up for more inflammation and diminished venous outflow, as well as bacterial overgrowth, which ultimately leads to abrasion and perforation of the thin diverticular wall. It is classified into four stages according to the extent of the inflammation and perforation (Table 17-1).

Table 17-1. Stages of diverticulitis

Stage I	Small, confined pericolic abscess
Stage II	Distant abscess (retroperitoneal or pelvic)
Stage III	Generalized suppurative peritonitis from rupture of abscess (noncommunicating with bowel lumen)
Stage IV	Fecal peritonitis caused by a free communicating perforation

Diagnosis

Patients usually present with visceral pain that localizes later to the left lower quadrant and is associated with fever, nausea, vomiting, or constipation. A right lower quadrant presentation would not exclude this diagnosis because ascending colon or cecal diverticulitis can occur. If a colovesical fistula is present, the patient may present with pneumaturia or fecaluria (a virtually pathognomic finding). On examination, the patient may have localized left lower quadrant tenderness or more diffuse abdominal tenderness with peritoneal irritation signs, such as guarding or rebound tenderness. The differential diagnosis includes painful diverticular disease without diverticulitis, acute appendicitis, Crohn disease, colon carcinoma, ischemic colitis, irritable bowel syndrome, and gynecologic disorders such as ruptured ovarian cyst, endometriosis, ectopic pregnancy, and pelvic inflammatory disease.

Plain film radiographs, including abdominal erect and supine films with a chest X-ray, are routinely performed but usually are not diagnostic. They help in identifying patients with

pneumoperitoneum and assessing their cardiopulmonary status, especially in patients with other comorbid conditions. Contrast enemas are contraindicated for fear of perforation and spillage of contrast into the abdominal cavity, a catastrophic complication. Endoscopy is also relatively contraindicated in the acute phase and usually is reserved for use at least 6 weeks after resolution of the attack and then is performed primarily to exclude colonic neoplasia, which may have a similar findings on imagines studies, such as luminal narrowing or thickened colonic wall. Computed tomography (CT) scan typically is the preferred modality of choice for diagnosing diverticulitis if there is a high pretest probability from clinical suspicion. Findings consistent with diverticulitis include the presence of pericolic fat stranding, thickening of the bowel wall to more than 4 mm, or the finding of a peridiverticular abscess.

Therapy

Factors that advocate for inpatient therapy include the need for narcotics to control pain, presence of peritoneal signs, presence of comorbid illnesses, inability to tolerate oral liquids, or presence of any of the complications that may potentially require surgical intervention (abscess or peritonitis). Indications for emergent surgical intervention include generalized peritonitis, uncontrolled sepsis, perforation, and clinical deterioration. In the absence of acute complications, elective resection is undertaken later in cases of complications including fistula formation and when there are recurrent episodes of diverticulitis.

Individuals treated as outpatients should be placed on a broad-spectrum antibiotic regimen that covers abdominal gram-negative rods and anaerobes, such as trimethoprim/sulfamethoxazole, *or* ciprofloxacin with metronidazole *or* clindamycin with gentamicin. Patients should be placed on a clear liquid diet and undergo close follow-up.

The treatment priorities in hospitalized patients are intravenous hydration, correction of electrolyte imbalances, and bowel rest (nothing by mouth). Some recommended broad- spectrum intravenous antibiotic regimens include standard triple therapy (ampicillin, an aminoglycoside, and metronidazole) and beta-lactamase inhibitor combinations (ampicillin- sulbactam or ticarcillin- clavulanate), among others. More empiric agents, such as imipenem or meropenem, usually are reserved for more severe and complicated cases. Pain, fever, and leukocytosis are expected to diminish with appropriate management in the first few days of treatment, at which point the dietary intake can be advanced gradually. Further imaging may be indicated to identify complications (Table 17-2) such as abscess, stricture, or obstruction in the patient with persistent fever or pain.

Table 17-2. Implications of diverticulitis

Complication	Characteristics	Treatment
Abscess	Suspected in patients with a tender mass on examination, persistent fever and leukocytosis in spite of adequate therapy, or a suggestive finding on imaging studies.	Conservative management for small pericolic abscesses. A CT-guided percutaneous drainage or surgical drainage for other abscesses depending on the size, content, location, and peritoneal contamination.
Fistulas	Majority is colovesical with male predominance (because of bladder protection by the uterus in females). Others include colovaginal, coloenteric, colouterine, and coloureteral. Colocutaneous fistulas are extremely rare.	Single-stage surgery with fistula closure and primary anastomosis.
Obstruction	Either acutely or chronically. Ileus or pseudo-obstruction is more likely than complete mechanical obstruction. Small-bowel obstruction may occur if a small-bowel loop was incorporated in the inflamed mass.	Usually amenable to medical management. If not, prompt surgical intervention is required.
Strictures	Occur as a result of recurrent attacks of diverticulitis. Insidious-onset colonic obstruction is likely. Colonoscopy is important for an accurate diagnosis and to exclude a stenosing neoplasm as the cause of the stricture.	A trial of endoscopic therapy (bougienage, balloon, laser, electrocautery, or a blunt dilating endoscope) reasonably can be attempted. Surgery is indicated if neoplasm could not be excluded or if such trial has failed.

Surgical management such as sigmoid resection may be indicated for patients who have suffered two or more documented episodes of diverticulitis requiring hospitalization. This is especially true for patients younger than 50 years of age, who may experience more aggressive disease.

Comprehension questions

1. A 48-year-old woman is admitted to the hospital with left lower quadrant abdominal pain, leukocytosis, and a CT showing sigmoid wall thickening consistent with diverticulitis. Her only significant medical history is a similar hospitalization with the same diagnosis less than a year previously. Which of the following is the most appropriate treatment?

- A. Urgent surgical consultation for exploratory laparotomy and sigmoid resection.
- B. Intravenous antibiotics with follow-up colonoscopy after hospital discharge, and surgical consultation for elective sigmoidectomy.
- C. Intravenous antibiotics and barium enema to evaluate for possible colonic malignancy.
- D. Intravenous antibiotics and recommendations for post discharge diet high in fiber with whole grains and nuts to minimize the risk of diverticular progression.

2. A 78-year-old is noted to have fever and chills, decreased mentation, tachycardia, and right lower quadrant abdominal tenderness and guarding. Which of the following is the most likely diagnosis?

- A. Ruptured diverticulitis
- B. Meningitis
- C. Ruptured appendicitis
- D. Ischemic bowel
- E. Urosepsis

3. A 58-year-old man presents to the emergency room with a temperature of 102°F, abdominal pain localizing to the left lower quadrant, and mild rebound tenderness. Which of the following diagnostic tests is the best next step?

- A. Barium enema
- B. Lower endoscopy
- C. CT imaging of the abdomen
- D. Laparoscopic examination

Answers

1. B. Patients with two or more episodes of diverticulitis should be considered for elective surgical management to try to prevent future complications such as fistulae, obstruction, or perforation. Colonoscopy is generally performed before surgical resection to exclude the possibility of malignancy, since the radiographic

2. C. The most common cause of an acute abdomen at any age is appendicitis.

3. C. A CT imaging is the modality of choice in evaluating diverticulitis. Barium enema and endoscopy tend to increase intraluminal pressure and can worsen diverticulitis or lead to

Clinical Pearls

- ▶ Acute diverticulitis usually presents with left lower quadrant pain, fever, leukocytosis, and constipation, and often with signs of peritoneal inflammation.
- ▶ A patient with mild diverticulitis can be treated as an outpatient with oral antibiotics; more severe cases require hospital admission for intravenous broad-spectrum antibiotics, bowel rest, and fluids.
- ▶ Diverticulitis can be complicated by perforation with peritonitis, pericolic abscess, fistula formation, often to the bladder, and strictures with colonic obstruction.

ANSWERS TO CASE 18:

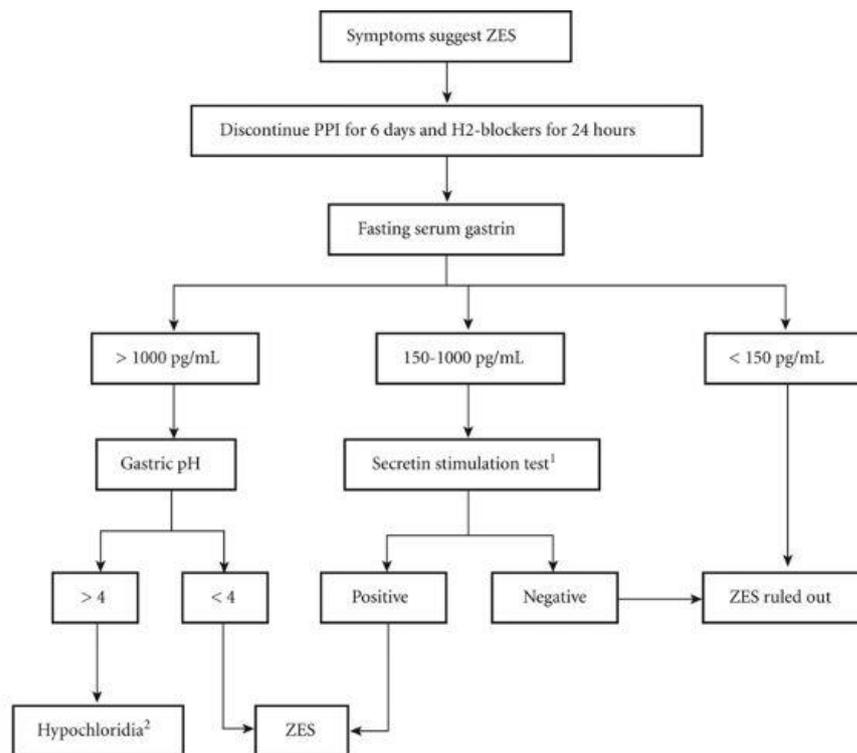
What diagnosis should you suspect?

Suspect Zollinger-Ellison syndrome (ZES) in the following patients with peptic ulcers:

- Multiple ulcers refractory to medical therapy
- Distal duodenal or jejunal ulcers
- Diarrhea
- Family history of parathyroid, pituitary, or pancreatic tumors (multiple endocrine neoplasia type 1 (MEN-1) syndrome)

What causes ZES? How can you confirm the diagnosis?

The cause of ZES is a pancreatic gastrinoma that releases excessive gastrin and stimulates acid hypersecretion. The tumor also inactivates pancreatic enzymes, which leads to malabsorptive diarrhea (foul-smelling watery diarrhea with steatorrhea). See Figure 18-1 for the diagnostic approach to ZES.



¹Secretin stimulation test: Secretin stimulates a rise in serum gastrin of > 200 pg/mL within 2-30 minutes of administration if the patient has a gastrinoma.

²Hypochloridia: Conditions like pernicious anemia and atrophic gastritis can result in secondary hypergastrinemia due to hypochloridia

Figure 18–1. Diagnostic approach to Zollinger-Ellison syndrome (ZES).

The patient discontinues esomeprazole for 1 week. Fasting serum gastrin is 1500 pg/mL and gastric pH is 2.5, which confirms the diagnosis. What are the next steps?

Perform somatostatin receptor scintigraphy (octreotide scan) to localize the tumor and detect liver metastases. If octreotide scan does not localize the primary tumor, perform EUS. Obtain serum PTH, prolactin, FSH, LH, and growth hormone levels to exclude MEN-1 syndrome.

How is gastrinoma treated?

- Metastases or MEN-1 syndrome: Medically manage with high-dose proton pump inhibitors, octreotide, interferon alpha, and chemotherapy (low cure rate).
- No metastases and no evidence of MEN-1: Main treatment is surgery (high cure rate).

The patient is a 32-year-old man with 4 weeks of epigastric burning and bloating that sometimes occurs during meals and sometimes between meals. Antacids occasionally relieve symptoms. He drinks at least a six-pack of beer every day. He takes aspirin every day because he heard it is “good for the heart.” He sometimes notices blood when he vomits after heavy drinking.

What is the next step in management?

This patient has dyspepsia and an alarm symptom (gastrointestinal bleeding). The next step in management is EGD.

ANSWERS TO CASE 19:

What diagnosis should you suspect?

Maintain a high index of suspicion for chronic mesenteric ischemia in any patient with a history of atherosclerosis who complains of food-induced dyspepsia and unintentional weight loss. Symptoms result from mesenteric atherosclerosis (“intestinal angina”). Abdominal examination is typically benign except for an upper abdominal bruit in 50%. Patients may also report nonspecific gastrointestinal symptoms like

nausea, vomiting, diarrhea, and constipation. Negative esophagogastroduodenoscopy rules out peptic ulcer disease, gastritis, and gastric cancer. Normal lab tests decrease the likelihood of biliary and pancreatic causes.

Risk factors for coronary artery disease and chronic mesenteric ischemia are the same.

How is this condition diagnosed and treated?

Perform mesenteric duplex ultrasound to screen for mesenteric atherosclerosis. If the results are equivocal or positive, perform mesenteric angiography to confirm the diagnosis and define the anatomy. Treatment is either surgery or percutaneous transluminal angioplasty (PTA) with or without stent placement.

No large controlled trials have compared surgery versus PTA versus PTA + stent.

ANSWERS TO CASE 20:

What diagnosis should you suspect?

Suspect bowel obstruction when a patient presents with acute onset of nausea, vomiting, and diffuse cramping abdominal pain ± obstipation (no passage of gas or feces). Common physical signs of obstruction are abdominal distension, tympany, an empty rectal vault, and high pitched or absent bowel sounds. Distension proximal to the obstruction causes reflex vomiting and decreased absorption, which leads to dehydration, hypokalemia, and metabolic alkalosis.

Proximal versus distal obstruction:

- Obstruction proximal to the jejunum: severe nausea and vomiting but minimal abdominal distension because the dilated proximal small intestine acts as a reservoir.
- Obstruction distal to jejunum: severe abdominal distension but minimal nausea and vomiting.

Partial versus complete obstruction:

- Partial obstruction: Patients can pass gas and may have bowel movements.
- Complete obstruction: Classic symptom is complete obstipation; in reality, patients may pass residual gas or stool distal to the obstruction.

What are the next steps in diagnosis?

• Obstructive series: The initial diagnostic tests to evaluate for obstruction are upright CXR and supine and upright abdominal x-rays. In small bowel obstruction (SBO), abdominal x-rays show multiple air-fluid levels and no air in the colon (see Fig. 20-1). In large bowel obstruction (LBO), the bowel is filled with air and dilated proximal to the obstruction with no air in the distal colon. Upright CXR is obtained to rule out bowel perforation (free air under the diaphragm). If abdominal films are positive, further work-up is unnecessary.

• CT scan: Order an abdominal computed tomography (CT) scan with oral and IV contrast if obstructive series is nondiagnostic.

• Gastrointestinal (GI) series: If both obstructive series and CT scan are nondiagnostic, order an upper or lower GI series with water-soluble contrast depending on whether you suspect SBO or LBO.

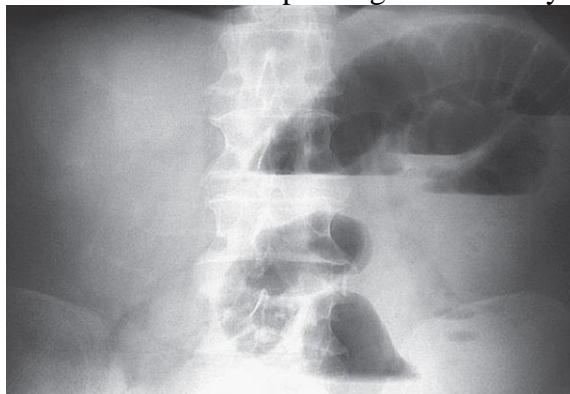


Figure 20–1. Abdomen x-ray showing SBO.

Occasionally, patients with SBO have feculent emesis due to bacterial overgrowth (bacteria ferment and break down food debris).

Abdominal x-ray shows multiple air-fluid levels, dilated loops of small bowel, and no air in the colon, which confirms the diagnosis of SBO. What is the most likely cause of obstruction in this patient?

Three fourths of SBOs result from extrinsic compression by adhesions that form after abdominal surgery (Table 20-1). Postoperative adhesions are the most likely cause in this patient who recently had an appendectomy.

Table 20–1 Etiologies of bowel obstruction in adults

Extrinsic compression	<ol style="list-style-type: none"> 1. Postoperative adhesions: Most common cause. 2. Hernia: Second most common cause; inguinal hernia always requires surgery. 3. Volvulus: Causes LBO more frequently than SBO.
Intrinsic compression	<ol style="list-style-type: none"> 1. Cancer: CRC, SI cancers, metastatic melanoma, and metastatic breast cancer. 2. Radiation enteritis 3. Crohn's disease: Patients may develop strictures, which lead to SBO. 4. Gallstones: Gallstones occasionally obstruct the intestines via an enteric-biliary fistula in patients with cholelithiasis or cholecystitis. Abdominal radiograph may show air in the biliary tree (pneumobilia). Surgery is the recommended treatment. 5. Fecal impaction: Treat with a mineral oil enema and/or manual disimpaction.

Abbreviation: CRC, colorectal cancer; LBO, large bowel obstruction; SBO, small bowel obstruction; SI, small intestine.

How is SBO treated?

Initial therapy for stable patients is supportive:

- NPO: fasting.
- IV fluids and electrolytes: Obtain IV access to determine the degree of dehydration by measuring serum electrolytes, hematocrit, and urine output; administer normal saline until the patient is euvolemic and correct electrolyte imbalances.
- NG suction: Perform NS suction to prevent further bowel distension.
- Reassess: Frequently reassess the patient for strangulation (signs of acute abdomen or shock), which is an indication for emergent surgery. Some centers also use serial computed tomography (CT) scans to detect early signs of bowel ischemia. Serial abdominal films are not helpful.

Strangulation: SBO increases intraluminal pressure, which can cut off blood flow and cause perforation, peritonitis, and septic shock. Closed loop obstruction (lumen occluded at two points) increases the risk of strangulation.

The patient's pain, nausea, and abdominal distension improve over the next 24 hours with fluids and NG suction. NG suction is discontinued. Over the next 4 hours, signs and symptoms of SBO recur. What is the next step in management?

Surgery is indicated for patients who fail medical management (continued symptoms despite 12 to 24 hours of NG suction or prompt recurrence after discontinuing suction).

ANSWERS TO CASE 21:

What is the diagnosis?

The abdominal film shows a large, kidney-shaped mass extending into the left upper quadrant (“coffee bean sign”), which is diagnostic of large bowel obstruction caused by a cecal volvulus. Volvulus is defined as twisting of a segment of bowel on its mesenteric attachment, which can lead to obstruction. The cecum is the most common location of volvulus.

What is the next step in management?

Treatment of cecal volvulus is emergent surgery to untwist (detorse) the volvulus.

What diagnosis would be more likely if Figure 21-2 was the patient's abdominal film?



Figure 21–2. Abdomen x-ray showing sigmoid volvulus.

The abdominal x-ray demonstrates a collection of gas extending from the pelvis to the right upper quadrant (“bent inner tube sign”). This finding is characteristic for a sigmoid volvulus, which is the second most common location of volvulus. Sigmoid volvulus is more common in elderly and institutionalized patients. Treatment is to untwist the volvulus with a sigmoidoscope. Surgery is reserved for refractory or recurrent cases.

ANSWERS TO CASE 22:

What diagnosis should you suspect?

Maintain a high index of suspicion for acute mesenteric ischemia when patients with risk factors for thrombosis or embolism (hypercoagulable state, atrial fibrillation, atherosclerosis, etc.) present with severe abdominal pain out of proportion to physical exam findings. Although initial findings are benign, patients can develop signs of acute abdomen as ischemia progresses. Fecal occult blood test may be positive late in the course of the illness.

Laboratory tests are nonspecific. Common findings include increased white blood cells (WBCs), increased hematocrit (due to dehydration), and metabolic acidosis (due to lactic acidosis).

What are the types of acute mesenteric ischemia?

- Mesenteric artery embolism: most common cause of acute mesenteric ischemia (due to cardiac embolism to the superior mesenteric artery); onset of symptoms is more sudden and painful than other types.
- Mesenteric artery thrombosis: due to atherosclerosis.
- Mesenteric vein thrombosis: associated with hypercoagulable states, portal hypertension, malignancy, and trauma.
- Nonocclusive mesenteric ischemia: due to splanchnic hypoperfusion in patients who are critically ill or have severe atherosclerosis; 25% deny abdominal pain.

What are the next steps in management of patients with suspected mesenteric ischemia?

The initial step is to stabilize the patient and to obtain an obstructive series (to rule out mechanical obstruction). If obstructive series is negative, the next test depends on whether or not the patient has a hypercoagulable state or acute abdomen (see Fig. 22-1).

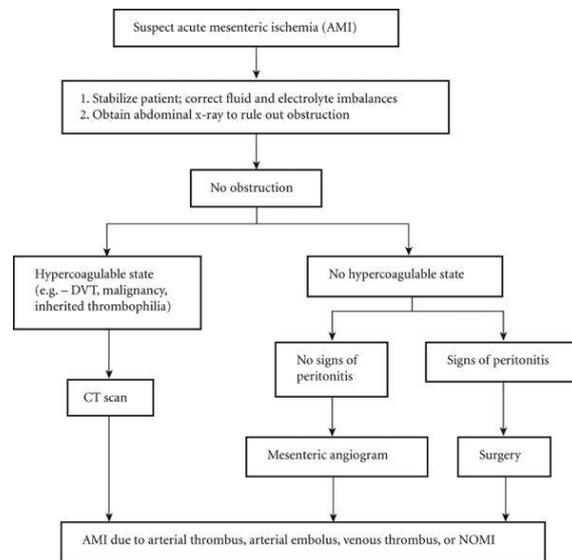


Figure 22–1. Algorithm for diagnosis of acute mesenteric ischemia.

Mesenteric angiography is the gold standard for establishing the diagnosis and cause of acute mesenteric ischemia.

Abdominal plain films do not reveal any signs of obstruction. The patient does not have any risk factors for hypercoagulability. He undergoes mesenteric angiogram, which is diagnostic for mesenteric artery embolism. How are the different causes of acute mesenteric ischemia (AMI) treated?

AMI is associated with a high mortality (overall mortality is 70%; after bowel infarction, mortality is >90%). Initial therapy for all types of acute mesenteric ischemia is stabilization, broad-spectrum antibiotics, and NG tube placement. After these initial steps, management strategies for the different types of AMI are as follows:

- Mesenteric artery embolism: Standard treatment is surgical embolectomy. An alternative to surgery is thrombolytics and papaverine (a vasodilator). After recovery, long-term use of warfarin can prevent recurrence.
- Mesenteric artery thrombosis: If angiography shows good collateral flow, consider heparin and observation. If collaterals are insufficient, treat with a papaverine drip and emergent surgery. After recovery, long-term use of aspirin can prevent recurrence.
- Mesenteric vein thrombosis: Treatment is heparin followed by surgery. After recovery, long-term use of warfarin can prevent recurrence.
- Nonocclusive mesenteric ischemia: Treatment is IV papaverine. Some clinicians also use heparin. After recovery, long-term use of aspirin can prevent recurrence.

Unstable patients with acute abdomen: Surgery is required regardless of the type of AMI; avoid vasopressors because they worsen ischemia.

“Drip”: medical slang for continuous infusion.

ANSWERS TO CASE 23

What is most likely cause of the patient's current symptoms?

The most common cause of left lower quadrant (LLQ) pain and tenderness in elderly patients is diverticulitis, which results from inflammation of diverticula. Pain is initially mild, so most patients present days rather than hours after symptom onset. Approximately 50% of patients have a palpable mass. Patients often have a low-grade fever and mild leukocytosis.

What is the next step in this patient with suspected diverticulitis?

Computed tomography (CT) scan of the abdomen and pelvis is the preferred test to diagnose diverticulitis. This test can also detect complications of diverticulitis. In addition to CT scan, obtain abdominal and chest radiographs to rule out other causes of abdominal pain. Colonoscopy and barium enema are contraindicated during the initial stages of acute diverticulitis because they can cause perforation.

Complications of diverticulitis: POP A Fistula (Perforation, Obstruction, Peritonitis, Abscess, and Fistulas).

CASE DISCUSSION

What are diverticula?

Diverticula are pouches in weak areas of the colon wall near blood vessels. They result from increased intraluminal pressure. Patients with diverticula are termed as having diverticulosis. Diverticulosis may be asymptomatic (detected incidentally on colonoscopy or barium enema) or present with symptoms similar to IBS. Incidence of diverticulosis increases with age. No imaging is recommended to diagnose suspected diverticulosis. Prevent complications of diverticulosis with increased fiber intake.

Complications of diverticulosis:

- Painless rectal bleeding: 95% are self-limited, 5% are massive.
- Diverticulitis: caused by infection/inflammation of a microperforated diverticulum.

CT scan confirms uncomplicated diverticulitis. How is this condition treated?

First, triage patients for outpatient versus inpatient management. Criteria for admission are:

- Elderly patients, immunosuppressed patients, or patients with severe comorbid diseases
- Patients with signs of acute abdomen, high fever, or WBC count

Admit this elderly patient to the hospital and treat with NPO, IV fluids, and IV antibiotics (clindamycin or metronidazole to cover anaerobes plus a third-generation cephalosporin or fluoroquinolone to cover Gram-negative aerobes). Symptoms should resolve in 2 to 3 days. Surgery is indicated after 72 hours if symptoms or leukocytosis worsens or fails to improve after 72 hours.

Outpatient treatment of diverticulitis: Clear liquids and a 7- to 10-day course of amoxicillin-clavulanate or ciprofloxacin and metronidazole.

Symptoms improve within 2 days. The patient is ready for discharge. What should you recommend after resolution of symptoms?

Recommend colonoscopy 2 to 6 weeks after recovery to evaluate the extent of diverticulitis and to rule out other conditions like cancer. Instruct the patient to consume a high fiber diet to prevent recurrences.

Some physicians recommend that patients avoid nuts and seeds, which can theoretically lodge in the diverticulum and cause another episode of diverticulitis. There is no convincing evidence to support this recommendation.

What is the risk of recurrence after an episode of diverticulitis treated medically?

Diverticulitis recurs in one third of patients treated medically. Consider elective surgical resection after more than two episodes because recurrences carry a higher risk of complications.

Consider elective surgery after the first attack in the following groups:

- Diverticulitis patients with complications
- Immunosuppressed patients
- Patients <40 years old (controversial)

Two months later, the patient complains that he has been passing air and stool through his penis when he urinates. Occasionally, he passes urine through his rectum. What is the most likely complication?

The patient has developed a fistula between the bladder and the colon (colovesical fistula). Diagnose with sigmoidoscopy followed by barium enema. If these studies are nondiagnostic perform abdomen and pelvis CT scan. Treatment is elective surgery.

ANSWERS TO CASE 24:

What is the most likely diagnosis?

The most likely diagnosis is acute ischemic colitis, caused by a sudden decrease in blood flow to watershed areas of the colon. Patients are usually elderly and report acute onset of abdominal pain (most commonly in the left lower quadrant (LLQ) followed by small amounts of hematochezia and bloody diarrhea within 24 hours (Table 4-5). Vital signs are usually normal and mild leukocytosis is the only laboratory abnormality.

Table 4-5 acute ischemic colitis versus acute mesenteric ischemia.

	Location of Abdominal Pain	GI Bleeding
--	----------------------------	-------------

Acute ischemic colitis	Lateral (usually left lower quadrant)	Hematochezia and bloody diarrhea
Acute mesenteric ischemia	Periumbilical or diffuse	Occult blood late in course

What diagnostic tests are indicated?

Consider fecal leukocytes and stool culture to rule out infectious diarrhea. Consider an abdominal plain film to rule out obstruction and perforation. Patients with advanced ischemic colitis may have distension and pneumatosis (intestinal air) on abdominal plain films. Computed tomography (CT) scan of the abdomen often establishes the diagnosis. Perform colonoscopy only if the etiology is unclear despite history, physical, abdominal film, and CT scan.

Colonoscopy findings in acute ischemic colitis are pale mucosa, petechiae, blue-based ulcers, and bluish hemorrhagic nodules. On barium enema, these hemorrhagic nodules may appear as “thumbprints” (may also be seen in AMI).

Abdominal plain film is nondiagnostic, but CT scan shows segmental thickening of bowel wall indicative of acute ischemic colitis. What treatment is indicated?

Treat supportively with NPO, IV fluids, broad-spectrum IV antibiotics, and an NG tube if the patient has an ileus. Approximately 80% to 90% of patients recover with supportive care alone. Some patients may progress to gangrene and perforation, so frequently reassess for excessive bloody diarrhea or acute abdomen (peritonitis). Clinical deterioration is an indication for surgical management.

ANSWERS TO CASE 25:

What is the most likely diagnosis?

The patient's symptoms are suggestive of IBS, the most commonly diagnosed gastrointestinal (GI) disorder. Patients present with a variety of GI complaints, but the primary symptoms are chronic abdominal pain and altered bowel habits. Patients may also report abdominal bloating.

Rome Criteria for IBS: Recurrent abdominal pain or discomfort at least 3 days of the month for at least 3 months accompanied by at least two of the following:

- Altered stool appearance
- Altered stool frequency
- Symptoms improve with defecation

Subtypes of IBS are diarrhea-predominant IBS, constipation-predominant IBS, mixed IBS (diarrhea and constipation), and unsubtyped IBS.

What is the next step in management?

This patient's symptoms are consistent with mixed IBS. She does not have any alarm symptoms. Limit diagnostic testing to complete blood count (CBC), serum electrolytes, fecal occult blood test ± celiac panel.

What are alarm findings that would warrant further diagnostic testing?

Remember alarm findings that warrant further diagnostic testing with the mnemonic “DOLLAR”: Dysphagia, Odynophagia, Large-volume diarrhea, Loss of weight, Anorexia, and decreased RBCs (anemia or GI bleeding).

Laboratory testing is normal. Stool is guaiac-negative. How is IBS treated?

- Education and reassurance: This is the most important intervention in the management of IBS. Acknowledge that the patient's symptoms are real and explain that they are in part caused by visceral hypersensitivity and an imbalance in the brain-gut connection. Reassure her that although there is no simple cure for this chronic condition, IBS does not degenerate into a serious illness or have any effect on mortality.

- Dietary modification: Consider an empiric trial of lactose avoidance. Avoid excessive caffeine. If bloating is a symptom, avoid foods that increase flatulence. If the patient complains of constipation in the absence of bloating, try to increase fiber intake.

- Behavioral therapy: Although psychosocial distress does not cause IBS, patients with anxiety, depression, and somatization often perceive symptoms as more severe. Psychotherapy, hypnosis, and biofeedback may benefit motivated patients.

- Pharmacologic therapy: Consider medications as a short-term adjunctive measure during severe symptom flares. Treat bloating with antispasmodics like dicyclomine. Treat diarrhea with loperamide

(use cautiously in this patient with mixed constipation and diarrhea). Tricyclic antidepressants and selective serotonin reuptake inhibitors are an option if the patient also suffers from depression.

Tegaserod: Serotonin-4 agonist improves GI motility and may improve symptoms in constipation-predominant IBS.

Alosetron (serotonin-3 antagonist) has been approved for diarrhea-predominant IBS. Poses risk of ischemic colitis and severe constipation, so consider only for the small subset of patients with intolerable symptoms unresponsive to conventional therapy.

Emerging data suggest altered bacteria in the small intestine play a role in IBS. Treatment with antibiotics and probiotics is a promising new strategy to treat IBS.

ANSWERS TO CASE 26:

What condition should you suspect?

A pulsatile mass at or above the level of the umbilicus suggests that the patient has an abdominal aortic aneurysm (AAA). Symptoms of AAA are abdominal and back pain. However, AAA is often detected incidentally on abdominal imaging because patients may not have any signs or symptoms. Risk factors for this condition include age, smoking, hypertension, and atherosclerosis.

What is the next step in management?

Perform an abdominal ultrasound to confirm the diagnosis.

Screening for AAA: The USPSTF recommends one-time screening ultrasound for all patients aged 65 to 75 years who have ever smoked.

Ultrasound detects a 4.2-cm AAA. What treatment is recommended at this time?

Aneurysms <6 cm in diameter have a low risk of rupture. The recommended management of an asymptomatic AAA between 4 and 5.4 cm is smoking cessation, cardiovascular (CV) risk factor control, β -blockers, and monitoring with ultrasound every 6 to 12 months. Computed tomography (CT) scan is an alternative to ultrasound at some centers.

Management of asymptomatic AAA <4 cm: Monitor with ultrasound every 2 to 3 years; have the patient quit smoking, control CV risk factors, and take β -blockers.

When is elective surgery warranted for AAA?

Consider elective surgery or endoluminal stenting in the following patients:

- Size > 5.4 cm
- Rate of growth > 0.5 cm in 6 months
- Symptomatic AAA (regardless of size or rate of growth)

The patient does not return for his follow-up appointment. He presents to the emergency department 2 years later with severe abdominal pain radiating to the back. Physical exam is significant for a pulsatile abdominal mass above the umbilicus. Blood pressure is 90/60. What is the diagnosis?

The triad of pulsatile abdominal mass, hypotension, and severe abdominal and/or back pain indicates that the patient has a ruptured AAA. Treatment is emergent surgery. When a patient presents with the classic triad, additional confirmatory tests are not needed.

Severe abdominal/back pain + pulsatile abdominal mass but no hypotension: Most likely diagnosis is expanding but unruptured aneurysm; confirm diagnosis with ultrasound and treat with urgent surgery.

ANSWERS TO CASE 27:

What is the diagnosis?

The patient has Budd-Chiari syndrome (thrombosis of the hepatic vein or inferior vena cava). This uncommon cause of cirrhosis usually occurs in young women with a history of myeloproliferative disorders like polycythemia vera or hypercoagulable states such as pregnancy, oral contraceptive pill use, and inherited thrombophilia. Liver function tests (LFTs) are usually abnormal but nonspecific. The initial diagnostic test is right upper quadrant ultrasound. If ultrasound is negative but index of suspicion is high, order magnetic resonance imaging (MRI) angiogram. Confirm the diagnosis with venography (invasive gold standard).

How is Budd-Chiari syndrome treated?

Treat the underlying cause if possible. Other treatment options prior to transplant are medical (anticoagulation, thrombolytics), radiologic (hepatic angioplasty, stenting, and transjugular intrahepatic

portosystemic shunt (TIPS)), and surgical shunting. The specific treatment depends on patient preference and physician expertise.

ANSWERS TO CASE 28:

What diagnosis should you suspect?

Suspect chronic pancreatitis when a patient presents with chronic epigastric pain radiating to the back, particularly if the patient has a history of alcoholism. Pain is sometimes associated with nausea and vomiting. Laboratory findings including amylase and lipase are all normal (occasionally amylase and lipase are mildly elevated).

Pain does not radiate to the back in 50% of patients. Even in the absence of back pain, a history of alcoholism and the above pattern of symptoms would make chronic pancreatitis and not other causes of dyspepsia the most likely diagnosis.

What are the causes of chronic pancreatitis in adults?

- Alcohol (number one cause): occurs in 5% to 10% of chronic alcoholics.
- Idiopathic (number two cause).
- Obstruction of pancreatic duct by gallstones (number three cause) and strictures.
- Hereditary: Autosomal dominant mutation accounts for a small percentage of cases.
- Autoimmune disorders such as systemic lupus erythematosus and primary hyperparathyroidism.
- Tropical pancreatitis: number one cause in south India; cause is unknown.

What is the next diagnostic step?

Order a CT scan of the abdomen to establish the diagnosis and rule out pseudocysts and pancreatic malignancies. The characteristic findings on computed tomography (CT) scan are pancreatic calcifications \pm pancreatic duct dilation (Fig. 28-1). If CT scan is nondiagnostic, perform endoscopic retrograde cholangiopancreatography (ERCP) (gold standard for diagnosis). The characteristic ERCP findings are dilated side duct branches and beading of the main duct in a “chain of lakes” pattern.



Figure 28–1. CT scan of chronic pancreatitis (calcifications \pm pancreatic duct dilations).

False-negative ERCP: Possible in early chronic pancreatitis. Consider endoscopic ultrasound and/or pancreatic function tests if ERCP is normal despite severe pain.

Abdominal x-ray: Detects pancreatic calcifications but low sensitivity (30%).

CT scan demonstrates pancreatic calcifications.

What is the natural history of chronic pancreatitis?

The presenting complaint is usually abdominal pain that is initially episodic but progresses to constant, unremitting pain. Later in the course, progressive damage to the pancreatic islet cells leads to insulin-dependent diabetes mellitus (endocrine dysfunction). After the disease disrupts approximately 90% of pancreatic function, patients do not secrete sufficient digestive enzymes and therefore develop malabsorptive diarrhea and vitamin A, D, E, and K deficiency (exocrine dysfunction).

What are common complications of chronic pancreatitis?

Remember complications of chronic pancreatitis with the acronym “SOAP”: Splenic vein thrombosis, Obstruction of common bile duct (CBD) or duodenum, Ascites or pleural effusion, and Pseudocyst.

- Splenic vein thrombosis: Pancreatic inflammation can affect the nearby splenic vein and cause thrombosis. Suspect this complication if the patient develops bleeding gastric varices and splenomegaly. Treatment is splenectomy.

- CBD obstruction: Suspect if the patient develops jaundice and cholestatic pattern of LFTs. Diagnose with ERCP. Treat with therapeutic ERCP. If obstruction persists, consider surgery (choledochoenterostomy).

- Duodenal obstruction: Suspect if the patient develops postprandial pain and early satiety. Diagnose with upper endoscopy or upper gastrointestinal (GI) series. Treatment is often surgery (gastrojejunostomy).

- Pancreatic ascites and pleural effusions: Ascites or effusions sometimes occur in the absence of pseudocyst due to ductal disruption. Treat with aspiration, diuretics, and octreotide. If symptoms persist, consider surgery.

- Pancreatic pseudocyst: Unlike acute pancreatitis, the mechanism is pancreatic duct disruption. Management is similar to that of a pseudocyst that occurs in the setting of acute pancreatitis.

How is chronic pancreatitis treated?

The main goal of therapy is pain control. Approach this goal in a stepwise fashion:

- Conservative measures: First attempt to control pain with nonsteroidal anti-inflammatory drugs (NSAIDs) and lifestyle measures (quit alcohol and eat small, low-fat meals). If unsuccessful, attempt an 8-week trial of pancreatic enzymes + H2-blockers.

- Analgesics: If pain does not respond to the above measures, admit the patient during a painful episode, keep him NPO, and administer a short course of narcotic analgesics, amitriptyline, and an NSAID. This approach often breaks the cycle of pain.

- Narcotics versus invasive therapy: If the patient continues to have refractory pain, discuss the risks of narcotic addiction versus invasive therapies and base the next step on the outcome of this discussion. Invasive therapies include therapeutic ERCP, extracorporeal shock wave lithotripsy, celiac nerve block, and surgery.

Steatorrhea: Treat with decreased fat intake, pancreatic enzymes, and vitamins.

When fibrosis completely “burns out” the pancreas, the pain spontaneously resolves. However, this process can take years or may never occur at all.

The patient stops drinking alcohol and begins to eat small meals. He is able to control his symptoms with NSAIDs, pancreatic enzymes, H2-blockers, and intermittent narcotic analgesics. Ten years later, he reports increased abdominal pain and anorexia. He has unintentionally lost 10 lbs in the last 2 months. He has noticed bluish-black discoloration in his left leg that disappeared, and now he has similar lesions on his right arm (migratory thrombophlebitis or Trousseau syndrome). Physical examination is significant for jaundice.

What is the most likely cause of his symptoms?

Smoking and chronic pancreatitis are associated with an increased risk of pancreatic adenocarcinoma. Suspect pancreatic adenocarcinoma when patients report increased abdominal pain, weight loss, anorexia, or jaundice. Jaundice is more common if the lesion is in the head of the pancreas.

- Migratory thrombophlebitis: This condition is associated with lung and pancreatic cancer.

- Courvoisier's sign: Painless, palpable gallbladder is a late finding in some patients.

- Virchow node: Enlarged left supraclavicular node can indicate abdominal cancer, lung cancer, breast cancer, lymphoma, or infection.

- Pancreatic adenocarcinoma (exocrine pancreas tumor): also called pancreatic cancer because it accounts for 95% of pancreatic malignancies.

- Neuroendocrine tumors (endocrine pancreas tumors): include gastrinoma (ZES), insulinoma, glucagonoma, somatostatinoma, and VIPoma; these tumors account for 5% of pancreas malignancies.

What are risk factors for pancreatic cancer?

- Cigarette smoking (number one risk factor)

- Chronic pancreatitis

- Diabetes mellitus

- Partial gastrectomy (15 to 20 years later)

The role of other agents such as diet, coffee, and alcohol is less clear.

How can you confirm your suspicion of pancreatic cancer?

- Order LFTs and CA 19-9 (levels often increase in pancreatic cancer).

- Obtain abdominal ultrasound (first imaging test in patient with jaundice).

If patient is not jaundiced, the first test for suspected pancreatic cancer is abdominal CT scan.

LFTs reveal a cholestatic pattern of elevation. CA 19-9 is elevated. Ultrasound detects a solid mass lesion in the head of the pancreas.

What is the next step in management?

Pancreatic mass on ultrasound or CT scan is considered diagnostic of pancreatic cancer, particularly when CA 19-9 is also elevated. The next step is helical CT angiography to assess the degree of tumor invasion. This test helps determine whether or not the tumor is amenable to surgical resection (Whipple procedure). Most patients present at an advanced stage and are not candidates for curative surgery. In such patients, palliation is the most important goal of therapy.

No mass lesion on CT scan or ultrasound: The next step in management is ERCP. If ERCP identifies a mass (diagnostic of cancer), the next step is helical CT angiography.

Helical CT angiography: helical CT plus IV contrast (angiography).



ANSWERS TO CASE 29:

What is the most likely diagnosis?

Acute, steady, epigastric pain radiating to the back with nausea and vomiting is highly suggestive of acute pancreatitis, particularly in an alcoholic with a recent binge-drinking episode. Patients may report that pain improves on leaning forward. Physical findings vary depending on the severity of illness. Possible findings are abdominal distension, decreased bowel sounds, and epigastric tenderness with guarding. Vital signs may show tachycardia, tachypnea, and a low-grade fever.

Some patients have diffuse/ right upper quadrant pain rather than the classic epigastric pain.

What are the causes of acute pancreatitis in adults?

Remember the causes of acute pancreatitis using the mnemonic “BAD SHIT”:

- Biliary (gallstones): number one cause in women
- Alcohol: number one cause in men
- Drugs: “Drugs SAVE TIA” (thiazide and loop Diuretics, Sulfonamides, Anti-inflammatory drugs including nonsteroidal anti-inflammatory drugs (NSAIDs) and 5-ASA drugs, Valproic acid, Estrogen, Tamoxifen, Immunosuppressants like Azathioprine, AIDS drugs)
 - Scorpion bite: common in Trinidad but not in the United States
 - Hypertriglyceridemia and Hypercalcemia
 - Idiopathic (number three cause) and Infectious (viruses such as mumps and coxsackievirus), and Iatrogenic (postoperative, post-ERCP)
- Trauma

Pancreas divisum: Dorsal and ventral portions of embryonic pancreas do not fuse, resulting into two pancreatic ductal systems. This is a common anatomic variant in humans, and its association with pancreatitis is controversial.

What are the next diagnostic steps?

Base the diagnosis of acute pancreatitis on a combination of clinical, laboratory, and radiologic findings. Order the following initial tests in hemodynamically stable patients:

- Serum amylase and lipase: Serum amylase and lipase levels are usually more than three to five times the upper limit of normal in acute pancreatitis. Elevated lipase is more sensitive and specific for acute pancreatitis than amylase (increased in many other conditions).
- Abdominal radiograph: The main utility of abdominal radiograph is to exclude other causes of abdominal pain such as obstruction and perforation. Patients with severe acute pancreatitis may have the sentinel loop sign (localized ileus of a segment of small intestine) and colon cutoff sign (increased air in transverse colon, decreased air distal to splenic flexure).
- Complete blood count (CBC), serum electrolytes, liver function tests (LFTs), and LDH: Abnormal LFTs suggest a biliary cause. Elevated calcium suggests hypercalcemia as the cause. The other tests do not aid in diagnosis, but they are included in scoring systems that estimate disease severity such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Ranson's (Table 29-1).

Table 29–1. Ranson's criteria for acute pancreatitis prognosis

At Admission (“A Good LAW”)	At 48 Hours (“Can BOB Have Flu?”)	Prognosis
--------------------------------	--------------------------------------	-----------

• Age > 55 years	Electrolytes:	1–3 criteria:
• Glucose > 200 mg/dL	• Calcium < 8 mg/dL	• Mild pancreatitis
• LDH > 350 U/L	• BUN ↑ > 8 mg/dL	
• AST > 250 U/L	Arterial blood gas:	>3 criteria:
• WBC > 16,000/cubic mm	• PaO ₂ < 60 mm Hg	• Severe pancreatitis (high mortality)
	• Base deficit > 4 mEq/L	
	Complete blood count:	

Abbreviations: BUN, blood urea nitrogen; WBC, whole blood count.

The level of amylase and lipase elevation is not indicative of disease severity.

- Signs of hemorrhagic pancreatitis: hypovolemic shock, Grey-Turner's sign (flank ecchymoses) and Cullen's sign (periumbilical ecchymosis).

- Computed tomography (CT) scan with contrast: Most accurate test for detecting acute pancreatitis and its complications. Do not order this test initially unless the patient has signs of intraabdominal hemorrhage.

Serum amylase is 400 U/L, and serum lipase is 900 U/L. LFTs are normal. WBC count is 17,000. There is no evidence of obstruction or perforation on abdominal radiograph.

What additional test is indicated at this time?

Order abdominal ultrasound to evaluate for gallstones and common bile duct (CBD) dilation (suggests gallstone pancreatitis).

Laboratory findings in alcohol versus gallstone pancreatitis:

- ALT >150 U/L suggests gallstone pancreatitis.
- Lipase/amylase ratio >2 suggests alcohol-induced pancreatitis.

There are no gallstones or CBD dilation on ultrasound.

What is the next step?

The patient has clinical and laboratory evidence of acute alcohol-induced pancreatitis. He does not have signs of severe pancreatitis. Management is supportive (NPO, IV fluids, NG suction if the patient is vomiting, opioid analgesics, and reassess).

- Classic teaching: Morphine increases SOD spasm, so use meperidine instead.

- Current guidelines: There is no evidence that morphine increases SOD spasm. Avoid meperidine because it poses an increased risk of seizures, myoclonus, and tremors.

Gallstone pancreatitis: In addition to supportive care, initial management includes early ERCP if the patient has signs of jaundice or cholangitis.

The patient reports increased abdominal pain 48 hours later. Abdomen is tender to palpation with rebound and guarding. Vital signs are temperature 38.3°C, pulse 120 bpm, respirations 25/min, and blood pressure 110/80. He has sequestered approximately 7 L of fluid (fluids administered – fluids lost in urine, stool, etc.). Base deficit is 5 mEq/L.

What is the next step in management?

Obtain a CT scan of the abdomen with contrast if the patient does not improve or worsens despite initial supportive care. Also, transfer this patient to the intensive care unit regardless of CT scan findings because he has more than three of Ranson's criteria, which is associated with a high mortality (age >55 years, admission WBC count >16,000, fluid sequestration >6 L at 48 hours, and base deficit >4 mEq/L at 48 hours).

CT scan confirms the diagnosis of acute pancreatitis. The report also mentions approximately 40% necrosis of the pancreas.

What is the next step in management?

Acute pancreatitis causes pancreatic enzyme activation and leakage. These enzymes can digest pancreatic parenchyma and cause necrotizing pancreatitis. Initiate IV imipenem if the patient has >30% pancreatic necrosis to prevent secondary pancreatic infection. Also continue supportive care. Patients with necrotizing pancreatitis often require large volumes of IV fluids.

<30% necrosis: Continue supportive care; do not initiate antibiotics.

One week later, the patient continues to report persistent abdominal pain despite IV imipenem and supportive care. Temperature is 38.9°C, pulse 120 bpm, respirations 28/min, blood pressure 110/80.

What is the next step in management?

Patients who do not improve despite 7 days of antibiotics and supportive care require percutaneous

CT-guided fine-needle aspiration of the necrotic material. Perform Gram stain and culture of the aspirated material to evaluate whether it is infected. Infected pancreatic necrosis requires surgical debridement (necrosectomy).

Some surgeons prefer continued supportive care and antibiotics rather than necrosectomy if the patient with infected pancreatic necrosis is stable.

Gram stain and culture of the necrotic material is negative (sterile pancreatic necrosis). Imipenem and supportive care are continued for 4 weeks. The patient improves and is discharged. He is asymptomatic during a follow-up visit 3 weeks later. Vital signs are normal. Figure 29-1 is the follow-up CT scan at 3 weeks.

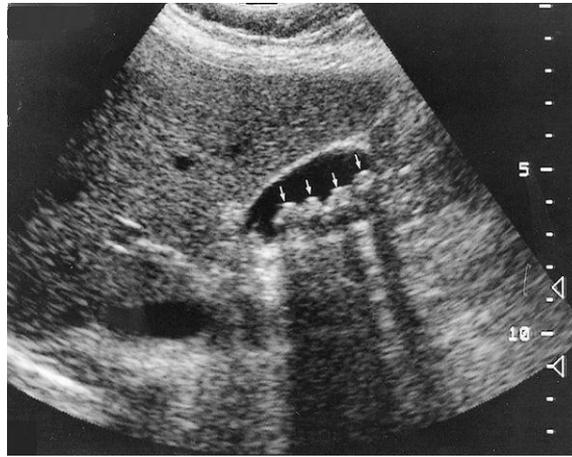


Figure 29–1. Ultrasound for cholecystitis.

What is the diagnosis?

The CT scan (see Figure 29-2) shows a pancreatic pseudocyst (a collection of fluid in the lesser sac of the abdomen). Approximately 10% of patients develop pseudocysts within 2 to 3 weeks of an episode of acute pancreatitis. These cysts develop from liquefaction of the necrotic pancreatic material. Unlike true cystic lesions of the pancreas, pseudocysts are lined by granulation tissue and not epithelial tissue.

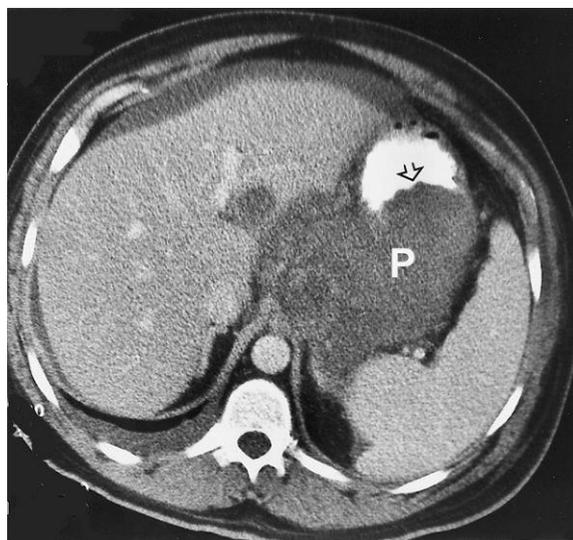


Figure 29–2. CT of pancreatic pseudocyst.

How are pancreatic pseudocysts managed?

Most pseudocysts resolve spontaneously and do not require any specific treatment. Consider resection or drainage if the patient develops uncontrollable symptoms (abdominal pain) or complications. Important complications include:

- Pseudocyst infection: Suspect if the patient develops fever. CT scan will show an abscess in the region of the pseudocyst.
- Pseudocyst rupture: Suspect if the patient develops ascites or pleural effusion with increased amylase in ascitic or pleural fluid.
- Pseudoaneurysm: Digestion of an adjacent blood vessel by pancreatic enzymes in the pseudocyst. Suspect if the pseudocyst expands or the patient has unexplained GI bleeding (or decreased hematocrit).

Confirm diagnosis with spiral CT scan, MRI, or mesenteric angiography. Treat with embolization prior to drainage.

Three drainage options: surgery, endoscopy, and percutaneous catheter drainage. ERCP findings (perform prior to drainage) and local expertise determines which technique to use. Pseudoaneurysm is a contraindication to endoscopic drainage.

Cyst in lesser sac with no history of pancreatitis: Suspect cystic pancreatic neoplasm. Consider tumor markers (CEA, CA 19-9) and endoscopic ultrasound with fine-needle aspiration to examine cystic fluid. Differentiation between cystic lesions is challenging.

Remember complications of acute pancreatitis with the mnemonic “New Pancreatitis Has Cruel Complications”: pancreatic Necrosis (sterile or infected), pancreatic Pseudocyst (\pm abscess, rupture, pseudoaneurysm), Hemorrhagic pancreatitis, Cholangitis (if the patient has gallstone pancreatitis), and Chronic pancreatitis.

ANSWERS TO CASE 30:

What is the differential diagnosis of acute diarrhea?

The number one cause of acute diarrhea is infections (viral > bacterial > parasitic). Other common causes are medications, food intolerance, inflammatory bowel disease, and ischemic colitis (in elderly patients). Carcinoid syndrome and thyrotoxicosis are uncommon etiologies.

What is the next step in management?

Most cases of diarrhea are benign and self-limited. This patient with mild watery diarrhea, nausea, vomiting, and mild abdominal cramping most likely has a viral gastroenteritis. The next step for this stable patient with no concerning findings on history and physical exam is to advise supportive measures such as adequate nutrition, rehydration, and loperamide on an as-needed basis. Avoid dairy products because infectious enteritis often temporarily causes lactose malabsorption.

- Diarrhea: ≥ 3 loose or watery stools per day
- Acute diarrhea: duration ≤ 14 days
- Persistent diarrhea: duration 15 to 30 days
- Chronic diarrhea: duration >30 days

CASE DISCUSSION

When are diagnostic tests indicated in patients with acute diarrhea?

Remember the indications for diagnostic testing in patients with acute diarrhea using the mnemonic “BAD SHIT”:

- Bloody stools
- Age ≥ 70 years or recent Antibiotic use
- Duration >48 hours
- Severe abdominal pain
- Hypovolemia (or >6 unformed stools/day) or recent Hospitalization
- Immunosuppression
- Temperature >38.5°C

When is empiric antibiotic therapy indicated for patients with acute diarrhea?

Consider empiric therapy with an oral fluoroquinolone after obtaining samples for initial diagnostic tests if the patient has any of the following (mnemonic: “BaD sHIT”):

- Bloody stools
- Duration >7 days
- Hypovolemia or frequency >8 stools/day
- Immunosuppression
- Temperature >38.5°C or mild to moderate Traveller's diarrhea.

The patient returns to the clinic 2 days later. Her diarrhea has worsened and she now has nine watery stools per day. On physical examination, skin turgor is decreased. Temperature is 37°C and heart rate is 90 bpm. Blood pressure is 120/80 supine but falls to 100/60 in the standing position. What is the next step in management?

This patient has had diarrhea for 4 days (>48 hours). She has nine stools per day and signs of hypovolemia (decreased skin turgor and orthostatic hypotension). The next step is to sample stool for occult blood and fecal leukocytes:

- Negative fecal occult blood test and fecal leukocytes: Consider empiric oral fluoroquinolone.
- Elevated fecal leukocytes: Perform stool culture. Consider empiric oral fluoroquinolone while waiting for the results of the stool culture. If stool culture is positive, tailor antibiotics on the basis of the particular microorganism (Table 30-1).

Table 30–1. Common infectious causes of diarrhea in immunocompetent patients

	Organism	First Choice Antibiotic
Bacteria associated with fever and bloody diarrhea (inflammatory diarrhea)	Nontyphoidal salmonella	Usually not indicated
	Campylobacter	Erythromycin (only for severe infection)
	<i>Escherichia coli</i> 0157:H7 (enterohemorrhagic)	Antibiotics contraindicated
	Enteroinvasive <i>E. coli</i>	Oral fluoroquinolone
	Yersinia	Oral fluoroquinolone
	Shigella	Oral fluoroquinolone
Bacteria associated with watery diarrhea a (noninflammatory diarrhea)	<i>Vibrio cholerae</i>	Doxycyclin
	<i>Clostridium perfringens</i>	Not indicated
	Enterotoxigenic <i>E. coli</i>	Oral fluoroquinolone
	<i>Staphylococcus aureus</i>	Usually not indicated
	<i>Clostridium difficile</i>	Metronidazole
Parasite associated with fever and bloody diarrhea (inflammatory diarrhea)	<i>Entamoeba histolytica</i>	Metronidazole
Parasites associated with watery diarrhea (noninflammatory diarrhea)	Cryptosporidium	Usually not indicated
	<i>Giardia lamblia</i>	Metronidazole
	Cyclospora	Trimethoprim-sulfamethoxazole

a Viruses that cause watery diarrhea are Norwalk virus, rotavirus, enterovirus, and adenovirus. No antimicrobial is necessary.

Notes: SBO: voluminous watery diarrhea, periumbilical cramps, bloating, nausea, or vomiting; fecal leukocytes not elevated (noninflammatory diarrhea). LBO: invasion of colon tissue causes fever, and bloody diarrhea, also known as dysentery; fecal leukocytes are elevated (inflammatory diarrhea). Elevated fecal leukocyte levels indicate inflammatory diarrhea or inflammatory bowel disease. Common source of *E. coli* 0157:H7 is undercooked beef; produces symptoms within 2 days due to Shiga-like toxin; antibiotics increase risk of hemolytic uremic syndrome and thrombocytopenia purpura. Shigella symptoms are caused by Shiga toxin; patients often have tenesmus. *Vibrio cholerae*: stool often described as voluminous rice water diarrhea. *Staphylococcus aureus* and Norwalk virus produce symptoms hours after consuming contaminated food due to preformed toxin; major presenting symptom is vomiting. *Salmonella typhi* causes typhoid fever (systemic signs, salmon color spots on trunk).

When should you test a patient for ova and parasites?

Also test for ova and parasites with three separate specimens on consecutive days in the following situations:

- Waterborne Outbreak in community
- Persistent diarrhea
- Travel (recent)
- Immunosuppression
- Bloody diarrhea with negative fecal leukocytes
- Daycare center job

ANSWERS TO CASE 31:

A 28-year-old man comes in with a moderate to severe presentation of colitis, as manifested by

crampy abdominal pain with tenesmus, low- volume bloody mucoid stool, and colonic dilatation on X-ray. He has no travel or exposure history to suggest infection. He reports a history of previous similar episodes, which suggests a chronic inflammatory rather than acute infectious process.

- > Most likely diagnosis: Colitis, probably ulcerative colitis.
- > Next step: Admit to the hospital, obtain stool samples to exclude infection, and begin therapy with corticosteroids.

Considerations

Although the likelihood of infection seems low, it must be excluded, and it is necessary to check for infections with organisms such as *Entamoeba histolytica*, *Salmonella*, *Shigella*, and *Campylobacter*, as well as *Clostridium difficile*, which can occur in the absence of prior antibiotic exposure.. The main consideration in this case would be IBD versus infectious colitis. The absence of travel history, sick contacts, and the chronicity of the illness all point away from infection.

At the moment, the patient does not appear to have any life-threatening complication of colitis, such as perforation or toxic megacolon, but he must be monitored closely, and surgical consultation may be helpful. The combination of abdominal pain, bloody diarrhea, and the abdominal X-ray localizing the disease to the colon points to a “colitis.”

Approach to colitis

Definitions

COLITIS: Inflammation of the intestines typically the large intestines, although the small bowel can be affected.

INFLAMMATORY BOWEL DISEASE: Autoimmune forms of colitis primarily due to either Crohn’s disease or ulcerative colitis.

Clinical approach

The differential diagnosis for colitis includes ischemic colitis, infectious colitis (*C difficile*, *E coli*, *Salmonella*, *Shigella*, *Campylobacter*), radiation colitis, and inflammatory bowel disease (IBD) (Crohn’s disease vs ulcerative colitis). Mesenteric ischemia usually is encountered in people older than 50 years with known atherosclerotic vascular disease or other cause of hypoperfusion. The pain usually is acute in onset following a meal and not associated with fevers. With an infectious etiology, patients often have engaged in foreign travel, the symptoms are acute, or the patients recently used antibiotics. Also, family members often have the same symptoms.

The IBD is most commonly diagnosed in young patients between the ages of 15 and 25 years. There is a second peak in the incidence of IBD (usually Crohn’s disease) between the ages of 60 and 70 years. The IBD may present with a low-grade fever. The chronic nature of this patient’s disease (several months) is typical of IBD. Anemia may be present, either due to iron deficiency from chronic gastrointestinal (GI) blood loss, or anemia of chronic disease. Patients with IBD may also report fatigue and weight loss.

Ulcerative colitis usually presents with grossly bloody stool, whereas symptoms of Crohn’s disease are much more variable, mainly chronic abdominal pain, diarrhea, and weight loss. Ulcerative colitis involves only the large bowel, whereas Crohn’s disease may affect any portion of the GI tract, typically the colon and terminal ileum. Ulcerative colitis always begins in the rectum and proceeds proximally in a continuous pattern; disease is limited to the colon. Crohn’s disease classically involves the terminal ileum but may occur anywhere in the GI tract from the mouth to the anus. Anal fissures and nonhealing ulcers are often seen in Crohn’s disease. Additionally, the pattern of Crohn’s disease is not contiguous in the GI tract; classically, it has a patchy distribution that is often referred to as “skip lesions.” Patients with Crohn’s may develop strictures caused by fibrosis from repeated inflammation which can lead to bowel obstruction, with crampy abdominal pain and nausea/vomiting. Ulcerative colitis is characterized by diarrhea and typically leads to bowel obstruction. The diagnosis usually is confirmed after colonoscopy with biopsy of the affected segments of bowel and histologic examination. In ulcerative colitis, inflammation will be limited to the mucosa and submucosa, whereas in Crohn’s disease, the inflammation will be transmural (throughout all layers of the bowel). Tables 31-1 and 31-2 list further clinical features. Surgery is indicated for complications of Crohn’s disease, such as obstruction, fistulas, or perforation, but recurrent disease is common.

Table 31-1. Comparison of Crohn’s disease versus ulcerative colitis

	Crohn’s disease	Ulcerative colitis
--	------------------------	---------------------------

Site of origin	Terminal ileum	Rectum
Pattern of progression	"Skip" lesions/irregular	Proximally contiguous
Thickness of inflammation	Transmural	Submucosa or mucosa
Symptoms	Crampy abdominal pain	Bloody diarrhea
Complications	Fistulas, abscess, obstruction	Hemorrhage, toxic megacolon
Radiographic findings	String sign on barium X-ray	Lead pipe colon on barium X-ray
Risk of colon cancer	Slight increase	Marked increase
Surgery	For complications such as stricture	Curative

Crohn's disease versus ulcerative colitis

The treatment of ulcerative colitis can be complex because the pathophysiology of the disease is incompletely understood. Management is aimed at reducing the inflammation. Most commonly, sulfasalazine and other 5-aminosalicylic acid (ASA) compounds such as mesalamine are used and are available in oral and rectal preparations. They are used in mild to moderate active disease and to induce remission, and in the maintenance of disease to reduce the frequency of flare-ups. Corticosteroids may be used (po, PR, or IV) to treat patients with moderate to severe disease. Once remission is achieved, the steroids should be tapered over 6 to 8 weeks and then discontinued if possible to minimize their side effects. Immune modulators are used for more severe, refractory disease. Such medications include 6-mercaptopurine, azathioprine, methotrexate, and the tumor necrosis factor (TNF) antibody infliximab. Anti-TNF therapy, such as infliximab, has been an important treatment of patients with Crohn's disease who are refractory to steroids, and more recently has shown efficacy in ulcerative colitis. Patients receiving the potent immunomodulator infliximab are at increased risk of infection, including reactivation of latent tuberculosis.

Table 31-2 Extraintestinal manifestations of inflammatory bowel disease

	Crohn's disease	Ulcerative colitis
Skin manifestations	Erythema nodosum: 15% Pyoderma gangrenosum: rare	Erythema nodosum: 10% Pyoderma gangrenosum: 1%-12%
Rheumatologic	Arthritis (polyarticular, asymmetric): common Ankylosing spondylitis: 10%	Arthritis: less common Ankylosing spondylitis: less common
Ocular	Uveitis: common (photophobia, blurred vision, headache)	Uveitis: common (photophobia, blurred vision, headache)
Hepatobiliary	Cholelithiasis fatty liver: common Primary sclerosing cholangitis: rare	Fatty liver: common Primary sclerosing cholangitis: uncommon but more often than Crohn
Urologic	Nephrolithiasis (10%-20%) after small bowel resection or ileostomy	

Surgery is indicated for complications of ulcerative colitis. Total colectomy is performed in patients with carcinoma, toxic megacolon, perforation, and uncontrollable bleeding. Surgery is curative for ulcerative colitis if symptoms persist despite medical therapy. Two very important and potentially life-threatening complications of ulcerative colitis are toxic megacolon and colon cancer. Toxic megacolon occurs when the colon dilates to a diameter more than 6 cm. It usually is accompanied by fever, leukocytosis, tachycardia, and evidence of serious toxicity, such as hypotension or altered mental status. Therapy is designed to reduce the chance of perforation and includes IV fluids, nasogastric tube placed to suction, and placing the patient NPO (nothing by mouth). Additionally, IV antibiotics are given in anticipation of possible perforation, and IV steroids are given to reduce inflammation. The most severe consequence of toxic megacolon is colonic perforation complicated by peritonitis or hemorrhage.

Patients with ulcerative colitis have a marked increase in the incidence of colon cancer compared to the general population. The risk of cancer increases over time and is related to disease duration and extent. It is seen both in patients with active disease and in patients whose disease has been in remission. Annual or biennial colonoscopy is advised in patients with ulcerative colitis, beginning 8 years after diagnosis of pancolitis, and random biopsies should be sent for evaluation. If colon cancer or dysplasia is

found, a colectomy should be performed.

Comprehension questions

1. A 32-year-old woman has a history of chronic diarrhea and gallstones and now has rectovaginal fistula. Which of the following is the most likely diagnosis?
 - A. Crohn's disease
 - B. Ulcerative colitis
 - C. Systemic lupus erythematosus
 - D. Laxative abuse
2. A 45-year-old man with a history of ulcerative colitis is admitted to the hospital with 2 to 3 weeks of right upper quadrant abdominal pain, jaundice, and pruritus. He has no fever and a normal WBC count. Endoscopic retrograde cholangiopancreatography (ERCP) shows multifocal strictures of the both intrahepatic and extrahepatic bile ducts with intervening segments of normal and dilated ducts. Which of the following is the most likely diagnosis?
 - A. Acute suppurative cholangitis
 - B. Cholangiocarcinoma
 - C. Primary sclerosing cholangitis (PSC)
 - D. Choledocholithiasis with resultant biliary strictures
3. A 25-year-old man is hospitalized for ulcerative colitis. He has now developed abdominal distention, fever, and transverse colonic dilation of 7 cm on X-ray. Which of the following is the best next step?
 - A. 5-ASA
 - B. Steroids
 - C. Antibiotics and prompt surgical consultation
 - D. Infliximab
4. A 35-year-old woman has chronic crampy abdominal pain and intermittent constipation and diarrhea, but no weight loss or gastrointestinal bleeding. Her abdominal pain is usually relieved with defecation. Colonoscopy and upper endoscopy with biopsies are normal, and stool cultures are negative. Which of the following is the most likely diagnosis?
 - A. Infectious colitis
 - B. Irritable bowel syndrome
 - C. Crohn's disease
 - D. Ulcerative colitis

Answers

1. A. Fistulas are common with Crohn's disease because of its transmural nature but are uncommon in ulcerative colitis. Gallstones are common in patients with Crohn's disease due to ileal bile salt malabsorption and depletion, causing the formation of more cholesterol-rich lithogenic bile.
2. C. The ERCP shows the typical appearance for primary sclerosing cholangitis (PSC), which is associated with IBD in 75% of cases. Stone-induced strictures should be extrahepatic and unifocal. Cholangiocarcinoma is less common but may develop in 10% of patients with PSC.
3. C. With toxic megacolon, antibiotics and surgical intervention are often necessary and life-saving. Medical therapy is usually ineffective.
4. B. Irritable bowel syndrome is characterized by intermittent diarrhea and crampy abdominal pain often relieved with defecation, but no weight loss or abnormal blood in the stool. It is a diagnosis of exclusion once other conditions, such as inflammatory bowel disease and parasitic infection (eg, giardiasis), have been excluded.

Clinical pearls

- ▶ Ulcerative colitis always involves the rectum and may extend proximally in a continuous distribution.
- ▶ Crohn's disease most commonly involves the distal ileum, but it may involve any portion of the gastrointestinal tract and has "skip lesions."
- ▶ Because of transmural inflammation, Crohn's disease often is complicated by fistula formation.
- ▶ Toxic megacolon is characterized by dilation of the colon along with systemic toxicity; failure to improve with medical therapy may require surgical intervention.

► Both ulcerative colitis and Crohn's disease can be associated with extraintestinal manifestations, such as uveitis, erythema nodosum, pyoderma gangrenosum, arthritis, and primary sclerosing cholangitis.

ANSWERS TO CASE 32:

What is your differential diagnosis of his recent symptoms?

The differential diagnosis in this patient includes three possibilities. First, this episode could be an acute flare-up or exacerbation of his ulcerative colitis. Second, he could have an acute, self-limited colitis superimposed on his ulcerative colitis; infection with *Campylobacter*, *Salmonella*, or *Shigella* species, or with parasites can cause such a colitis. Third, the rectal bleeding and anemia could be the result of adenocarcinoma.

What tests are necessary to make the correct diagnosis?

Stool cultures and the examination of stool for ova and parasites would be an important initial laboratory test in this patient. These proved to be negative.

Flexible sigmoidoscopy or colonoscopy with the acquisition of biopsy specimens is also an important diagnostic procedure. In contrast to chronic inflammatory bowel diseases (CIBD), the histologic features of acute self-limited colitis consist of normal crypt architecture and an acute but not chronic inflammatory infiltrate in the lamina propria. Inflammation is more likely to be found in the upper mucosa in acute colitis, and in the crypt bases in CIBD. When an acute self-limited colitis, such as infection with *Campylobacter jejuni*, *Salmonella*, or *Shigella*, resolves, the mucosa is normal, whereas crypt distortion and atrophy are often seen in the setting of healed CIBD. In other acute colitides, the histologic features found in mucosal biopsy specimens may suggest a specific infection; these include viral inclusions, parasites, or pseudomembranes.

In this patient, flexible sigmoidoscopy was performed to a depth of 30 cm and revealed mild granularity of the mucosa without bleeding, although some blood was seen coming from above 30 cm. Active chronic ulcerative colitis (CUC) almost always involves the rectum, so the finding of only mild changes in this patient's rectum suggests that the significant pathologic process was higher in the colon. A colonoscopic examination showed a sessile, fungating mass in the descending colon, which proved to be an adenocarcinoma.

How should this patient's CUC have been managed over the previous 18 years?

There is not yet agreement on the most cost-effective approach for the surveillance for colonic cancer in patients with CUC. However, after a patient has had extensive disease for 8 to 10 years, it is probably wise to perform complete colonoscopy every 1 to 2 years, with multiple biopsy specimens obtained every 10 to 12 cm from normal-appearing mucosa and targeted specimens obtained from villous areas of mucosa, areas of ulceration with a raised edge, and strictures. Colectomy is recommended if multifocal or high-grade dysplasia is seen in the biopsy specimens and confirmed by an experienced pathologist. If a mass lesion associated with any degree of dysplasia is identified, this is also a generally accepted indication for colectomy. The management of persistent low-grade dysplasia without a mass is more controversial, but, increasingly, colectomy is being recommended for low-grade dysplasia (Fig. 32 - 1).

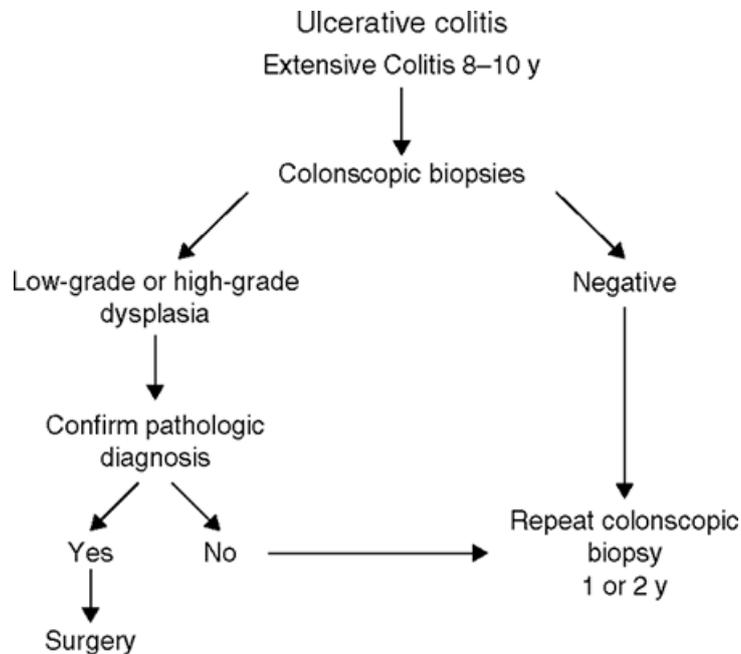


Figure 32-1 A proposed system of surveillance for cancer in ulcerative colitis using colonoscopy and biopsy.

Cancer prevention is an important topic to consider when advising young patients with extensive colitis about the possible need for surgical treatment. The decision to recommend prophylactic proctocolectomy after many years of colitis must be based on several considerations in the individual patient. These include the intractability of symptoms, age, psychological makeup, medical compliance, and the availability of newer surgical procedures. A prophylactic colectomy should be recommended to a noncompliant patient who acquires extensive ulcerative colitis at a young age. Patients who have CUC should be fully informed of their risk for development of cancer, as well as the limitations of endoscopic surveillance and the availability of surgical alternatives. If a patient is unwilling to assent to the surgical procedure, then he or she must be committed to undergoing regular surveillance.

Case Discussion

What is the pathogenesis responsible for CUC and Crohn's disease?

The cause and pathogenesis of both these chronic inflammatory bowel diseases (CIBDs) are unknown. Both are characterized by a chronic inflammatory cell infiltrate of the bowel. However, whereas CUC is restricted to the colon, Crohn's disease can involve the entire alimentary tract from the mouth to the anus, although the distal ileum and colon are the portions most frequently affected. Another distinguishing feature of Crohn's disease is the involvement of all layers of the bowel, whereas the inflammation seen in CUC is mostly limited to the mucosa. In addition, focal granulomas are common in Crohn's disease but rare in CUC. However, neither disease has pathognomonic features, and Crohn's disease of the colon cannot be histologically distinguished from CUC in 15% to 25% of cases of chronic colitis.

Compare and contrast the principal clinical features of CUC and Crohn's disease.

The severity, clinical course, and prognosis of CUC and Crohn's disease are widely variable. Onset in both diseases occurs most often in early adulthood. The symptoms of CUC may range from slight rectal bleeding to fulminant diarrhea with colonic hemorrhage and hypotension. Most patients have intermittent attacks, although some can have continuous symptoms without remission. The clinical features of Crohn's disease depend on the severity and location of the bowel involvement; the principal features are diarrhea, abdominal pain, hematochezia, intestinal obstruction, fissures, and fistulas.

Extraintestinal manifestations are common in both Crohn's disease and CUC, but more common in CUC. The manifestations include arthritis, arthralgia, iritis, uveitis, liver disease, and skin lesions. The arthritis may present as a migratory arthritis, involving large joints, sacroiliitis, or ankylosing spondylitis. Primary sclerosing cholangitis, which is associated with an increased frequency of cholangiocarcinoma, and chronic hepatitis are common hepatobiliary abnormalities.

The principal features that differentiate Crohn's disease from CUC are listed in Table 32-1.

What are the respective risks of intestinal malignancy in CUC and Crohn's disease?

The frequency of intestinal cancer is increased in Crohn's disease, but not to the extent in CUC. According to some reports, the frequency of colon cancer in adults who have CUC involving the entire colon is approximately 25 times greater than that in the general population. The risk of colon cancer developing in patients with CUC is positively correlated with the extent and duration of the disease.

What are the principal medical therapeutic measures used for patients with CUC and Crohn's disease?

The general measures to control the symptoms of both diseases include correction of fluid/electrolyte imbalances; iron, folate, or vitamin B₁₂ supplementation as needed for the treatment of anemia; and dietary adjustments aimed at maintaining adequate nutrition. Total parenteral nutrition may be required for the short-term treatment of severe acute disease, but bowel rest and hyperalimentation are of dubious value in the long term. Antidiarrheal agents such as loperamide are usually contraindicated in patients with CUC because they may contribute to the development of toxic megacolon, but they may help alleviate the diarrhea and abdominal cramps in the setting of stable Crohn's disease.

Table 32-1 Features that Distinguish between Crohn's Disease and Ulcerative Colitis

Factors	Crohn's Disease	Ulcerative Colitis
Pathologic features	Transmural inflammation	Mucosal inflammation
	Deep ulcers	Superficial ulcers
	Granulomas common	Granulomas absent
Distribution	Mouth to anus (ileum and proximal colon most common)	Colon
Clinical features		
Rectal bleeding	20%-40%	98%
Fulminating episodes	Uncommon	Common
Obstruction	Common	Rare
Fistulas	Common	Rare
Perianal disease	Common	Less common
Sigmoidoscopic and radiographic findings		
Rectal involvement	50%	95%-100%
Extent	Patchy	Continuous
Ulcers	Longitudinal, deep	Shallow, collar button
Pseudopolyps	Uncommon	Common
Strictures	Common	Uncommon
Ileal involvement	Narrowed lumen with thickened wall	Dilated lumen with diminished folds but histologically normal

In CUC, corticosteroids are useful for inducing remissions or improvement in an acute attack, and they may be required for long-term management. However, the possible benefits of corticosteroids in the long term are offset by their many adverse side effects. The rectal administration of steroids or mesalamine can be beneficial, especially when rectal involvement (proctitis) is severe. However, significant absorption of rectal steroids can occur, so systemic effects of the agents (both beneficial and undesirable) may arise when they are given by this route. Sulfasalazine is metabolized by colonic bacteria, releasing sulfapyridine and 5-aminosalicylate (5-ASA); the latter is believed to be the active compound. Sulfapyridine is absorbed systemically, which accounts for the side effects of sulfasalazine (e.g., headache, occasional megaloblastic anemia, skin rash). The greatest utility of sulfasalazine in patients with CUC is in long-term management, where it has been proved to reduce the frequency of relapses. 5-ASA, given rectally by enema or suppository, is well tolerated and effective. Given orally, 5-ASA is rapidly denatured by gastric acid, so alternatives to plain 5-ASA, such as microencapsulated (Pentasa; Hoechst Marion Roussel, Kansas City, MO) or acrylic-based resin-coated (Asacol; Procter & Gamble Pharmaceutical, Norwich, NY) forms of 5-ASA, may be used. Because the relative risk for development of CUC is greater in nonsmokers than in smokers (the opposite is true in Crohn's disease), nicotine is being tried in the treatment of CUC; some benefit has been reported, but additional research is needed.

There is no uniformly effective treatment available for Crohn's disease. However, corticosteroids have documented efficacy in diminishing the activity of the disease process. Long-term use of

corticosteroids is not recommended because of their many side effects, such as osteoporosis, diabetes, and cataracts. Sulfasalazine has some effectiveness, especially in colonic Crohn's disease, but is less effective than corticosteroids. Pentasa, in doses of more than 3 mg per day may be efficacious in mild to moderate Crohn's disease, particularly in ileal disease. Metronidazole may be at least as effective as sulfasalazine. When Crohn's disease cannot be controlled by these medications, the immunosuppressive agent azathioprine and its metabolite 6-mercaptopurine are often used. These drugs are effective in both inducing and maintaining remission in inflammatory-type and fistulizing-type Crohn's disease. Their use can result in a reduction in the corticosteroid dose needed, but this advantage may be offset by their toxic effects (e.g., pancreatitis, allergic reactions, and leucopenia). More recently, infliximab, a chimeric monoclonal antitumor necrosis factor antibody, has been shown to be effective in Crohn's disease, both in the inflammatory and the fistulizing types. The role of immunodulator drugs in CUC is less clear than in Crohn's disease.

ANSWERS TO CASE 33:

What additional history should you obtain from the patient?

This patient has chronic diarrhea, which is arbitrarily defined as diarrhea that lasts longer than 3 weeks. Chronic diarrhea is a fairly common complaint, with a lengthy differential diagnosis. The clinical history remains the mainstay of the initial approach to diagnosis, and the history taking must include questions concerning the following factors:

- Food: Milk consumption, sorbitol (added to diet foods and fruit), fructose (found in nondiet soft drinks, candy, and fruit), and unpasteurized milk (Yersinia infection).
- Travel: To areas where giardiasis, amebiasis, or schistosomiasis might be contracted.
- Iatrogenic factors: Surgeries in the gastrointestinal (GI) tract. A partial gastrectomy can result in dumping (rapid emptying of the gastric contents into the small intestine) and, if a stagnant area of bowel is created, bacterial overgrowth can result (the blind loop syndrome). Medications are also a common cause of diarrhea. The administration of antibiotics can result in *C. difficile* colitis, and antacid use can produce an osmotic diarrhea. OI-Adrenergic antagonists, colchicine, laxatives, and innumerable other drugs can also cause diarrhea.
- Risk factors for acquired immunodeficiency syndrome (AIDS).
- Review of systems: This may reveal arthritis, which can accompany inflammatory bowel disease or Whipple's disease; peptic ulcer disease, which can be associated with the Zollinger-Ellison syndrome; symptoms or a history of diabetes; or hyperthyroidism.
- Past medical problems, with an emphasis on childhood diarrhea or malnutrition and surgeries.
- Further characterization of the diarrhea: Does it awaken the patient at night? Is it constant or does it alternate with constipation? The most common cause of chronic diarrhea in the U.S. population is the irritable bowel syndrome, which is a poorly understood motility disorder. It rarely results in diarrhea that awakens the patient at night, rarely produces weight loss, and may have diarrhea alternating with constipation.

What might lead you to suspect that malabsorption is the cause of this patient's diarrhea, and why? What test should be performed to confirm this, and why?

Malabsorption is suspected as the cause of the diarrhea because of the iron deficiency that does not respond to oral iron treatment and because the prothrombin time is elevated without signs of liver disease. A 2- or 3-day stool collection for quantitative fat analysis is the single most useful test to document malabsorption. Because fat absorption is a complex process (requiring the digestion of triglycerides by pancreatic lipase, solubilization of these products by bile salts, and absorption of the subsequent products by enterocytes of the small intestine), abnormalities in any of these steps result in fat malabsorption and an increase in fecal fat excretion. Therefore, measurement of the fecal fat content is a test for many steps in the digestion and absorption pathways. One of the few kinds of malabsorption that does not cause increased fecal fat loss is that due to the lack of an intestinal enzyme needed in the digestion of a particular carbohydrate, despite a histologically normal intestine. The most common example of this is primary lactase deficiency, in which lactose is not absorbed normally but fat is.

Considering that the patient has either maldigestion or malabsorption, what are the two disorders that may decrease the bile acid pool, two disorders that decrease pancreatic lipase activity, and two disorders that may decrease absorption by small bowel enterocytes?

Resection or disease of the distal small bowel can cause a decreased reabsorption of bile acids, resulting in insufficient bile salt concentrations in the proximal intestine to allow the normal solubilization and absorption of fat. Complete blockage of the common bile duct, as by pancreatic cancer or cancer of the duct, prevents bile acids from entering the duodenum.

Chronic pancreatitis or pancreatic cancer can block the pancreatic duct, resulting in decreased secretion of lipase. Increased acid content in the duodenum, such as occurs in the Zollinger-Ellison syndrome, can inactivate pancreatic lipase in the intestinal lumen.

Decreased absorption by small bowel enterocytes may be caused by celiac sprue, tropical sprue, Whipple's disease, small intestinal lymphoma, AIDS enteropathy, and several other diseases.

How does the D-xylose test differentiate problems with digestion (e.g., bile salt depletion and pancreatic lipase deficiency) from problems with absorption? Name one disorder that may produce a false-positive result.

D-xylose is a five-carbon sugar that can be absorbed without the aid of bile salts, pancreatic enzymes, or intestinal enzymes. It should be absorbed normally if the small bowel is intact. Therefore, the test is useful in distinguishing pancreatic enzyme insufficiency from enterocyte abnormalities. However, bacterial overgrowth in the proximal intestine is a condition that can cause malabsorption of D-xylose without affecting the enterocyte (the bacteria will consume the D-xylose before it can be absorbed), thereby producing a false-positive result.

On the basis of the results of the D-xylose test, what test should be performed now?

The small bowel should be examined, and there are two appropriate ways to do this: small bowel biopsy and a small bowel barium radiograph. A biopsy specimen gives more information about the mucosa, whereas the radiograph may permit better evaluation of diverticula, regional ileitis, or blind loops.

Although the biopsy findings indicate celiac sprue, what other disorders could produce such a flat mucosa?

Tropical sprue, soy and milk protein allergy (primarily in children), diffuse intestinal lymphoma, hypogammaglobulinemia, and the Zollinger-Ellison syndrome can produce a flat mucosal lesion that resembles that of celiac sprue.

How can the diagnosis of celiac sprue be confirmed?

The diagnosis of celiac sprue can be confirmed by observing the patient's response to a gluten-free diet. Adherence to a gluten-free diet should bring about a cessation or marked reduction in the diarrhea and other intestinal symptoms, weight gain, and histologic improvement in the intestinal mucosa. Gluten is found in wheat, rye, barley, and oats, but not in rice and corn.

If the D-xylose test result was abnormal, but the small bowel biopsy findings were normal, a bacterial overgrowth in the proximal small intestine might be suspected. How should this possibility be evaluated?

This would be more likely to occur in patients who have had a surgery that resulted in a blind loop of small intestine, or in elderly patients who are more likely to have multiple small bowel diverticula. A small bowel barium radiographic examination should reveal these abnormalities. The bile acid breath test could be used to document bacterial deconjugation of bile acids. In this test, a radiolabeled conjugated bile acid, such as [^{14}C]-glycocholic acid, is given orally, and the amount and the time course of the [^{14}C]- O_2 exhaled is measured. Normally, most of the labeled bile acid is absorbed intact in the distal ileum; a minor amount reaches the colon, where anaerobic bacteria cleave the glycine moiety from the cholic acid moiety. The [^{14}C]- O_2 released in the colon is absorbed and exhaled. If the upper intestine is populated by excessive numbers of anaerobic bacteria, the deconjugation of [^{14}C]-glycocholic acid occurs earlier and to a greater degree than normal, resulting in an early and high rise in the exhaled [^{14}C]- O_2 level.

If this patient's D-xylose absorption test result had been normal, what disorder might you suspect and how should you evaluate this possibility?

Pancreatic insufficiency should be suspected in patients who have a history of chronic pancreatitis or, less commonly, in middle-aged or elderly people who may present with a pancreatic cancer obstructing the pancreatic duct. A patient who has malabsorption and a history of pancreatitis should undergo a trial of pancreatic enzyme treatment. If this alleviates the diarrhea, the trial can be both diagnostic and therapeutic. The secretin test can be used to evaluate pancreatic function, but it is expensive and difficult to perform, so it is rarely used. If a pancreatic cancer is suspected, an imaging

study such as computed tomography (CT) scanning or endoscopic retrograde cholangiopancreatography (ERCP) should be performed.

Why did the symptoms in this patient, who had celiac sprue, abate when she stopped drinking milk?

Celiac sprue damages the intestinal epithelium, thereby decreasing the amounts of digestive enzymes, such as lactase, that are normally present in the villus cells.

Discussion

What are the major steps in the digestion and absorption of dietary lipids, carbohydrates, and proteins?

The process of digestion can be divided into three major steps: (a) intraluminal digestion, including the action of bile acids and pancreatic enzymes; (b) digestion by the intestinal epithelium; and (c) the transport of nutrients across the epithelium to the circulation.

The major events in the digestion and absorption of dietary lipid include (a) the lipolysis of dietary triglycerides by pancreatic lipase; (b) micellar solubilization of the resulting long-chain fatty acids and OI-monoglycerides by bile acids; (c) the absorption of fatty acids and OI-monoglycerides into enterocytes; (d) the reesterification and incorporation (along with cholesterol, cholesterol esters, phospholipid, and OI-lipoproteins) into chylomicrons and very low/density lipoproteins; and (e) the transport of chylomicrons from the mucosal cell into the intestinal lymphatics.

In the digestion and absorption of dietary carbohydrates, starch, which accounts for most of the carbohydrate intake, is initially hydrolyzed mostly by pancreatic amylase, yielding smaller sugars (maltose, maltotriose, and dextrans). These products, as well as ingested disaccharides such as lactose (milk sugar) and sucrose, are hydrolyzed further into their component monosaccharides by glucosidases (maltase, sucrase O±-dextrinase, and lactase), which are present in the brush border of epithelial cells in the proximal intestine. The monosaccharides are then absorbed by the epithelial cells and enter the portal circulation.

For the digestion and absorption of dietary protein to take place, proteins are first hydrolyzed by pancreatic enzymes in the intestinal lumen. These enzymes include endopeptidases (trypsin, chymotrypsin, and elastase) and exopeptidases (carboxypeptidases A and B). Oligopeptides produced by the pancreatic enzymes are further hydrolyzed by aminopeptidases located on the brush border as well as in the cytoplasm of intestinal epithelial cells. The resultant amino acids, and certain dipeptides and tripeptides, then enter the portal circulation.

What are the principal sites of intestinal absorption of various nutrients?

All dietary nutrients, with the exception of vitamin B₁₂ (cobalamin), are absorbed preferentially in the proximal small intestine; most absorption of the components of a meal occurs within the first 150 cm, although absorption (especially of sugars and amino acids) can occur more distally (as in the event of disease or surgical bypass of the proximal intestine). Vitamin B₁₂ is absorbed by the distal ileum, where there is a specific receptor for the cobalamin / intrinsic factor complex.

Of what does the enterohepatic circulation of bile acids consist?

Bile acids are synthesized from cholesterol by the liver and are conjugated to either taurine or glycine before secretion into bile. During fasting, the bile acids are stored in the gallbladder. After a meal, they are secreted into the duodenum. The bile acids are very efficiently absorbed from the distal ileum, carried back to the liver by the portal vein, efficiently extracted and reconstituted by the liver, and then secreted again into bile. During each cycle, more than 95% of the bile acids are absorbed, but only small amounts are absorbed in the proximal small intestine.

What are some of the major disorders of maldigestion or malabsorption?

Table 4.3 lists the representative disorders.

Table 4-3 Major Disorders of Maldigestion or Malabsorption

- Intraluminal disorders
 - Pancreatic exocrine (enzyme) insufficiency
- Chronic pancreatitis
- Pancreatic resection
- Cystic fibrosis
 - Bile acid deficiency

- Pancreatic or bile duct carcinoma
- Extensive distal ileal resection or disease
 - Bacterial overgrowth in the proximal intestine
 - Surgical disruption of the continuity of the upper bowel (a Billroth II gastrojejunostomy)
- Disorders of enterocytes
 - Primary defects (epithelium histologically normal)
- Primary lactase deficiency
- Sucrase/isomaltase deficiency
 - Secondary defects (epithelium histologically abnormal)
- Nontropical sprue (celiac disease and gluten-sensitive enteropathy)
- Tropical sprue
- Acquired immunodeficiency syndrome enteropathy
- Whipple's disease

Disturbed transfer of metabolites from enterocytes into lymph or portal blood
 Infiltrative processes of the mucosa (amyloidosis and lymphoma)
 Intestinal lymphangiectasia

ANSWERS TO CASE 34:

What is the diagnosis?

This patient has erythema nodosum, in this case secondary to previously undiagnosed Crohn's disease. Erythema nodosum is due to inflammation of the small blood vessels in the deep dermis. Characteristically it affects the shins, but it may also affect the thighs and forearms. The number and size of the lesions is variable. Lesions tend to heal from the centre and spread peripherally. The rash is often preceded by systemic symptoms - fever, malaise and arthralgia. It usually resolves over 3-4 weeks, but persistence or recurrence suggests an underlying disease.

Diseases linked to erythema nodosum

- | | |
|---------------------------|--------------------------------|
| • Streptococcal infection | • Lymphoma/leukaemia |
| • Tuberculosis | • Sarcoidosis |
| • Leprosy | • Pregnancy/oral contraceptive |
| • Glandular fever | • Reaction to sulphonamides |
| • Histoplasmosis | • Ulcerative colitis |
| • Coccidioidomycosis | • Crohn's disease |

What are the major causes of this condition?

The history of mouth ulcers, abdominal pain and diarrhoea strongly suggests that this woman has Crohn's disease. She should therefore be referred to a gastroenterologist for investigations which should include a small-bowel enema and colonoscopy with biopsies. Treatment of her underlying disease with steroids should cause the erythema nodosum to resolve. With no serious underlying condition, erythema nodosum usually settles with non-steroidal anti-inflammatory drugs.

Clinical pearls

- > Patients presenting with erythema nodosum should be investigated for an underlying disease.
- > Erythema nodosum is most often seen on the shins but can affect the extensor surface of the forearms or thighs.

ANSWERS TO CASE 35:

What diagnostic test is indicated in addition to fecal leukocytes and faecal occult blood test?

Order an assay for *C. difficile* cytotoxin when a patient presents with acute diarrhea during or shortly after hospitalization or antibiotic administration. *C. difficile* colonizes the gut after antibiotics alter the normal gut flora. The most commonly implicated antibiotics are clindamycin and ampicillin.

Spectrum of *C. difficile* infection:

- Asymptomatic: Most patients are asymptomatic carriers.
- Mild diarrhea without colitis: Second most common presentation is mild watery diarrhea without fever, leukocytosis, or dehydration.
 - Colitis without pseudomembranes: Five to 15 watery stools per day, fever, and abdominal cramps are relieved by defecation.
 - Pseudomembranous colitis: Symptoms are the same as colitis without pseudomembranes. Patient also has white-yellow plaques on colon mucosa.

Fulminant colitis: Rarely, patients may present with obstruction, toxic megacolon, or perforation.

C. difficile cytotoxin assay is positive. How is C. difficile infection treated?

Discontinue clindamycin and other antibiotics. Correct any fluid and electrolyte imbalances. Avoid loperamide and opiates. Antibiotics are only indicated for patients with symptoms of colitis or persistent diarrhea. This patient with symptoms of colitis should receive a 10- to 14-day course of metronidazole. If symptoms do not resolve with metronidazole, use oral vancomycin. If the patient develops signs of peritonitis, surgical management is indicated.

Pregnancy is a contraindication to metronidazole. Pregnant patients with C. difficile colitis should take oral vancomycin.

Prevention of hospital-acquired C. difficile infection: Wear gloves prior to contact with infected patients. Wash hands with soap and water after removing gloves.

ANSWERS TO CASE 36:

What initial workup is indicated for this patient with chronic diarrhea?

History and physical often suggests a possible cause for chronic diarrhea (Table 37-1). Because a specific cause is not apparent in this case, order the following initial tests:

- Complete blood count (CBC) and differential: identifies anemia (indicates chronic gastrointestinal (GI) bleeding versus chronic inflammation), leukocytosis (indicates inflammation), and eosinophilia (indicates allergy versus collagen vascular disease versus parasite infection versus eosinophilic gastritis versus cancer).
- Fecal occult blood test: identifies GI bleeding.
- Thyroid function tests: hyperthyroidism can cause chronic diarrhea.
- Serum electrolytes and liver function tests (LFTs): May identify liver abnormalities or systemic conditions associated with diarrhea such as diabetes mellitus.
- Total protein and albumin: indicators of general nutritional status.

Table 36–1 Causes of chronic diarrhea in immunocompetent adults

Inflammatory diarrhea	Classic presentation: Fever, hematochezia, abdominal pain ± pertinent travel history, recent antibiotic use, recent hospitalization, or history of radiation. Causes: 1. Chronic infections 2. Inflammatory bowel disease 3. Radiation enteritis
Secretory diarrhea	Classic presentation: Voluminous diarrhea that does not decrease with fasting. Causes: 1. Laxative abuse 2. Bile salt malabsorption (e.g., after cholecystectomy) 3. Hormonal tumors (VIPoma, carcinoid, medullary thyroid carcinoma, ZES)
Malabsorptive diarrhea	Classic presentation: Voluminous pale, greasy, foul-smelling diarrhea and weight loss despite adequate food intake. Many patients do not present with classic symptoms. Causes: 1. Bacterial overgrowth 2. Small bowel mucosa disorders (celiac sprue, tropical sprue, Whipple's disease) 3. Pancreas insufficiency (chronic pancreatitis, pancreatic carcinoma, cystic fibrosis) 4. Small bowel resection 5. Lymphatic obstruction (intestinal lymphoma, intestinal tuberculosis, carcinoid)

Osmotic diarrhea	Classic presentation: History of fat-free foods, lactulose, antacids, or symptoms worse with dairy products. Causes: 1. Sorbitol (found in fat-free foods) 2. Medications (lactulose, antacids) 3. Lactose intolerance
Motility disorders	Classic presentation: History of systemic disease or prior abdominal surgery Causes: 1. Systemic diseases (diabetes, scleroderma, hyperthyroidism) 2. Abdominal surgery (gastrectomy, gastric vagotomy)
Functional causes	Classic presentation: Abdominal pain relieved by defecation. Stool weight <200 g/day. No weight loss, anemia, gastrointestinal bleeding, or nocturnal diarrhea. Causes: 1. Irritable bowel syndrome 2. Functional diarrhea

Abbreviation: ZES, Zollinger-Ellison syndrome.

The only significant laboratory abnormalities are mild iron deficiency anemia and a mildly decreased total protein and albumin. What is the next step in the evaluation?

Order a quantitative stool analysis. The analysis should include stool weight, pH, sodium, potassium, fecal leukocytes, stool occult blood, fecal fat, and a laxative screen.

Developing countries: An empiric trial of metronidazole or oral fluoroquinolone is appropriate prior to stool analysis in countries where parasitic or bacterial causes of diarrhea are highly prevalent.

What stool analysis findings are associated with the different categories of diarrhea?

- Inflammatory diarrhea: increased fecal leukocytes and guaiac-positive stool.
- Secretory diarrhea: no abnormal stool analysis findings; normal osmotic gap.
- Malabsorptive diarrhea: increased osmotic gap and increased fecal fat; stool may or may not be guaiac-positive, and fecal pH is decreased in carbohydrate malabsorption.
- Osmotic diarrhea: increased osmotic gap; fecal pH is decreased only if osmotic diarrhea is caused by lactose intolerance.
- Normal fecal fat is <6 g/day
- Normal fecal pH is 5.6.
- Fecal osmotic gap (normally <50) = $290 - 2([\text{fecal sodium}] + [\text{fecal potassium}])$.

Positive findings on stool analysis are osmotic gap 120, steatorrhea, and guaiac-positive stool. Fecal leukocytes are not elevated. Laxative screen is negative. What is the next step in management?

Stool analysis suggests that malabsorption is the cause of this patient's diarrhea. Consider diagnostic testing in the following order:

- Order H₂ breath test (to test for carbohydrate malabsorption), tissue transglutaminase IgA antibody (to test for celiac disease), and stool examination for ova and parasites.
- If these are negative, perform upper and lower endoscopy with biopsy of both ends of the small intestine. Also consider upper GI series with small bowel follow-through.
- If small intestine biopsy and upper GI series fail to reveal any small bowel pathology, test for pancreatic insufficiency.

No diagnostic testing is indicated if patients have a known cause for malabsorption such as small intestine resection (causes short bowel syndrome) or cystic fibrosis (causes pancreatic insufficiency).

H₂-breath test is positive. Anti-gliadin and anti-endomysial antibodies are elevated. What is the most likely diagnosis?

This patient likely has celiac disease (gluten-sensitive enteropathy). This autoimmune, small-bowel, mucosal abnormality tends to occur more frequently in persons of northern European or Indian ancestry (HLA DQ2 or HLA DQ8). Patients often have coexisting autoimmune conditions such as type 1 diabetes mellitus, autoimmune thyroid disease, and IgA deficiency.

What are the next steps in management?

Confirm the diagnosis of celiac sprue with small-bowel biopsy. Mucosal inflammation, crypt hyperplasia, and villous atrophy are the characteristic findings on biopsy. Patients with a confirmed

diagnosis of celiac disease should follow a gluten-free diet (no wheat, rye, or barley). Consider prophylactic pneumococcal vaccine because patients often have hyposplenism. Some physicians perform a repeat biopsy 3 to 4 months after the patient initiates a gluten-free diet to demonstrate resolution of villous atrophy.

What are possible extraintestinal manifestations of celiac sprue?

Remember extraintestinal manifestations of celiac disease (may occur in the absence of diarrhea) using the mnemonic “A gluten-free diet Demands HI-MAINtenance”:

- Dermatitis herpetiformis: pruritic clusters of vesicles on erythematous, edematous papules on the extremities and trunk (unrelated to herpes virus despite name)
- Hyposplenism: absent or decreased spleen function
- Iron deficiency anemia
- Metabolic bone disease: Patients may develop osteoporosis due to secondary hyperparathyroidism and osteomalacia due to vitamin D deficiency.
- Arthritis
- IgA nephropathy and Infertility
- Neuropsychiatric disease: headache, ataxia, and depression

The patient asks about her long-term prognosis. What should you tell her?

Overall mortality is higher than the general population because celiac disease is associated with a modestly increased risk of non-Hodgkin lymphoma and GI cancers. The effect of a gluten-free diet on the risk of malignancy is not clear.

Tropical sprue is seen in certain tropical countries. Symptoms and small-bowel biopsy findings are often similar to celiac sprue, but the most likely cause is infection. Treatment is tetracycline and folic acid.

ANSWERS TO CASE 37:

What is constipation?

Constipation is an extremely common complaint in the general population. Any of the following symptoms can be considered constipation: frequency < 3 stools/week, excessive straining, lumpy or hard stools, incomplete evacuation, or need for digital manipulation to evacuate. Constipation can be idiopathic or due to secondary causes.

What are some common secondary causes of constipation?

- Medications: opioids, anticholinergics, antacids, calcium channel blockers, and iron
- GI: IBS, obstruction, pseudo-obstruction, paralytic ileus, and colon cancer
- Endocrine: hypothyroidism, diabetes mellitus, hypercalcemia, hypokalemia
- Neurologic: Parkinson's disease, multiple sclerosis

What is the next step in management?

The goal of the history and physical exam is to identify any “red flags” that would suggest a secondary cause. This patient does not have any such red flags for a secondary gastrointestinal (GI) disorder. She does not meet clinical criteria for IBS. She had a colonoscopy last year, which rules out colon cancer. The next step is to advise gradually increasing fiber intake. If symptoms persist, consider milk of magnesium.

Red flags for a structural GI cause for constipation are cramping abdominal pain, nausea, vomiting, fever, weight loss, and GI bleeding.

The patient returns 3 months later with persistent constipation. She has increased her dietary fiber intake. She has tried milk of magnesia, as well as a number of over-the-counter laxatives without relief. Physical exam and vital signs are normal. What is the next step in management for this patient with chronic constipation?

Order the following inexpensive tests to screen for a secondary cause: faecal occult blood test (FOBT), complete blood count (CBC), thyroid-stimulating hormone, and serum electrolytes. If this patient had not already had a screening colonoscopy last year, colon cancer screening would have been an option if FOBT was positive or all tests were negative.

Laboratory tests are all negative. What are the next steps in management?

Consider using a stimulant such as dulcolax. If the patient continues to have refractory and bothersome symptoms, refer to a gastroenterologist for more specialized testing. These tests can identify

patients with pelvic floor dysfunction (which often responds to biofeedback and relaxation training) and slow colonic transit.

What specialized tests are available for patients with constipation?

- Anorectal manometry: Patients with pelvic floor dysfunction may have increased anal sphincter pressure.

- Colonic transit test: Patient swallows a capsule with multiple radio-opaque markers. Serial abdominal radiographs are obtained. In slow colonic transit, the markers are scattered all over the colon and do not pass by day 5. In pelvic floor dysfunction, markers accumulate in the rectum and can get stuck in the rectum.

- Balloon expulsion test: Insert a balloon into the rectum. Normal patients can expel the balloon, but patients with pelvic floor dysfunction cannot.

- Defecography: Thickened barium solution is injected into the rectum. The movement of barium when the patient strains and squeezes the rectum is observed under fluoroscopy to detect rectal prolapse and rectoceles.

ANSWERS TO CASE 38:

The microcytic, hypochromic anaemia and the altered bowel habit, the only symptom referable to the gastrointestinal tract, point to a carcinoma of the colon, which would also explain her weight loss. A barium enema revealed a neoplasm in the sigmoid colon, confirmed by colonoscopy and biopsy. Chest X-ray and abdominal ultrasound showed no pulmonary metastases and no intra-abdominal lymphadenopathy or hepatic metastases respectively.

She proceeded to a sigmoid colectomy and end-to-end anastomosis, and was regularly followed-up for any evidence of recurrence. Histology showed a grade I tumour.

Carcinoma of the colon is increasing in frequency. If it presents at an early stage then the prospect for cure is good. Rectal bleeding, alteration in bowel habit for longer than 4 month at any age, or iron-deficient anaemia in men or postmenopausal women are indications for investigation of the gastrointestinal tract.

Smoking is a risk factor for carcinoma of the colon.

Clinical pearls

- > Carcinoma of the colon can present with few or no symptoms or signs in the gastrointestinal tract
- > Carcinoma of the colon must be considered as a cause of iron-deficient anaemia.

ANSWERS TO CASE 39:

A 28-year-old man complains of nausea, vomiting, diffuse abdominal pain, fever, and myalgias. He has had 12 different lifetime sexual partners and currently is taking acetaminophen. He appears icteric and has a low-grade fever and tender hepatomegaly. Results of his laboratory studies are consistent with severe hepatocellular injury and somewhat impaired hepatic function.

- > Most likely diagnosis: Acute hepatitis, either viral infection or toxic injury, possibly exacerbated by acetaminophen use.

- > Most important immediate diagnostic test: Acetaminophen level, because acetaminophen toxicity may greatly exacerbate liver injury but is treatable.

Considerations

This patient has an acute onset of hepatic injury and systemic symptoms that predate his acetaminophen use. The markedly elevated hepatic transaminase and bilirubin levels are consistent with viral hepatitis or possibly toxic injury. This patient denied intravenous drug use, which would be a risk factor for hepatitis B and C infections. His sexual history is a possible clue. The degree and pattern of transaminase (ALT and AST) elevation can provide some clues to help differentiate possible etiologies. Transaminase levels more than 1000 IU/L are seen in conditions that produce extensive hepatic necrosis, such as toxic injury, viral hepatitis, and ischemia (“shock liver”). Patients with alcoholic hepatitis almost always has levels less than 500 IU/L and often have an AST/ALT ratio of 2:1. In this case, it is important to consider the possibility of acetaminophen toxicity, both because the condition can produce fatal liver failure and because an effective antidote is available. By obtaining a serum acetaminophen level and

knowing the time of his last ingestion, these data can be plotted on a nomogram (Figure 39-1) to help predict acetaminophen-related liver damage and the possible need for N-acetylcysteine.

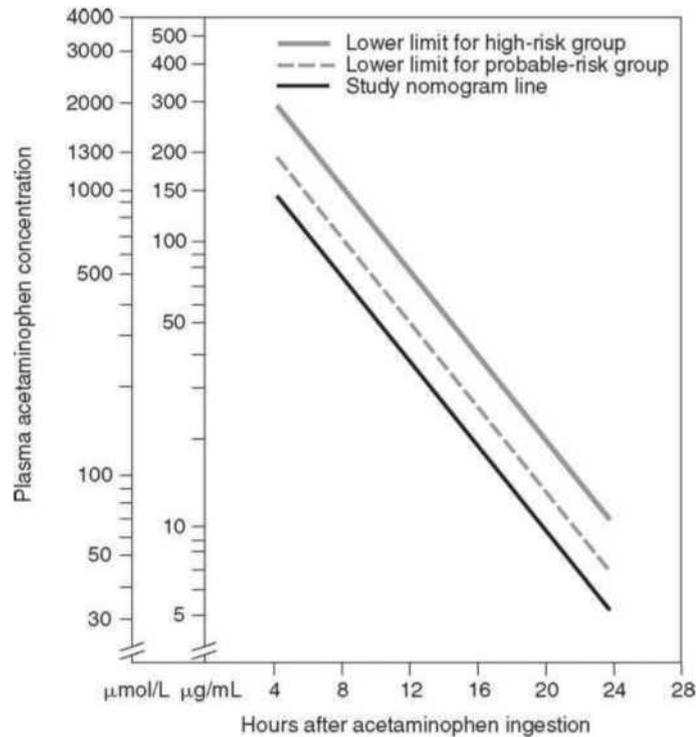


Figure 39-1. Acetaminophen nomogram.

APPROACH TO SUSPECTED HEPATITIS

Definitions

HEPATITIS: An inflammation of the liver. At least six forms of hepatitis have been identified, referred to as hepatitis A, B, C, D, E, and G.

CHRONIC HEPATITIS: A syndrome that is defined clinically by evidence of liver disease for at least 6 consecutive months.

Clinical approach

Most cases of acute hepatitis are caused by infection with one of five viruses: hepatitis A, B, C, D, or E. They can produce virtually indistinguishable clinical syndromes, although it is unusual to observe acute hepatitis C. Affected individuals often complain of a prodrome of nonspecific constitutional symptoms, including fever, nausea, fatigue, arthralgias, myalgias, headache, and sometimes pharyngitis and coryza. This is followed by the onset of visible jaundice caused by hyperbilirubinemia, with tenderness and enlargement of the liver, and dark urine caused by bilirubinuria. The clinical course, and prognosis then vary based on the type of virus causing the hepatitis.

Hepatitis A and E both are very contagious and transmitted by fecal-oral route, usually by contaminated food or water where sanitation is poor, and in daycare by children. Hepatitis A is found worldwide and is the most common cause of acute viral hepatitis in the United States. Hepatitis E is much less common and is found in Asia, Africa, Central America, and the Caribbean. Both hepatitis A and E infections usually lead to self-limited illnesses and generally resolve within weeks. Almost all patients with hepatitis A recover completely and have no long-term complications. A few may have fulminant disease resulting in liver failure. Most patients with hepatitis E also have uncomplicated courses, but some patients, particularly pregnant women, have been reported to develop severe hepatic necrosis and fatal liver failure.

Hepatitis B is the second most common type of viral hepatitis in the United States, and it is usually sexually transmitted. It also may be acquired parenterally, such as by intravenous drug use, and during birth from chronically infected mothers. The outcome depends on the age at which the infection was acquired. Up to 90% of infected newborns develop chronic hepatitis B infection, which places the affected infant at significant risk of hepatocellular carcinoma later in adulthood. For individuals infected later in life, approximately 95% of patients will recover completely without sequelae. Between 5% and 10% of patients will develop chronic hepatitis, which may progress to cirrhosis. A chronic carrier state

may be seen in which the virus continues to replicate, but it does not cause irreversible hepatic damage in the host.

Hepatitis C is transmitted parenterally by blood transfusions or intravenous drug use, and rarely by sexual contact. The mode of transmission is unknown in approximately 40% of cases. It is uncommonly diagnosed as a cause of acute hepatitis, often producing subclinical infection, but is frequently diagnosed later as a cause of chronic hepatitis.

Hepatitis D is a defective RNA virus that requires the presence of the hepatitis B virus to replicate. It can be acquired as a coinfection simultaneously with acute hepatitis B or as a later superinfection in a person with a chronic hepatitis B infection. Patients afflicted with chronic hepatitis B virus who then become infected with hepatitis D may suffer clinical deterioration; in 10% to 20% of these cases, individuals develop severe fatal hepatic failure.

Fortunately, in most cases of acute viral hepatitis, patients recover completely, so the treatment is generally supportive. However, fulminant hepatic failure as a result of massive hepatic necrosis may progress over a period of weeks. This usually is caused by infection by the hepatitis B and D viruses, or is drug-induced. This syndrome is characterized by rapid progression of encephalopathy from confusion or somnolence to coma. Patients also have worsening coagulopathy as measured by increasing prothrombin times, rising bilirubin levels, ascites and peripheral edema, hypoglycemia, hyperammonemia, and lactic acidosis. Fulminant hepatitis carries a poor prognosis (the mortality for comatose patients is 80%) and often is fatal without an emergency liver transplant.

Diagnosis

Clinical presentation does not reliably establish the viral etiology, so serologic studies are used to establish a diagnosis. Anti-hepatitis A immunoglobulin M (IgM) establishes an acute hepatitis A infection. Anti-hepatitis C antibody is present in acute hepatitis C, but the test result may be negative for several weeks. The hepatitis C RNA assay, which becomes positive earlier in the disease course, often aids in the diagnosis. Acute hepatitis B infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg) in the clinical context of elevated serum transaminase levels and jaundice. HBsAg later disappears when the antibody (anti-HBs) is produced (Figure 39-2). There is often an interval of a few weeks between the disappearance of HBsAg and the appearance of anti-HBsAb. This period is referred to as the “window period.” During this interval, the presence of anti-hepatitis B core antigen IgM (anti-HBc IgM) is indicative of an acute hepatitis B infection. Hepatitis B precore antigen (HBeAg) represents a high level of viral replication. It is almost always present during acute infection, but its persistence after 6 weeks of illness is a sign of chronic infection and high infectivity. Persistence of HBsAg or HBeAg is a marker for chronic hepatitis or a chronic carrier state; elevated versus normal serum transaminase levels distinguish between these two entities, respectively.

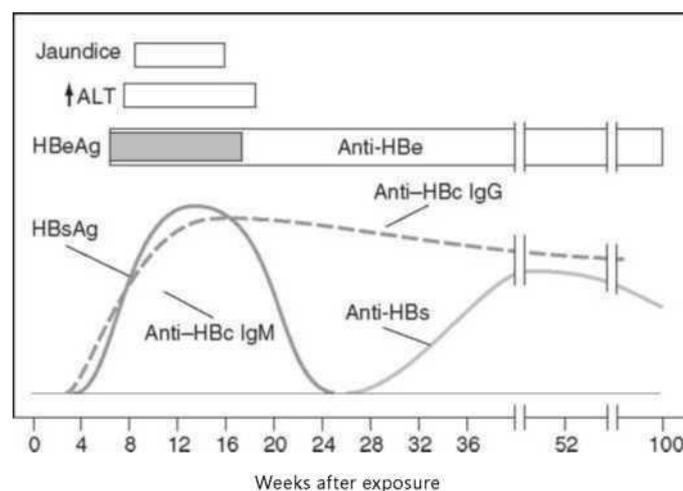


Figure 39-2. Serologic markers in acute hepatitis B infection.

Prevention

The efficacy of the hepatitis A vaccine for hepatitis A (available in two doses given 6 months apart) exceeds 90%. It is indicated for individuals planning to travel to endemic areas. Postexposure prophylaxis with hepatitis A immunoglobulin, along with the first injection of the vaccine, should be

given to household and intimate contacts within 2 weeks of exposure. The hepatitis B vaccine (given in three doses over 6 months) provides effective immunity in more than 90% of patients. It is recommended for health-care workers, as well as for universal vaccination of infants in the United States. Hepatitis B immunoglobulin (HBIG) is given after exposure, such as a needle-stick injury from an infected patient, or to a newborn of infected mothers. The first inoculation of the vaccine usually is given concurrently. There is no immunization and no proven postexposure prophylaxis for persons exposed to hepatitis C. Interferon treatment may be used in individuals with hepatitis B or C infection, and lamivudine is used to treat patients with chronic hepatitis B.

Acetaminophen hepatitis

Acetaminophen-induced hepatocellular injury may result after a single, large ingestion, as in a suicide attempt, or by chronic use of over-the-counter acetaminophen-containing preparations for treatment of pain or fever. Hepatic toxicity most often occurs after an acute ingestion of 10 g or more, but lower doses may cause injury in patients with preexisting liver disease, particularly in those who abuse alcohol. Acetaminophen is metabolized in the liver by the cytochrome P450 enzyme system, which produces a toxic metabolite; this metabolite is detoxified by binding to glutathione. Potential hepatic injury is greater when P450 activity is augmented by drugs such as ethanol or phenobarbital, or when less glutathione is available, as in alcoholism, malnutrition, or AIDS (acquired immunodeficiency syndromes). Acetaminophen levels are measured between 4 and 24 hours after an acute ingestion and plotted on a nomogram to predict possible hepatotoxicity and determine if treatment is necessary (Figure 39-1). Sometimes, empiric therapy is started even before labs results return.

If acetaminophen levels are above the level that predisposes to hepatic injury, treatment is started with gastric decontamination with charcoal and administration of N-acetylcysteine, which provides cysteine to replenish glutathione stores. N-Acetylcysteine should be started within the first 10 hours to prevent liver damage and is continued for 72 hours. Meanwhile, the patient should not receive any medications that are known to be hepatotoxic.

Comprehension Questions

1. A 25-year-old medical student is stuck with a hollow needle during a procedure performed on a patient known to have hepatitis B and C viral infection, but who is HIV negative. The student's baseline laboratory studies include serology: HBsAg negative, anti-HBsAb positive, anti-HBc IgG negative. Which of the following regarding this medical student's hepatitis status is true?

- A. Prior vaccination with hepatitis B vaccine
- B. Acute infection with hepatitis B virus
- C. Prior infection with hepatitis B virus
- D. The student was vaccinated for hepatitis B but is not immune

2. What postexposure prophylaxis should the student described in Question 11.1 receive?

- A. Hepatitis B immunoglobulin (HBIG)
- B. Oral lamivudine
- E. Intravenous immunoglobulin (IVIG)
- C. Reassurance

3. In a suicide attempt, an 18-year-old adolescent female takes 4 g of acetaminophen, approximately 8 hours previously. Her acetaminophen level is 30 pg/mL. Which of the following is the best next step to be performed for this patient?

- A. Immediately start N-acetylcysteine
- B. Observation
- C. Alkalinize the urine
- D. Administer intravenous activated charcoal

Answers

1. A. This student's serology is most consistent with vaccination and not prior infection. Like all health-care workers, the student should have been vaccinated against the hepatitis B virus, which induces anti-HBs IgG antibody, which is thought to be protective. Not all people receiving the vaccine develop an adequate antibody titer; if none were detected, it would indicate the need for revaccination. Patients with prior hepatitis B infection will also likely have anti-HBsAb but will also have anti-HBc IgG. Acute infection would be signified by the presence of either HBsAg or anti-HBc IgM.

2. D. No postexposure prophylaxis is definitively indicated. The student has detectable protective antibody levels against the hepatitis B virus, and if the levels are judged to be adequate, the student is

protected against infection. Oral lamivudine is a treatment for chronic hepatitis B infection and is part of an antiretroviral prophylaxis if the patient was HIV positive. There is no effective prophylaxis for hepatitis C exposure.

3.B. The serum acetaminophen level of 30 pg/mL, with last ingestion 8 hours previously, is plotted on the nomogram and falls below the “danger zone” of possible hepatic injury. Thus, this patient should be observed. Sometimes, patients will take more than one medication so that serum and/or urine drug testing may be worthwhile. Gastrointestinal activated charcoal, not intravenous charcoal, is used for other ingestions.

Clinical Pearls

- ▶ The three most common causes of acute hepatitis with elevated transaminase levels exceeding 1000 IU/L are viral infection, toxic exposure, and ischemic injury.
- ▶ The large majority of adults with acute hepatitis B viral infection recover completely, but 5% to 10% develop chronic hepatitis.
- ▶ Fulminant hepatic failure, characterized by the rapid development of hepatic encephalopathy, coagulopathy, peripheral edema, and ascites, usually is fatal unless a liver transplant is performed.
- ▶ Prevention of hepatitis B viral infection hinges on long-term immunity with a highly effective recombinant vaccine and short-term postexposure prophylaxis with hepatitis B immunoglobulin (HBIG).
- ▶ The likelihood of toxic acetaminophen injury and the need for treatment can be predicted from a nomogram based on serum level and the time since last ingestion.

ANSWERS TO CASE 40:

What is the diagnosis?

The patient has acute hepatitis B virus infection (Table 40-1). He is among the 30% of patients with acute HBV who develop jaundice (the other 70% are asymptomatic). Less than 1% of patients develop acute liver failure. Most patients who develop acute liver failure have coexisting hepatitis D virus infection or other comorbid liver diseases.

Table 40–1 Hepatitis B serology

	HBsAg ^a	HbsAb ^b	HbcAb ^c	HbeAg ^d
Acute infection	Positive	Negative	IgM	Positive
Window period	Negative	Negative	IgM	Negative
Chronic infection (infectious)	Positive	Negative	IgG	Positive
Chronic infection (not infectious)	Positive	Negative	IgG	Negative
Recovery	Negative	Negative	IgG	Negative
Immunization	Negative	Positive	Negative	Negative

Abbreviations: HBV, hepatitis B virus; Ig, immunoglobulin.

Note: HBV DNA assay: Levels of HBV DNA detected by PCR and other tests are used mainly to determine whether the patient is a candidate for antiviral therapy.

a Hepatitis B surface antigen (HBsAg): Appears before onset of symptoms and indicates HBV infection. If the patient recovers, HBsAg becomes negative in 4–6 months. If the patient develops chronic hepatitis, HBsAg remains positive.

b Hepatitis B surface antibody (HbsAb): HbsAb appears shortly after HBsAg disappears and persists for life. Presence of HbsAb indicates either complete recovery or prior immunization. Chronic carriers do not form HbsAb.

c Hepatitis B core antibody (HBcAb): IgM HBcAb appears during initial infection. Its main purpose is to remain positive during the “window period” after HBsAg disappears and before HbsAb appears. After acute infection, IgM HBcAb disappears and IgG HBcAb appears. IgG HBcAb remains positive in both chronic infection and completely recovered patients.

d Hepatitis B e antigen (HBeAg): Marker of HBV infectiousness and replication. HBeAg appears during acute infection. It disappears if the patient recovers. When HBeAg disappears, anti-HBe antibody appears, indicating decreased viral replication. HBeAg persists in some chronically infected patients, which indicates continued viral replication and infectivity.

Hepatitis D virus: Infection is benign unless superimposed with HBV infection. Diagnose with anti-hepatitis D virus antibodies.

What treatment is recommended for this patient with acute infection?

No antiviral therapy is indicated in the absence of coexisting liver disease or acute liver failure because 95% of patients infected during adulthood do not progress to chronic hepatitis. Monitor HBV serologies and LFTs over the next 3 to 6 months.

The patient admits to sharing needles with a male friend while using intravenous (IV) drugs. The male friend recently immigrated to the United States from China. He has the following serologies: HCV Ab (–), HBsAg (+), HbcAb IgG (+), HBsAb (–), and HBeAg (+). HBV DNA is 25,000 IU/ml. AST is 150 and ALT is 220 U/L.

CASE DISCUSSION

How is HBV transmitted?

There are three modes of transmission:

- Vertical transmission: Transmission from mother to baby during the perinatal period is the major mode of infection in developing countries.
- Unprotected sexual intercourse: Major mode of transmission in developed countries.
- Exposure to infected blood: Sharing needles, razors, toothbrushes, or chewing gum are possible modes of exposure to infected blood. Such horizontal transmission is common in developing countries.

There is no evidence for any other coexisting liver diseases on further testing.

What is the diagnosis?

The partner has chronic HBV infection and is infective; he is the most likely source of infection. It is possible he acquired the infection via perinatal transmission from his mother because 90% of patients who acquire HBV as neonates progress to chronic infection.

Chronic HBV increases the risk of developing polyarteritis nodosa.

What therapy is recommended for the male friend?

Many hepatologists would recommend antiviral therapy for this patient. Antiviral options include interferon-alfa, lamivudine, adefovir, and entecavir. Deciding when to treat HBV and which agent to use is an area of active investigation and debate. Some general indications for treatment are:

- No signs of cirrhosis: Consider treatment if HBV DNA >20,000 IU/mL and ALT is greater than twice the upper limit of normal.
- Compensated cirrhosis: Treat if HBV DNA >2000 IU/mL.
- Decompensated cirrhosis: Treat if patient has any detectable HBV DNA.

The patient often shares razors with his roommate. The roommate is asymptomatic. Physical exam and vital signs are normal. Complete blood count (CBC) and LFTs are normal. Viral serologies are HCVAb (–), HBsAg (–), HbcAb (–), HBsAb (+), and HBeAg (–).

How should you interpret these serologies?

Negative HBsAg indicates no current infection. Negative HbcAb indicates no past history of infection. Positive HBsAb indicates immunity against HBV. The serologies indicate prior immunization (see Table 5-4).

Six months later, the original patient's serologies are HBsAg (–), IgG HbcAb (+), HBsAb (+), and HBeAg (–).

What is the next step in management?

The patient has recovered from HBV infection and has developed immunity against repeat infection (see Table 5-4). No further therapy is necessary.

The patient has had unprotected sexual intercourse with one woman over the last 7 to 8 months. Her amino transaminases are ALT 190 and AST 160 U/L. Sclera are icteric. Viral serologies are HCVAb (+), HBsAg (–), HbcAb (–), HBsAb (+), and HBeAg (–).

What is the diagnosis?

The female sexual partner does not have HBV infection because of prior immunization, but she does have HCV infection. The major mode of HCV transmission is infected blood. Perinatal transmission and transmission through unprotected sex can occur, but the risk is lower than with HBV. Acute infection is usually asymptomatic. Unlike HBV, approximately 80% of patients with HCV develop chronic hepatitis.

Lichen planus: Shiny, flat, violaceous, polygonal papules ± white lacelike striae can occur on skin,

nails, and mucosal surfaces such as the mouth and genitalia. Lichen planus is more common in patients with HCV infection. First-line therapy is topical steroids.

What is the next step in management for the sexual partner?

Confirm the diagnosis with HCV RNA testing. If HCV RNA is positive, obtain liver biopsy to assess the chronicity and severity of disease.

Chronic hepatitis C increases the risk of developing cryoglobulinemia (suspect if patient develops purpura, arthralgias, or Raynaud's phenomenon).

PCR for HCV RNA confirms the diagnosis of HCV infection, and liver biopsy indicates that the patient has chronic hepatitis.

How is chronic HCV treated?

First-line therapy for chronic HCV infection is pegylated-interferon alfa plus ribavirin.

Treatment of acute HCV is controversial, and there is currently no drug approved by the United States Food and Drug Administration for this indication. Many hepatologists advocate an interferon-based regimen because of the high risk of progressing to chronic hepatitis.

ANSWERS TO CASE 41:

What is the most likely diagnosis?

Fever, right upper quadrant (RUQ) pain, and jaundice are the classic signs of acute ascending cholangitis (Charcot's triad). Like cholecystitis, patients have leukocytosis with a left shift ± mildly elevated amylase. Unlike cholecystitis, LFTs reveal a cholestatic pattern because the infection is in the chronic bowel diseases (CBD).

What are risk factors for cholangitis?

- Biliary obstruction: Stones, strictures, or pancreatic/biliary tumors obstruct the biliary tree, which increases biliary pressure and promotes migration of bacteria from portal to biliary circulation.
- Mechanical barrier disruption: endoscopic retrograde cholangiopancreatography (ERCP) or biliary surgery can disrupt the mechanical barrier provided by the SOD, which allows bacteria to enter the biliary tree.
- Foreign body: Gallstones and stents can act as a nidus for bacterial growth.

What are the next diagnostic steps?

Order ultrasound (detects gallstones and biliary dilation). Then perform diagnostic ERCP to confirm the diagnosis.

- MRCP is a noninvasive alternative to ERCP (uses MRI to visualize biliary and pancreatic ducts). Consider MRCP rather than ERCP if the patient with suspected cholangitis does not have Charcot's triad or ultrasound findings are ambiguous.

- Percutaneous transhepatic cholangiography is indicated if ERCP cannot establish the diagnosis. Locate bile ducts using fluoroscopy and inject contrast percutaneously into the ducts.

Diagnostic ERCP confirms the diagnosis of cholangitis.

How is this condition treated?

Treat with supportive care and broad-spectrum antibiotics to cover enteric Gram-negative bacteria and enterococci (e.g., ampicillin and gentamycin). Fever and abdominal pain should improve within 24 hours. After clinical improvement, perform therapeutic ERCP (sphincterotomy and stone extraction ± stent placement) on an elective basis.

Reynold's pentad: Charcot's triad with hypotension and altered mental status. Indicates severe (suppurative) cholangitis. Requires urgent rather than elective therapeutic ERCP.

Twenty-four hours later, the patient appears confused. Physical exam is significant for RUQ tenderness and jaundice. Vital signs are temperature 39.2°C, pulse 120 bpm, respirations 25/min, and blood pressure 90/60.

What is the next step in management?

Patients with persistent fever, abdominal pain, or signs of septic shock (Reynold's pentad) despite supportive care and antibiotics require urgent therapeutic ERCP. If ERCP is unsuccessful, percutaneously insert a cholecystostomy tube (T-tube) to decompress the biliary tree.

The patient recovers after ERCP but returns 1 week later with fever, chills, malaise, and RUQ pain. Physical exam is significant for jaundice and RUQ tenderness. Complete blood count (CBC) demonstrates leukocytosis. LFTs reveal a cholestatic pattern. Murphy's sign is negative. Ultrasound

demonstrates a well-demarcated, hypoechoic lesion in the right lobe of the liver that the radiologist interprets as a possible liver abscess.

What is the next step in management?

Contiguous spread of bacteria from the biliary tree to the liver to form a pyogenic liver abscess is a potentially life-threatening complication. Fever and RUQ pain are the most common symptoms. Patients may have jaundice and nonspecific symptoms like nausea, vomiting, anorexia, and malaise. Complete blood count (CBC) usually shows leukocytosis. LFTs may or may not be elevated (elevated alkaline phosphatase is the most common abnormality). Ultrasound usually establishes the diagnosis. If ultrasound is equivocal, confirm the diagnosis with computed tomography (CT) scan. Treatment is broad-spectrum IV antibiotics and percutaneous ultrasound or CT-guided aspiration and catheter drainage of the abscess. Tailor antibiotics when culture results of the abscess fluid are available.

50% of patients do not have RUQ pain or jaundice.

Sources of bacteria in pyogenic liver abscess: contiguous spread from biliary tree to liver (number one source), contiguous spread from peritonitis (number two source), and hematogenous spread.

ANSWERS TO CASE 42:

What is your interpretation of these findings?

The liver function tests show a predominantly obstructive picture with raised alkaline phosphatase and gamma-glutamyl transpeptidase, while cellular enzymes are only slightly raised. The symptoms and investigations are characteristic of primary biliary cirrhosis, an uncommon condition found mainly in middle-aged women. In the liver there is chronic inflammation around the small bile ducts in the portal tracts. Hypercholesterolaemia, xanthelasmata and xanthomata are common. The dry eyes and dry mouth may occur as part of an associated sicca syndrome. Itching occurs because of raised levels of bile salts, and can be helped by the use of a binding agent such as cholestyramine which interferes with their reabsorption. The presence of antimicrobial antibodies in the blood is typical of primary biliary cirrhosis. These antibodies are found in 95 per cent of cases.

Hypothyroidism might explain some of her symptoms but the normal thyroid-stimulating hormone (TSH) level shows that her current dose of 150 µg thyroxine is providing adequate replacement. The thyroid antibodies reflect the autoimmune thyroid disease which is associated with other autoantibody-linked conditions such as primary biliary cirrhosis.

What is the likely diagnosis and how might this be confirmed?

The diagnosis is confirmed by a liver biopsy. This should only be carried out after an ultrasound confirms that there is no obstruction of larger bile ducts. Ultrasound will help to rule out other causes of obstructive jaundice although the clinical picture described here is typical of primary biliary cirrhosis. No treatment is known to affect the clinical course of this condition.

Clinical pearls

- > The pattern of liver enzyme abnormalities usually reflects either an obstructive or hepatocellular pattern.
- > Symptoms such as itching have a wide differential diagnosis. Dealing with the underlying cause, wherever possible, is preferable to symptomatic treatment.

ANSWERS TO CASE 43:

What is the diagnosis?

Cholestatic pattern of LFTs and positive anti-mitochondrial antibodies (AMA) indicate that the patient has primary biliary cirrhosis (PBC). The pathophysiology involves autoimmune (T lymphocyte-mediated) destruction of intrahepatic bile ducts. Retained bile acids cause liver inflammation (hepatitis) that eventually progresses to cirrhosis. Most patients are asymptomatic at diagnosis. Among symptomatic patients, the most common presenting complaints are fatigue and pruritis. Some patients may report right upper quadrant (RUQ) discomfort. Jaundice is a late finding in PBC.

- False-positive AMA: Confirm PBC with liver biopsy because false-positive AMA can occur.
- Autoimmune cholangitis: Negative AMA but histological features of PBC appear on liver biopsy.

Also referred to as AIH/PBC overlap syndrome.

- ANA: 70% of PBC patients are positive for ANA. Some of these patients may have histological findings of both PBC and AIH.

PBC epidemiology: 90% of symptomatic patients are middle-aged women.

Liver biopsy confirms the diagnosis.

What other conditions are associated with PBC?

Remember conditions associated with PBC using the mnemonic “ABCD”:

- Autoimmune disorders: Approximately 50% of patients have symptoms of Sjögren's syndrome, and 10% have CREST syndrome. Patients also have increased incidence of other autoimmune disorders such as type 1 diabetes mellitus and rheumatoid arthritis.

- Bones: 25% of patients develop osteoporosis; 10% develop inflammatory arthritis of the peripheral joints (PBC arthritis).

- Cardiovascular: 50% of patients have hyperlipidemia, often with xanthomas.

- Dermatologic: Some patients have skin hyperpigmentation similar to hemochromatosis.

How is PBC managed?

- Treatment of underlying disease: Ursodeoxycholic acid is the only therapy that delays progression to end-stage liver disease. This medication decreases endogenous bile acids by unknown mechanisms.

- Treatment of cholestatic symptoms (pruritis, fat malabsorption, etc.) and associated conditions.

First-line treatments for pruritis are bile acid-binding resins (cholestyramine and colestipol).

Intractable osteoporosis or pruritis are potential indications for liver transplant even if the patient does not have complications of cirrhosis or a high MELD score.

ANSWERS TO CASE 44:

How do you interpret these findings?

This woman has a 5-year history of intermittent upper abdominal pain. Her current pain has lasted longer than previous episodes and on examination she is jaundiced. The acute pain on inspiration while palpating in the right upper quadrant is a positive Murphy's sign of inflammation of the gallbladder. The relative bradycardia in the presence of the acute illness is likely to be related to the beta-blocker therapy (atenolol) rather than hypothyroidism or any other problem. The dark urine would fit with increased conjugated bilirubin because of obstruction. The conjugated bilirubin is water soluble and excreted in the urine. Without conjugated bilirubin entering the bowel one would expect pale stools.

Her investigations show a raised bilirubin. The alanine aminotransferase is slightly raised but the main abnormalities in the liver enzymes are high values of alkaline phosphatase and gamma-glutamyl transpeptidase. This is the pattern of obstructive jaundice which can be caused by mechanical obstruction by tumour or by gallstones, or by adverse effects of some drugs, e.g. phenothiazines, flucloxacillin. The drugs she is taking are not likely causes of liver problems.

The previous episodes of pain and fever over the last 5 years are likely to have been cholecystitis secondary to gallstones. If the gallbladder were to be palpable on examination this would suggest an alternative diagnosis of malignant obstruction, since by this time these previous episodes of cholecystitis would usually have caused scarring and contraction of the gallbladder. In order to produce obstructive jaundice one or more of her gallstones must have moved out of the gallbladder and impacted in the common bile duct. Migration of gallstones from the gallbladder occurs in around 15 per cent of cases.

Her thyroid condition seems to be stable and not relevant to the current problem. Her angina is indicative of coronary artery disease and needs to be considered when treatment is being planned for her gallstones. An electrocardiogram (ECG) should be part of her management.

What is the appropriate management?

Only a minority of gallstones are radio-opaque and visible on a plain radiograph so the next investigation should be an ultrasound of the liver and biliary tract. Ultrasound will show dilatation of the biliary tree but is not so reliable for identifying common bile duct stones. Endoscopic retrograde cholangiopancreatography (ERCP) is the best tool for this, and sphincterotomy with or without stone retrieval may be possible to remove stones obstructing the common bile duct.

Clinical pearls

- > Obstructive jaundice with a dilated, palpable gallbladder is likely to be caused by carcinoma at the head of the pancreas (Courvoisier's sign).

- > Obstructive jaundice causes preferential elevation of alkaline phosphatase and gamma- glutamyl

transpeptidase.

- > When the main rise is in alanine aminotransferase, this indicates primarily hepatocellular damage.
- > What further investigations should be performed?

ANSWERS TO CASE 45:

What is the likely diagnosis?

The patient has an obstructive jaundice as indicated by the history of dark urine and pale stools and the liver function tests. The pain has two typical features of carcinoma of the pancreas: relief by sitting forward and radiation to the back. An alternative diagnosis could be gallstones but the pain is not typical.

As with obstruction of any part of the body the objective is to define the site of obstruction and its cause. The initial investigation was an abdominal ultrasound which showed a dilated intrahepatic biliary tree, common bile duct and gallbladder but no gallstones. The pancreas appeared normal, but it is not always sensitive to this examination owing to its depth within the body.

What further investigations should be performed?

Further investigation of the region at the entrance of the common bile duct into the duodenum and head of the pancreas was indicated and was undertaken by computed tomography (CT) scan. It showed a small tumour in the head of the pancreas causing obstruction to the common bile duct, but no extension outside the pancreas. No abdominal lymphadenopathy was seen. No hepatic metastases were seen on this investigation or on the ultrasound.

The patient underwent partial pancreatectomy with anastomosis of the pancreatic duct to the duodenum. The jaundice was rapidly relieved. Follow-up is necessary not only to detect any recurrence but also to treat any possible development of diabetes.

Clinical pearls

- > Carcinoma of the pancreas can present with non-specific symptoms in its early stages.
- > It is an important cause of obstructive jaundice.
- > Patients who have had a partial removal of the pancreas are at risk of diabetes

ANSWERS TO CASE 46:

A 57-year-old man presents with pruritus, weight loss, and light-colored stools. He is found to be jaundiced with markedly elevated alkaline phosphatase level and conjugated hyperbilirubinemia. All of these findings point toward cholestasis. The light-colored, or acholic, stools suggest the cholestasis is most likely caused by biliary obstruction. The absence of abdominal pain makes gallstone disease less likely.

- > Most likely diagnosis: Biliary obstruction, most likely caused by malignancy.
- > Next step: Imaging procedure of his biliary system, either ultrasonography or computed tomographic (CT) scan.

Considerations

In patients with jaundice, one must try to distinguish between hepatic and biliary disease. In the patient with suspected biliary obstruction, without the pain typically associated with gallstones, one should be suspicious of malignancy or strictures. In the case presented, the clinical picture is worrisome for a malignant cause of biliary obstruction, such as pancreatic cancer.

APPROACH TO PAINLESS JAUNDICE

Definitions

CHOLESTASIS: Deficient bile flow that can result from intrahepatic disease or extrahepatic obstruction.

CONJUGATED BILIRUBIN (DIRECT-REACTING BILIRUBIN): Bilirubin that has entered the liver and has been enzymatically bound to glucuronic acid forming bilirubin monoglucuronide or diglucuronide.

JAUNDICE OR ICTERUS: Yellowing of the skin or whites of the eyes, indicating hyperbilirubinemia.

UNCONJUGATED BILIRUBIN (INDIRECT-REACTING BILIRUBIN):

Bilirubin that has not been enzymatically bound to glucuronic acid by the liver and is in the serum

reversibly and noncovalently bound to albumin.

Clinical approach

Jaundice, or icterus, is the visible manifestation of hyperbilirubinemia and usually can be noticed by physical examination when the serum bilirubin level exceeds 2.0 to 2.5 mg/dL. Traditional instruction regarding the jaundiced patient divides the mechanism of hyperbilirubinemia into prehepatic (excessive production of bilirubin), intrahepatic, or extrahepatic (as in biliary obstruction). For most patients with jaundice, it probably is more clinically useful to think about hepatic or biliary diseases that cause conjugated hyperbilirubinemia, because they represent the most clinically important causes of jaundice.

The term unconjugated hyperbilirubinemia is used when the conjugated (or direct- reacting fraction) does not exceed 15% of the total bilirubin. It is almost always caused by hemolysis, or Gilbert syndrome. In these conditions, the serum bilirubin level almost always is less than 5 mg/dL, and there is usually no other clinical signs of liver disease. In addition, there should be no bilirubinuria (only conjugated bilirubin can be filtered and renally excreted). Hemolysis usually is clinically apparent, as in sickle cell disease or autoimmune hemolytic anemia. Gilbert syndrome is a benign condition caused by a deficiency of hepatic enzymatic conjugation of bilirubin, which results in intermittent unconjugated hyperbilirubinemia, usually with a total bilirubin less than 4mg/dL, often precipitated by events such as stress, fasting, and febrile illnesses. It is associated with no liver dysfunction and requires no therapy.

Conjugated hyperbilirubinemia almost always reflects either hepatocellular disease or biliary obstruction. These two conditions can be differentiated by the pattern of elevation of the liver enzymes. Elevation of serum AST and ALT levels are characteristic of hepatocellular disease as a result of the inflammation/ destruction of the hepatocytes and the release of these enzymes into the blood. The serum alkaline phosphatase level is elevated in cholestatic disease as a consequence of inflammation, destruction, or obstruction of the intrahepatic or extrahepatic bile ducts with relative sparing of the hepatocytes. The serum AST and ALT levels may be mildly elevated in cholestasis but usually not to the levels seen in primary acute hepatocellular disease. Other tests, such as serum albumin or PT, generally reflect the capacity of hepatocytes to synthesize proteins such as clotting factors. When they are abnormal, they most often reflect hepatocellular disease. Table 46-1 summarizes the liver test patterns seen in various categories of hepatobiliary disorders.

Table 46-1. Liver lab findings in hepatobiliary disorders

Type of disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin time
Hemolysis/Gilbert syndrome	Normal to 5 mg/dL 85% due to indirect fractions. No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated. Peak usually follows aminotransferases Bilirubinuria.	Elevated, often >500 IU/L; ALT >AST	Normal to <3 times normal elevation	Normal	Usually normal if >5 times above control and not corrected by vitamin K; suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated. Bilirubinuria.	Elevated, but usually <300 IU/L	Normal to <3 times normal elevation	Often decreased	Often prolonged; fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis (obstructive jaundice)	Both fractions may be elevated. Bilirubinuria	Normal to moderate elevation Rarely >500 IU/L	Elevated, often >4 times normal elevation	Normal, unless chronic	Normal; if prolonged, will correct with parenteral vitamin K
Infiltrative diseases (tumor, granulomata):	Usually normal	Normal to slight elevation	Elevated, often > 4 times normal	Normal	Normal

partial bile duct obstruction			elevation Fractionate, or confirm liver origin with 5'-nucleotidase or GGT		
-------------------------------	--	--	----------------------------------------------------------------------------	--	--

The patient discussed in this case has a pattern consistent with cholestasis, and the first diagnostic test in a patient with cholestasis usually is an ultrasound. It is noninvasive and is very sensitive for detecting stones in the gallbladder as well as intrahepatic or extrahepatic biliary ductal dilation. The most common cause of biliary obstruction in the United States is gallstones, which may become lodged in the common bile duct. However, obstructing stones causing jaundice usually are associated with epigastric or right upper quadrant colicky pain. Extrahepatic dilatation without evidence of stones warrants further study with CT or endoscopic retrograde cholangiopancreatography (ERCP) to detect occult stones or strictures, and exclude malignant causes of common bile duct and pancreatic duct obstruction including cholangiocarcinoma, pancreatic cancer, and ampullary cancer (ampulla of Vater).

Other possible causes include strictures, which can result from prior biliary surgery, prior inflammatory conditions such as pancreatitis (rarely), inflammatory diseases of the biliary tree, and infection in the setting of acquired immunodeficiency syndrome (AIDS). The two most important primary conditions are primary sclerosing cholangitis and primary biliary cirrhosis.

The complications of biliary obstruction include development of acute cholangitis as a result of ascending infection, or secondary hepatic cirrhosis, if the obstruction is chronic or recurrent. The patient in this case scenario has painless jaundice, liver enzymes consistent with a cholestatic process, and light-colored stools, suggesting obstruction of bile flow into the intestine. Because he has no history of abdominal or biliary surgery that might have caused a stricture, malignancy is the most likely cause of his biliary obstruction. The most common malignancy to present in this way is pancreatic cancer. The patient should undergo an imaging procedure of his abdomen, including a right upper quadrant ultrasound to evaluate the biliary tree, as well as a CT scan or magnetic resonance imaging (MRI) to visualize the pancreas. Endoscopic ultrasound with fine-needle aspiration is highly accurate in establishing a tissue diagnosis.

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Peak incidence is in the seventh decade of life, with two-thirds of cases occurring in persons older than 65 years. There is a slight male predominance and a higher incidence in the black population. The median survival is 9 months, with an overall 5-year survival rate of 3%. Clinically apparent metastatic disease is found in 80% of patients at the time of diagnosis. For patients without obvious metastases, the best hope for cure is surgical resection by pancreaticoduodenectomy (Whipple procedure), which in experienced hands has a perioperative mortality rate less than 5%. Even when the cancer is considered to be respectable, there is a high rate of recurrence, so many treatment programs include neoadjuvant chemotherapy. Alternate palliative therapy includes pancreatic and common bile duct stenting to relieve the obstruction.

Table 46-2. Comparison of primary sclerosing cholangitis and primary biliary cirrhosis

	Younger males	Older females
Disease	Primary sclerosing cholangitis	Primary biliary cirrhosis
Location of disease	Larger intra- and extrahepatic ducts	Smaller intrahepatic bile ducts
Associated conditions	Ulcerative colitis	Autoimmune diseases such as rheumatoid arthritis
Serologic markers	None	Antimitochondrial antibody (AMA)
Complications	Stricture; infection (cholangitis); cholangiocarcinoma	Cirrhosis

Comprehension questions

For the following questions (41.1 to 41.4) choose the one diagnosis (A-F) that best matches with the most likely clinical situation.

- A. Hemolysis
 - B. Alcoholic hepatitis
 - C. Gilbert disease
 - D. Pancreatic cancer
 - E. Gallstones
 - F. Primary sclerosing cholangitis
1. A 38-year-old man with a 12 pack of beer per day alcohol history presents with jaundice, ascites, and dark urine. His laboratory results are AST 350 U/mL, ALT 150 U/mL, alkaline phosphatase 120 U/mL, total bilirubin 25 mg/dL, direct bilirubin 12 mg/dL, and albumin 2.1 g/dL.
 2. A 40-year-old moderately obese woman presents with abdominal pain after eating and mild scleral icterus. Her laboratory results are AST 200 U/L, ALT 150 U/L, alkaline phosphatase 355 U/L, total bilirubin 3.5 mg/dL, direct bilirubin 1.8 mg/dL, and albumin 3.5
 3. A 25-year-old man presents with 3 days of scleral icterus but has been otherwise feeling well. His laboratory results are AST 45 U/L, ALT 48 U/L, alkaline phosphatase 100 U/L, total bilirubin 3.2 mg/dL, direct bilirubin 0.2 mg/dL, and albumin 3.5 g/dL . Complete blood count and lactate dehydrogenase (LDH) are normal.
 4. A 32-year-old man with a 5-year history of episodic bloody diarrhea and abdominal cramping pain presents with scleral icterus and fever. His laboratory results are AST 100 U/L, ALT 125 U/L, alkaline phosphatase 550 U/L, total bilirubin 5.5 mg/dL, direct bilirubin 3.0 mg/dL, and albumin 2.9 g/dL.

Answers

1. B. The patient's laboratory results show a conjugated hyperbilirubinemia with evidence of hepatocellular disease (hypoalbuminemia, ascites). The AST and ALT levels show the 2:1 ratio consistent with alcohol-related liver disease.
2. E. The patient's laboratory results show a conjugated hyperbilirubinemia consistent with an obstructive pattern. She has the risk factors for gallstones (middle age, female, obese) and has symptoms of postprandial abdominal pain.
3. C. The patient's laboratory results show an unconjugated hyperbilirubinemia without other abnormality. He is otherwise healthy without symptoms of systemic disease or hemolytic anemia. No treatment is necessary.
4. F. The patient's laboratory results show a conjugated hyperbilirubinemia with an obstructive pattern. The history is consistent with inflammatory bowel disease, which is associated with primary sclerosing cholangitis. The initial evaluation should include ultrasonography to rule out gallstones; if negative, ERCP could confirm the diagnosis by demonstrating multiple strictures of the extrahepatic bile ducts. Treatment options include stenting of the larger bile duct strictures and immunosuppression to slow the progression of the disease.

Clinical Pearls

- ▶ Unconjugated hyperbilirubinemia usually is caused by hemolysis or Gilbert syndrome.
- ▶ Conjugated hyperbilirubinemia is commonly caused by hepatocellular disease, with elevated aspartate aminotransferase and alanine levels, or biliary obstruction, with elevated alkaline phosphatase level.
 - ▶ An imaging procedure such as ultrasonography is the initial study of choice in a patient with cholestasis to evaluate for intrahepatic or extra- hepatic biliary obstruction.
 - ▶ The most common causes of biliary obstruction are gallstones, which are painful if obstructing, and strictures or neoplasms, which are often painless.
 - ▶ The prognosis for pancreatic cancer is very poor; the best hope for cure is resection by a pancreaticoduodenectomy (Whipple procedure).

ANSWERS TO CASE 47:

What is the most likely diagnosis?

Hypergammaglobulinemia indicates that this patient has autoimmune hepatitis (AIH). This

condition is most common in girls and young women. Patients with AIH often have other coexisting autoimmune disorders such as type 1 diabetes and Hashimoto's thyroiditis.

What is the next step in management?

The next step is to obtain anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-liver kidney muscle antibodies (ALKM). Also, perform liver biopsy to confirm the diagnosis.

- Elevated ANA and/or ASMA = type 1 AIH
- Elevated ALKM = type 2 AIH

ANA and ASMA levels are elevated. Liver biopsy confirms the diagnosis of AIH. There is no evidence of cirrhosis on biopsy.

How should you treat this patient with AIH?

Treatment is indicated for the following patients with AIH:

- Liver biopsy shows signs of cirrhosis.
- Aminotransferases > 500 U/L.
- Aminotransferases > 250 U/L plus gamma globulins twice upper limit of normal.
- All children.

First-line therapy for AIH is corticosteroids. If patients do not achieve clinical remission within 3 months, consider adding azathioprine.

- Acute hepatitis: ↑ Amino transaminases and positive labs (viral serology, SPEP, etc.) for <6 months.
- Acute liver failure: Acute hepatitis with encephalopathy (altered mental status) or coagulopathy (INR >1.5); treatment is urgent liver transplantation.
- Chronic hepatitis: ↑ Amino transaminases and (+) liver biopsy findings for >6 months.
- Cirrhosis: Chronic hepatitis that progresses to irreversible fibrosis and nodular regeneration; amino transaminases are often normal or only slightly elevated.

The patient is lost to follow-up. She returns to the clinic 3 years later with a chief complaint of increased fatigue over the last few months. On physical exam, the patient has yellow discoloration of the nail bed and sclera (jaundice). Liver edge is palpable 4 cm below the costal margin (hepatomegaly). There are erythematous nodules on the face and trunk. The nodules blanch on palpation and are surrounded by smaller blood vessels (spider nevi). Abdominal inspection reveals dilated blood vessels (caput medusae). AST is 100 U/L and ALT is 80 U/L; alkaline phosphatase is 100 U/L and serum bilirubin is 2.3 g/dL. Liver biopsy shows extensive fibrosis, nodularity, and bridging necrosis.

What is the next step in management?

The patient now has physical signs as well as histological evidence of cirrhosis (Table 47-1). Treatment is directed at controlling complications and treating the underlying cause of cirrhosis, which include (mnemonic: Alcohol and Viruses Begin A Really Horrible Disease Named Cirrhosis):

- Alcoholic liver disease (number one cause in the United States)
- Chronic Viral hepatitis (hepatitis C is the number two cause in the United States)
- Budd Chiari syndrome (hepatic vein thrombosis)
- AIH
- Right heart failure
- Hereditary (hemochromatosis, Wilson's disease, α -1 anti-trypsin deficiency)
- Drugs (examples are acetaminophen and methotrexate)
- Nonalcoholic steatohepatitis
- Cholestasis

When no underlying cause is detected, the disease is classified as cryptogenic cirrhosis.

Table 47–1 Symptoms and signs of cirrhosis

SYMPTOMS OF CIRRHOSIS

Constitutional symptoms (fatigue, weakness, anorexia, weight loss) and abdominal pain

SIGNS OF CIRRHOSIS

Skin

- Spider angioma (nevi): Central arteriole is surrounded by smaller vessels radiating outward and is located on the upper half of the body. The lesions are telangiectasias, so they blanch when compressed by a glass slide.
- Palmar erythema: Mottled redness on thenar and hypothenar areas.

- Caput medusae: Portal hypertension causes prominent abdominal wall veins.
- Jaundice

Nails

- Muerhcke nails: Horizontal white bands separated by normal color.
- Terry nails: Proximal two thirds of the nail bed is white and distal one third is normal color.

Fingers

- Clubbing: Angle between nail bed and proximal nail fold $>180^\circ$. Most common in primary biliary cirrhosis and other biliary causes of cirrhosis.
- Dupuytren's contracture: Thickening and contracture of palmar fascia causes flexion deformity in fingers.

Bones

- Hypertrophic osteoarthropathy: Pain and swelling in long bones.

Breast/genitals

- Gynecomastia
- Testicular atrophy

Abdomen

- Hepatomegaly: Liver edge palpated >3 cm below costal margin.
- Splenomegaly: A palpable spleen tip usually indicates splenomegaly.
- Epigastric murmur: Venous hum that increases with valsalva.

Feet

- Peripheral edema

Note: Palmar erythema, spider angiomata, gynecomastia, and testicular atrophy are caused by altered sex hormone metabolism. Muerhcke and Terry nails are caused by hypoalbuminemia.

Initial presentation of cirrhosis is usually one of the following:

- Nonspecific constitutional symptoms with characteristic physical findings
- Complication of cirrhosis
- Incidentally detected on laboratory/imaging tests in an asymptomatic patient

Diagnosis of cirrhosis requires one of the following:

- Abnormal physical exam signs, laboratory, and imaging findings
- Liver biopsy

MELD score (Model for End-stage Liver Disease): Predicts patient's likelihood of dying in the next 3 months using total bilirubin, INR, and creatinine.

Liver transplantation: Refer cirrhotic patients for liver transplant evaluation if they develop a complication of cirrhosis or have a MELD score >10 . Under the current system, the sickest patients (highest MELD score) receive the highest priority.

ANSWERS TO CASE 48:

A 49-year-old woman presents with new-onset abdominal swelling. Her history reveals a blood transfusion with postpartum hemorrhage and cocaine use. On examination, her temperature is 100.3°F , heart rate 88 bpm, and blood pressure 94/60 mm Hg. Her sclerae are icteric. Her abdomen is distended, with mild diffuse tenderness, shifting dullness to percussion, and a fluid wave, consistent with ascites. She has no peripheral edema. Laboratory studies show the following levels: Na 129 mmol/L, albumin 2.8 mg/dL, prothrombin time 15 seconds, hemoglobin 12 g/dL with MCV 102 fL, and platelet count $78,000/\text{mm}^3$.

> Most likely diagnosis: Ascites caused by portal hypertension as a complication of hepatic cirrhosis.

> Next step: Perform a paracentesis to evaluate the ascitic fluid to try to determine its likely etiology as well as evaluate for the complication of spontaneous bacterial peritonitis.

Considerations

This 49-year-old woman had been in good health until recently, when she noted increasing abdominal swelling and discomfort, indicative of ascites. The physical examination is consistent with ascites with the fluid wave and shifting dullness. Her icterus suggests liver disease as the etiology of the

ascites. Her laboratory studies are significant for hypoalbuminemia and coagulopathy (prolonged prothrombin time), indicating probable impaired hepatic synthetic function and advanced liver disease. She does have prior exposures, most notably a blood transfusion, which put her at risk for hepatitis viruses, especially hepatitis C. Currently, she also has a low-grade fever and mild abdominal tenderness, both signs of infection. Bacterial infection of the ascitic fluid must be considered, because untreated cases have a high mortality.

Although the large majority of patients with ascites and jaundice have cirrhosis, other etiologies of the ascites must be considered, including malignancy. Thus, paracentesis using a needle introduced through the skin into the peritoneal cavity can be used to assess for infection as well as to seek an etiology of the ascites.

APPROACH TO CHRONIC HEPATITIS

Definitions

ASCITES: Abnormal accumulation (>25 mL) of fluid within the peritoneal cavity.

CHRONIC HEPATITIS: Evidence of hepatic inflammation and necrosis for at least 6 months.

CIRRHOSIS: Histologic diagnosis reflecting irreversible chronic hepatic injury, which includes extensive fibrosis and formation of regenerative nodules.

PORTAL HYPERTENSION: Increased pressure gradient (>10 mm Hg) in the portal vein, usually resulting from resistance to portal flow and most commonly caused by cirrhosis.

SPONTANEOUS BACTERIAL PERITONITIS: Bacterial infection of ascitic fluid without any intra-abdominal source of infection. Occurs in 10% to 20% of cirrhotic patients with ascites.

CLINICAL APPROACH

Chronic hepatitis is diagnosed when patients have evidence of hepatic inflammation and necrosis (usually found by elevated transaminases) for at least 6 months. The most common causes of chronic hepatitis are viral infections, such as hepatitis B and C, alcohol use, chronic exposure to other drugs or toxins, and autoimmune hepatitis. Less common causes are inherited metabolic disorders, such as hemochromatosis, Wilson disease, or α_1 -antitrypsin deficiency. Table 48-1 lists the diagnostic markers for these disorders.

Table 48-1. Causes of chronic hepatitis

Cause	Test
Hepatitis C	Anti-HCV Ab, presence of HCV RNA
Hepatitis B	Persistent HBsAg, presence of HBeAg
Autoimmune	ANA, anti-LKM (liver kidney microsome)
Hemochromatosis	High transferrin saturation (>50%), high ferritin
Wilson disease	Low serum ceruloplasmin
α_1 -antitrypsin deficiency	Low A-antitrypsin enzyme activity

Abbreviations: ANA, antinuclear antibody; HBeAg, hepatitis B e antigen; HbsAg, hepatitis B surface antigen.

Hepatitis C infection is most commonly acquired through percutaneous exposure to blood. It also can be transmitted through exposure to other body fluids, although this method is less effective. Risk factors for acquisition of hepatitis C include intravenous drug use, sharing of straws to snort cocaine, hemodialysis, blood transfusion, tattooing, and piercing. In contrast to hepatitis B, sexual transmission is rare. Vertical transmission from mother to child is uncommon but occurs more often when the mother has high viral titers or is HIV positive.

Most patients diagnosed with hepatitis C are asymptomatic, and report no prior history of acute hepatitis. The clinician must have a high index of suspicion and offer screening to those individuals with risk factors for infection. To date, the best methods for detecting infection include the enzyme-linked immunosorbent assay (ELISA) test, which detects anti-HCV antibody (Ab), or the polymerase chain reaction (PCR) to detect HCV RNA. Approximately 70% to 80% of all patients infected with hepatitis C will develop chronic hepatitis in the 10 years following infection. Within 20 years, 20% of those will develop cirrhosis. Among those with cirrhosis, 1 % to 4 % annually may develop hepatocellular carcinoma. Therapy is directed toward reducing the viral load to prevent the sequelae of end-stage cirrhosis, liver failure, and hepatocellular carcinoma. Currently, the treatment of choice for chronic hepatitis C is combination therapy with pegylated alpha-interferon and ribavirin. Trials have demonstrated a sustained response (undetectable viral levels) in up to 75% to 80% of those with

favorable HCV genotypes (types 2 and 3). However, the therapy has many side effects, such as influenzalike symptoms and depression with interferon, and hemolysis with ribavirin. The goal of interferon therapy for hepatitis C is preventing the complications of chronic hepatitis.

Cirrhosis is the end result of chronic hepatocellular injury that leads to both fibrosis and nodular regeneration. With ongoing hepatocyte destruction and collagen deposition, the liver shrinks in size and becomes nodular and hard. Alcoholic cirrhosis is one of the most common forms of cirrhosis encountered in the United States. It is related to chronic alcohol use, but there appears to be some hereditary predisposition to the development of fibrosis, and the process is enhanced by concomitant infection with hepatitis C. Clinical symptoms are produced by the hepatic dysfunction as well as by portal hypertension, which is produced by increased resistance to portal blood flow, producing portal hypertension, and sometimes to resultant portosystemic shunting (Table 48-2). Loss of functioning hepatic mass leads to jaundice as well as impaired synthesis of albumin (leading to edema) and of clotting factors (leading to coagulopathy). Fibrosis and increased sinusoidal resistance lead to portal hypertension and its complications, such as esophageal varices, ascites, and hypersplenism. Portosystemic shunting via natural collaterals or iatrogenic shunts causes hepatic encephalopathy. Portal hypertension causes caput medusa and hemorrhoids. Decreased liver production of steroid hormone binding globulin (SHBG) leads to an increase in unbound estrogen manifested by spider angiomas, palmar erythema, and gynecomastia in men. Hepatic encephalopathy is characterized by mental status changes, asterix, and elevated ammonia levels.

Table 48-2. Complications of cirrhosis

Disorder	Diagnosis	Clinical Presentation	Treatment
Portal hypertension	Diagnosis is made by the appearance of the features described earlier, and evaluation of portal blood flow using Doppler ultrasonography	Clinical features are related to portal hypertension and its sequelae: ascites, splenomegaly, hypersplenism, encephalopathy, and bleeding varices	Nonselective beta-blockers such as propranolol lower portal pressure; during acute variceal hemorrhage, Sandostatin or octreotide causes splanchnic vasoconstriction
Ascites	Made by finding free peritoneal fluid on physical examination or on an imaging study	Abdominal distention, sometimes with peripheral edema	Sodium restriction, spironolactone; loop diuretics; large-volume paracentesis
Spontaneous bacterial peritonitis	Diagnosis can be made when the ascitic fluid contains > 250 polymorphonuclear neutrophils/mm ³ and confirmed with a positive culture; the most common organisms are <i>Escherichia coli</i> , <i>Klebsiella</i> , other enteric flora, enterococci, and pneumococci	Abdominal pain, distention, fever, decreased bowel sounds, or sometimes few abdominal symptoms but worsening encephalopathy	IV antibiotics, such as cefotaxime or ampicillin/sulbactam

The most common cause of ascites is portal hypertension as a consequence of cirrhosis. The pathogenesis involves a combination of decreased effective circulatory blood volume because of portal hypertension (underfill theory), inappropriate renal sodium retention leading to expansion of plasma volume (overfill theory), and decreased plasma oncotic pressure. When not caused by portal hypertension, ascites may be a result of exudative causes such as infection (eg, tuberculous peritonitis) or malignancy. The patient usually presents with abdominal swelling and demonstration of free fluid by physical examination or imaging procedures such as ultrasonography.

It is important to try to determine the cause of ascites in order to look for reversible causes and for serious causes, such as malignancy, and to guide therapy. Ascitic fluid is obtained by paracentesis and examined for protein, albumin, cell count with differential, and culture. The first step in trying to

determine the cause of ascites (Table 48-3) is to determine whether it is caused by portal hypertension or by an exudative process by calculating the serum-ascites albumin gradient (SAAG):

Table 48-3. Differential diagnosis of ascites based on SAAG

High gradient >1.1 g/dL: Portal hypertension	Low gradient <1.1 g/dL: Nonportal hypertension
Cirrhosis Portal vein thrombosis Budd-Chiari syndrome Congestive heart failure Constrictive pericarditis	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites Bowel obstruction or infarction Serositis, eg, as in lupus Nephrotic syndrome

*SAAG: *Serum-ascites albumin gradient* = *serum albumin* - *ascitic albumin*.

Serum-ascites albumin gradient = serum albumin - ascitic albumin.

The treatment of ascites usually consists of dietary sodium restriction coupled with diuretics. Loop diuretics are often combined with spironolactone to provide effective diuresis and to maintain normal potassium levels. Spontaneous bacterial peritonitis is a relatively common complication of ascites, thought to be caused by translocation of gut flora into the peritoneal fluid. Symptoms include fever and abdominal pain, but often there is paucity of signs and symptoms. Diagnosis is established by paracentesis and finding more than 250 polymorphonuclear neutrophils/mm³ or by a positive culture. Culture of ascitic fluid often fails to yield the organism. However, fluid cultures, when positive, usually reveal a single organism, most often gram-negative enteric flora but occasionally enterococci or pneumococci. This is in contrast to secondary peritonitis, for example, as a consequence of intestinal perforation, which usually is polymicrobial. Empiric therapy includes coverage for gram-positive cocci and gram-negative rods, such as intravenous ampicillin and gentamicin, or a third-generation cephalosporin or a quinolone antibiotic.

Comprehension questions

For the following questions choose the one cause (A-G) that is probably responsible for the patient's presentation:

- A. Wilson disease
 - B. Hemochromatosis
 - C. Primary biliary cirrhosis
 - D. Sclerosing cholangitis
 - E. Autoimmune hepatitis
 - F. Alcohol-induced hepatitis
 - G. Viral hepatitis
1. A 15-year-old adolescent female with elevated liver enzymes and a positive antinuclear antibody (ANA)
 2. A 56-year-old man with brittle diabetes, tan skin, and a family history of cirrhosis
 3. A 35-year-old man with ulcerative colitis
 4. A 56-year-old woman who presented with complaints of pruritus and fatigue
 5. A 32-year-old man with Kayser-Fleischer rings, dysarthria, and spasticity

Answers

1. E. Idiopathic or autoimmune hepatitis is a less-well-understood cause of hepatitis that seems to be caused by autoimmune cell-mediated damage to hepatocytes. A subgroup of these patients includes young women with positive ANAs and hypergammaglobulinemia who may have other symptoms and signs of systemic lupus erythematosus.
2. B. Hemochromatosis is a genetic disorder of iron metabolism. Progressive iron overload leads to organ destruction. Diabetes mellitus, cirrhosis of the liver, hypogonadotropic hypogonadism, arthropathy, and cardiomyopathy are among the more common end-stage developments. Skin deposition of iron leads to "bronzing" of the skin, which could be mistaken for a tan. Diagnosis is made early in the course of disease by demonstrating elevated iron stores but can be made through liver biopsy with iron stains. Genetic testing is available. Therapy involves phlebotomy to remove excess iron stores.
3. D. Sclerosing cholangitis is an autoimmune destruction of both the intrahepatic and extrahepatic

bile ducts and often is associated with inflammatory bowel disease, most commonly ulcerative colitis. Patients present with jaundice or symptoms of biliary obstruction; cholangiography reveals the characteristic beading of the bile ducts.

4. C. Primary biliary cirrhosis is thought to be an autoimmune disease leading to destruction of small- to medium-size bile ducts. Most patients are women between the ages of 35 and 60 years, who usually present with symptoms of pruritus and fatigue. An alkaline phosphatase level elevated two to five times above the baseline in an otherwise asymptomatic patient should raise suspicion for the disease. No specific therapy is available.

5. A. Wilson disease is an inherited disorder of copper metabolism. The inability to excrete excess copper leads to deposition of the mineral in the liver, brain, and other organs. Patients can present with fulminant hepatitis, acute nonfulminant hepatitis, or cirrhosis, or with bizarre behavioral changes as a result of neurologic damage. Kayser-Fleischer rings develop when copper is released from the liver and deposits in Descemet membrane of the cornea.

Clinical Pearls

▶ The most common causes of cirrhosis are alcohol use, hepatitis B and C, and autoimmune disorders.

▶ Hepatitis C is most commonly contracted through blood exposure and rarely through sexual contact. Most patients are asymptomatic until they develop complications of chronic liver disease.

▶ A serum ascites albumin gradient more than 1.1 g/dL suggests that ascites is caused by portal hypertension, as occurs in cirrhosis.

▶ Treatment of cirrhotic ascites requires sodium restriction and, usually, diuretics, such as spironolactone and furosemide.

▶ Spontaneous bacterial peritonitis is infection of the ascitic fluid characterized by more than 250 polymorphonuclear cells/mm³, sometimes with a positive monomicrobial culture.

ANSWERS TO CASE 49:

What features help you to diagnose chronic versus acute liver disease in this patient?

In this patient, there are no pathognomonic features of chronic liver disease, but several that suggest this condition. Large spider angiomas are common in the setting of chronic liver disease, but not acute liver disease, although small, nonpalpable spider angiomas may be present. Muscle wasting is common in moderately advanced chronic liver disease, but is not due to poor eating habits. Muscle wasting is not a feature of acute liver disease unless it is the result of a concomitant, unrelated problem. A palpable, firm left lobe of the liver (that portion palpable caudad to the xiphoid process) is usually a manifestation of chronic liver disease. It is always important to palpate and percuss for the liver in the midline, as well as in the midclavicular line. Ascites, due to portal hypertension, is much more a feature of chronic liver disease than of any other disorder. Ascites may occur in the setting of severe acute liver disease, but it is usually not of significant quantity to warrant treatment. One notable exception is the Budd-Chiari syndrome, in which there may be ascites, although the abdominal distention in this syndrome is partially due to a congested and enlarged liver stemming from the hepatic vein occlusion. Shifting dullness is indicative of a large amount (>1.0 to 1.5 L) of ascites.

Pancytopenia is related to the splenic sequestration of blood cells and is not a prominent feature of liver disease unless the spleen is affected; when it is, it is usually enlarged. The degree of pancytopenia (or of individual cytopenias) may not correlate with spleen size. Hepatitis C may be associated with the development of aplastic anemia, but this is rare. Transient cytopenias may be seen in hepatitis, as in other viral infections. A low serum albumin level may be seen in any form of liver disease that has lasted for more than several weeks. A high serum globulin (total protein-albumin) level is a feature of chronic liver disease regardless of the cause. Extremely high serum globulin levels (i.e., >10 g/dL) should suggest the possibility of autoimmune or lupoid hepatitis; this disorder is usually seen in women and is frequently accompanied by other autoimmune features, such as thyroiditis. Autoimmune hepatitis is important to recognize because it can usually be treated with corticosteroids.

Does any particular factor help you determine the cause of this man's liver disease?

There are no particular factors that point to the cause of this patient's liver disease. The major differential diagnoses here are alcoholic liver disease and chronic active hepatitis (hepatitis C from his

blood transfusion), probably in the cirrhotic stage. No feature of his history, physical examination, or routine laboratory tests helps distinguish between these two causes.

What reversible factors could be contributing to this man's presumed PSE?

Benzodiazepines, other sedative or hypnotic drugs, and opiates may precipitate PSE in a patient with severely impaired hepatic function. Constipation may also precipitate PSE in susceptible patients because of the colonic absorption of nitrogenous products. Both these reversible risk factors are present in this patient. Other reversible factors contributing to an episode of PSE include electrolyte disturbances, notably hypokalemia and metabolic alkalosis; increased intestinal absorption of nitrogenous products, resulting from relatively excessive dietary protein intake or an upper gastrointestinal (GI) hemorrhage; and a serious infection of any nature. In patients with chronic liver disease who have acute PSE, culture of the body fluids ascitic fluid, blood, urine, and sputum should be done. This patient's PSE indicates that he has severe liver disease.

When, if ever, should this man's ascites be sampled? If it should, how and where should it be sampled?

Diagnostic paracentesis should be performed as soon as possible to determine whether the patient has subacute bacterial peritonitis. This form of infectious peritonitis is a frequent cause of clinical deterioration in patients with chronic liver disease, and may be fatal if not recognized and treated early.

The three safest locations for paracentesis are the left lower quadrant, right lower quadrant, and the infraumbilical midline area. A supraumbilical approach should never be used because the umbilical or paraumbilical vessels, which course just under the parietal peritoneum, are frequently recanalized in patients with portal hypertension whose portal vein is patent. It is also important to always stay clear of (medial or lateral to) the rectus muscles because the superficial epigastric vessels course under them and may be punctured. Skin puncture through or near an abdominal scar in a patient with suspected or known portal hypertension should always be avoided.

What are three possible explanations for the occult blood in his stool?

Three possible explanations are (a) portal hypertensive gastropathy or enteropathy, (b) rectal varices, and (c) esophageal variceal hemorrhage due to portal hypertension. Variceal bleeding is usually a sudden event of large volume, although uncommonly varices ooze.

What is the serum/ascites albumin gradient, and of what value is it?

The serum/ascites albumin gradient is the numeric difference (not ratio) between the serum albumin concentration and the ascites albumin concentration. When the gradient is 1.1 or greater, portal hypertension is contributing to or entirely causing the ascites. When the gradient is less than 1.1, peritoneal carcinomatosis or inflammatory diseases are likely causes of the ascites. On the basis of this man's history, the two main causes to be considered are portal hypertension and peritoneal malignancy. Determination of the serum/ascites albumin difference is a simple, minimally invasive, and fairly accurate way to diagnose portal hypertension.

Would you start diuretic therapy now? Why or why not?

No. Diuretics are not essential now, and they may only worsen the PSE and increase the risk of hepatorenal syndrome.

Why are his testes small?

In the setting of hepatic disease, the production of estrone from circulating androstenedione may be increased. The exact cause of this conversion is unknown but may be related to the decreased clearance of androstenedione by the liver. The consumption of excessive amounts of ethanol may also have contributed to the testicular atrophy in this patient.

Why are his parotid glands enlarged?

Parotid enlargement is seen in people who ingest excessive amounts of ethanol, and is associated with fatty infiltration of the glands. A similar situation may be seen in diabetic patients.

Is this man at increased risk for hepatocellular carcinoma?

Yes. There is a risk for the development of hepatocellular carcinoma in the setting of any form of cirrhotic liver, which this man most likely has. Certain conditions are associated with higher risks than others. Those associated with highest risk are genetic hemochromatosis, chronic hepatitis B, chronic hepatitis C, and alcoholic liver disease.

How would you exclude hepatocellular carcinoma?

Useful tests for identifying hepatocellular carcinoma are an imaging test [ultrasonography or computed tomography (CT) or magnetic resonance imaging] and a serum O₆-fetoprotein level. The

preferred imaging test (to exclude a focal lesion) depends on the expertise of the institution. Arterial-phase CT is regarded as most reliable. Hepatocellular carcinomas are especially difficult to detect in cirrhotic livers; therefore it is important that arterial-phase CT be used in this setting. The serum α -fetoprotein level is very high in 60% of patients with alcoholic liver disease who have a superimposed hepatocellular carcinoma and in approximately 80% to 90% of patients with chronic hepatitis B who have this complication.

What is included in your differential diagnosis of this man's chronic liver disease?

The differential diagnosis in this patient includes alcoholic liver disease and chronic active hepatitis with cirrhosis, due to either hepatitis B or C, although hepatitis should be regarded as the more likely diagnosis. The hepatitis viruses may have been transmitted to him by the blood he received many years ago, or they may have been sporadically acquired.

Why is hepatitis A not in your differential diagnosis?

Hepatitis A has never been reported to cause chronic liver disease.

Do the findings from the additional tests on the ascitic fluid support the diagnosis of portal hypertension-associated ascites? Why or why not?

Yes, the findings from the tests on the ascitic fluid do support the diagnosis of portal hypertension-associated ascites because the serum/ascites albumin gradient (2.6) exceeds 1.1. There are two caveats to remember when using the serum/ascites albumin gradient in the diagnosis of ascites. First, if massive hepatic metastases cause enough liver disease to result in portal hypertension and ascites, the gradient resembles that seen in portal hypertension. Second, in ascites of mixed etiology (e.g., portal hypertension plus tuberculous peritonitis), the gradient usually resembles that seen in the setting of portal hypertension.

With these data in mind, what treatment would you offer this patient now, and why?

Hospital admission is required. Strict bed rest (for fear of self-harm) seems prudent. No benzodiazepines should be administered, although the patient should be monitored for the signs of ethanol withdrawal agitation, tachycardia, fever, and hallucinosis. The patient should receive an enema if he is constipated. Lactulose should also be administered (by mouth or nasogastric tube) if the patient becomes too disoriented and uncooperative. The oral or nasogastric lactulose dose is variable; the goal of therapy is to produce two to three soft stools per day. Alternatively, a nonabsorbable antibiotic could be used, such as neomycin at a dosage of 500 to 1,000 mg given orally or by nasogastric tube every 6 hours, or rifaximin. There is no evidence that giving lactulose and an antibiotic together is more effective than administering either alone. Lactulose is probably beneficial in the treatment of PSE by virtue of its ability to decrease the amount of nitrogen available for absorption (as urea) from the colon. Lactulose may accomplish this by altering the colonic flora to more urease-negative forms and by inducing an osmotic diarrhea.

What areas of the patient's history should you examine at greater length, and why?

One area of the patient's history that should be examined at greater length is his ethanol consumption history. This involves more interviewing of his family and friends. The alleged amount of ethanol ingested (per the patient's wife) is too low to cause liver disease in men because the alcohol content of two cans of beer is approximately 12 g. However, the parotid gland enlargement and testicular atrophy are findings that suggest his ethanol ingestion has been more than he has admitted. The amount and duration of alcohol ingestion necessary to cause chronic liver disease is highly variable among individuals, although the incidence of biopsy-proved cirrhosis, alcoholic hepatitis, or both, increases as consumption is increased. It is usually believed that the threshold amount of alcohol consumption that leads to these serious forms of chronic liver disease is in the order of 100 to 150 g per day for several years in men, but less in women. However, a large proportion of heavy drinkers do not contract serious liver diseases. It is advisable to record alcohol consumption in terms of grams per day times the number of years of consumption. A quart of 80 proof whiskey contains approximately 300 g of ethanol, a six-pack of 4% beer approximately 75 g, and 750 mL of wine approximately 90 g (150 g for fortified wine).

A second area of inquiry should be the patient's family history. In this patient, you should also ask whether anyone in the family has had liver disease, including genetic hemochromatosis. You might phrase the question in this way: Do you have any family members who have conditions that require blood to be removed as treatment? The manifestations of hemochromatosis may differ in various family members, and may consist of cardiomyopathy, diabetes, arthritis, or pituitary insufficiency. In this patient, the small liver is inconsistent with a diagnosis of hemochromatosis, although all else is.

Moreover, he is an older man the typical age and sex of patients who have severe chronic liver disease caused by hemochromatosis.

Would you offer this patient a liver biopsy and, if so, when?

A liver biopsy would be of no help in the initial management of his decompensated liver disease. However, when conclusive documentation of the diagnosis would help determine management, liver biopsy might be important. This might be the case in a patient with suspected Budd-Chiari syndrome because it is often treatable by hepatic decompression (as, e.g., with a side-to-side portacaval anastomosis), or it might be the case in a patient with hemochromatosis. Once the patient's condition has stabilized, a liver biopsy might be offered, for three reasons. First, he may be a candidate for specific therapy. However, it is unlikely that there is any therapy for this patient. If, as seems likely, he has alcoholic cirrhosis there is no effective treatment other than abstinence; if he has hepatitis C/related cirrhosis, interferon treatment may be dangerous because of the hepatocytolysis brought about by therapy. Second, some authorities believe that liver biopsy is indicated in patients with suspected alcoholic liver disease because confirmation of that diagnosis might help persuade the patient to abstain from further ethanol ingestion. Third, if the patient becomes a candidate for hepatic transplantation, most centers require a definitive preoperative diagnosis before going ahead with the procedure.

Discussion

What are some specific causes of chronic liver disease?

Chronic liver disease may be the sequela of several kinds of toxic, metabolic, infectious, immunologic, or hereditary conditions. Table 49-2 contains a partial list.

Table 49-2. Specific causes of chronic liver disease

<ul style="list-style-type: none"> • Drugs and chemicals <ul style="list-style-type: none"> ○ Acetaminophen ○ Alcohol^a ○ Amiodarone ○ Arsenic and inorganic salts ○ Isoniazid ○ Nitrofurantoin ○ Propylthiouracil ○ Vinyl chloride • Viral hepatitis <ul style="list-style-type: none"> ○ Hepatitis B and Ca ○ Cytomegalovirus hepatitis • Granulomatous infections <ul style="list-style-type: none"> ○ Bacterial (tuberculosis), spirochetal (secondary syphilis), mycotic^a ○ Drugs and foreign substances ○ Other sources ○ Sarcoidosis 	<ul style="list-style-type: none"> • Primary biliary cirrhosis • Immunity disorders • Complications of ulcerative colitis and Crohn's disease [primary biliary cirrhosis and small-duct primary sclerosing cholangitis (perichoangitis)]^a <ul style="list-style-type: none"> ○ Primary biliary cirrhosis ○ Autoimmune chronic hepatitis • Inherited diseases <ul style="list-style-type: none"> ○ Wilson's disease^a ○ Hemochromatosis ○ Inborn errors of metabolism (glycogen storage disease and Gaucher's disease) <p>○±1-Antitrypsin deficiency</p>
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

^aMost frequently encountered.

What are the principal laboratory abnormalities in the setting of chronic liver disease?

The clinically available liver function tests include those that assess, at least in part, liver synthetic function (serum albumin and bilirubin concentrations, and prothrombin time) and those that mostly evaluate the hepatocellular release of enzymes (aminotransferases and alkaline phosphatase). Often, the levels of aminotransferase [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase] are not markedly elevated in patients with chronic liver disease, and consequently do not accurately predict prognosis. The serum albumin and bilirubin concentrations and the prothrombin time are more likely to be distinctly abnormal, and more accurately reflect the true status of the liver's functional capacity.

What are the two major histologic categories of chronic hepatitis due to viral infection?

Categories of these diseases, constructed by international committees, consist of three components: the etiology of the diseases, grading of disease activity (i.e., the severity of the necroinflammatory

process), and staging of the disease (i.e., the degree of fibrosis subsequent to necroinflammatory insults). The grading and staging are usually given a semiquantitative score (0 to 4) or a descriptive characterization (e.g., minimal to severe inflammation, or no fibrosis to cirrhosis).

ANSWERS TO CASE 50:

What is the most likely cause of this patient's abdominal swelling?

Flank dullness that shifts with rotation indicates excessive serous (watery) fluid build-up in the peritoneum (ascites). Cirrhosis is the most common cause of ascites and ascites is the most common complication of cirrhosis.

Shifting fluid wave: Have an assistant press hands firmly down the midline of the abdomen. Then tap one flank sharply with fingertips. An easily palpable impulse at the other flank suggests ascites. This test is neither sensitive nor specific.

What causes ascites in patients with cirrhosis?

The major mechanism of ascites in patients with cirrhosis is the peripheral vasodilation theory, which incorporates the earlier “under-fill” and “overflow” theories (Fig. 50-1). Other contributing causes of ascites are decreased oncotic pressure (due to decreased liver production of albumin and clotting factors) and increased hepatic lymph production.

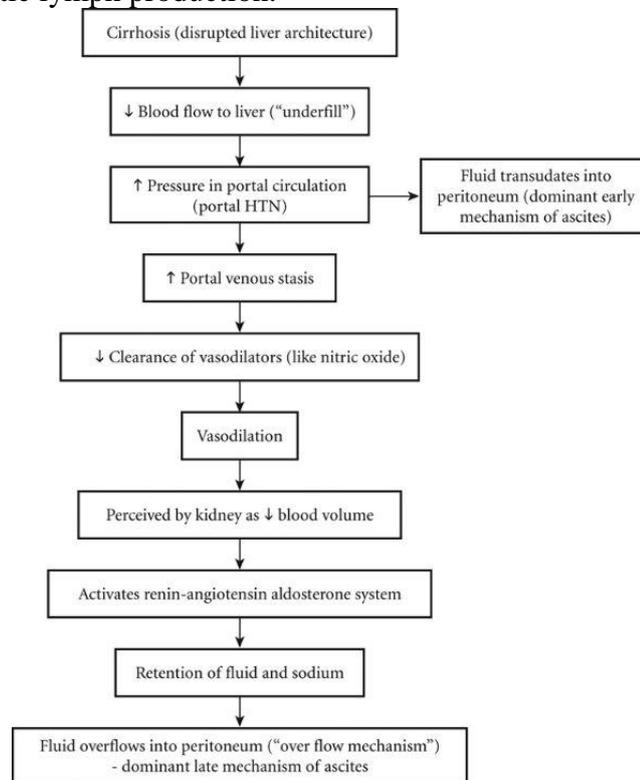


Figure 50–1. Peripheral vasodilation theory of ascites in patients with cirrhosis.

What is the next step in management?

Perform abdominal ultrasound to confirm the presence of ascites. Ultrasound detects as little as 30 mL of ascitic fluid (whereas flank dullness usually requires 1500 mL of fluid).

Ultrasound confirms the presence of ascites. What is the next step in management?

Perform diagnostic paracentesis in all patients with newly diagnosed ascites. Order peritoneal fluid cell count and differential, total protein and albumin, and bacterial culture. The goals of these initial tests are:

- To determine if the cause is due to portal hypertension.
- To determine if the peritoneal fluid is infected.
- Paracentesis: withdrawal of peritoneal fluid using a needle and syringe.
- Therapeutic paracentesis: large volume ascites can cause early satiety, umbilical hernia (tense ascites), and dyspnea (due to impingement on the diaphragm). In such patients, withdraw a large volume of fluid (therapeutic paracentesis) to improve symptoms.

The ascitic fluid contains 380 leukocytes/ μ L. 50% of the leukocytes are polymorphonuclear

neutrophils (PMNs). Ascitic fluid albumin is 1.8 g/dL, and ascitic fluid total protein (AFTP) is 0.8 g/dL. Culture results are pending.

What do these values tell you regarding the cause of ascites and the presence or absence of ascitic fluid infection?

- Cause: Calculate serum-ascites albumin gradient (SAAG = serum albumin minus ascitic fluid albumin). This patient's SAAG is >1.1, which indicates that the mechanism of ascites is portal hypertension. AFTP is <2.5 g/dL, which indicates that the cause of portal hypertension is cirrhosis (Table 50-1).
- Infection: Leukocyte count <500/μL with <250 PMNs/μL indicates that this patient does not have peritoneal inflammation or infection.

Table 50–1. Major causes of ascites

SAAG < 1.1 g/dL (indicates portal hypertension)
1. Cirrhosis: AFTP < 2.5 g/dL (responsible for >80% of ascites)
2. Right heart failure: Suspect when neck veins are distended and AFTP >2.5 g/dL HCC or liver metastases
SAAG > 1.1 g/dL (indicates ascites unrelated to portal hypertension)
1. TB peritonitis and peritonitis due to bowel perforation
2. Hypoalbuminemia (nephrotic syndrome, Menetrier's disease)
3. Abdominal or ovarian cancer (suspect if ↑ AFTP and enlarged supraclavicular or umbilical lymph node)
4. Pancreatitis (associated with ↑ peritoneal fluid amylase)
5. Hemodialysis (nephrogenic ascites)

Abbreviations: AFTP, ascitic fluid total protein; HCC, hepatocellular carcinoma; SAAG, serum-ascite albumin gradient (SAAG = serum albumin – ascitic fluid albumin); TB, tuberculosis.

What is the initial management of ascites due to cirrhosis?

- Treat the underlying cause of cirrhosis; this patient should abstain from alcohol.
- Restrict dietary sodium to <2 g/day.
- Initiate spironolactone and loop diuretics.

Patients with ascites should avoid nonsteroidal anti-inflammatory steroids (NSAIDs) because these agents cause sodium retention.

The patient abstains from alcohol and restricts sodium intake. He initiates spiro lactone and furosemide. The ascites resolves. Two months later, he has an episode of tense ascites that is treated with therapeutic paracentesis. Over the next 6 months, he continues to have ascites despite maximal diuretic dosage.

What is the next step in management?

Perform a 24-hour urine collection and measure urine sodium. Urine sodium >78 mEq indicates noncompliance with dietary sodium restrictions. Urine sodium <78 mEq indicates true diuretic-resistant ascites. Treat diuretic-resistant ascites with repeated, large-volume paracentesis or TIPS. Without liver transplant, mortality is very high in cirrhotic patients with diuretic-resistant ascites.

Measure cell count and differential of peritoneal fluid to exclude peritoneal fluid infection in patients with recurrent ascites.

The patient's 24-hour urine sodium is 150 mEq. After careful counseling, he restricts sodium intake and his ascites improves. Three months later, he has a recurrent episode of tense ascites. Temperature is 38.6°C. Leukocyte count of peritoneal fluid is 780/μL with 60% PMNs.

What is the next step in management?

Leukocyte count >500/μL indicates peritoneal inflammation (peritonitis), and PMN >250/μL indicates bacterial infection of the peritoneal fluid. The next step in management is to order peritoneal fluid protein, glucose, lactate dehydrogenase (LDH), and bacterial culture as well as culture of blood and urine. These tests help distinguish between spontaneous bacterial peritonitis (SBP) and secondary bacterial peritonitis (Table 50-2). Then initiate empiric antibiotic therapy for SBP with cefotaxime or another third-generation cephalosporin.

Table 50–2 Spontaneous bacterial peritonitis versus secondary bacterial peritonitis

	Spontaneous bacterial peritonitis	Secondary bacterial peritonitis
Cause	Primary bacterial infection of	Secondary bacterial infection of ascitic fluid due to

	ascitic fluid	bowel perforation or intra-abdominal abscess
AFTP	<1 g/dL	<1 g/dL
Glucose	<50 mg/dL	<50 mg/dL
LDH	<225 U/L	<255 U/L
Culture	One organism	Multiple organisms
Treatment	Antibiotics	Antibiotics + surgery

Abbreviation: LDH, lactate dehydrogenase.

Although a tender abdomen is the hallmark of peritonitis, patients with ascites often do not report this classic finding.

Patients with alcoholic cirrhosis often have low-grade fever, abdominal pain, and peritoneal fluid leukocyte count $>500/\mu\text{L}$ but PMNs are not $>250/\mu\text{L}$ unless the patient has bacterial peritonitis.

Suspect bacterial peritonitis in any patient with ascites due to cirrhosis who has fever, abdominal pain, or sudden, unexplained altered mental status.

Peritoneal fluid glucose is 80 mg/dL, AFTP is 0.8 g/dL, and LDH is 80 U/L. Culture of peritoneal fluid grows *Escherichia coli*.

What are the next steps in management?

The patient has SBP. The next step is to tailor antibiotic therapy. Also administer IV albumin on day 3 (may improve survival). Patients who have had one or more episodes of SBP should take an oral quinolone or trimethoprim/sulfamethopyrazine after recovery to prevent further episodes.

Organisms responsible for SBP:

- Gram-negative rods (70%): *E. coli* is the number one organism and *Klebsiella* is number two organism overall.

- Gram-positive cocci (30%): *Streptococcus pneumoniae* is the number three organism overall.

The patient follows up in clinic 5 days after discharge. He has been unable to urinate for the last 3 days. He has not taken NSAIDs or any other nephrotoxic drugs recently. Blood pressure is 95/65. Baseline creatinine in the hospital was 1.3 mg/dL. Current creatinine is 4 mg/dL. Urine sodium is 8 mEq/L. Analysis of urine sediment does not indicate any specific cause. He receives 2 L of normal saline, but blood pressure does not increase.

What is the most likely cause of his symptoms?

Suspect hepatorenal syndrome when a patient with end-stage liver disease develops acute renal failure (rapidly rising creatinine over days or weeks) that does not respond to volume repletion. A recent infection like SBP is often the precipitating cause. Urine sodium is <10 mEq and kidney parenchyma is normal because this is a prerenal cause of acute renal failure. To make this diagnosis, you must first rule out other causes of acute renal failure.

How is hepatorenal syndrome treated?

Prognosis is dismal without liver transplantation. If the patient is a candidate for liver transplant, treat with hemodialysis. If the patient is not a liver transplant candidate, consider midodrine and octreotide (not very effective, but commonly used because currently there is little else to offer in this situation).

ANSWERS TO CASE 51:

What is the most likely finding on endoscopy?

The most likely finding in this patient with cirrhosis is bleeding varices. Varices are dilated, tortuous blood vessels that develop in the esophagus or stomach as a result of portal hypertension. The most common causes of portal hypertension in the United States are alcoholic liver disease and chronic active hepatitis.

EGD detects an actively bleeding esophageal varix. What is the next step?

Banding and sclerotherapy are the two endoscopic hemostatic procedures commonly used to treat upper gastrointestinal bleeding due to varices. Most endoscopists prefer sclerotherapy for patients with active bleeding because it is quicker than banding in this situation. Banding is preferred when variceal bleeding has stopped by the time diagnostic endoscopy is performed because risk of rebleeding and other complications are lower.

The patient continues to bleed copiously despite octreotide and endoscopic sclerotherapy of the bleeding varix. What are the next steps in management?

Repeat endoscopy and attempt hemostasis with sclerotherapy, banding, or thermocoagulation. If this is unsuccessful, perform balloon tamponade followed by a transjugular intrahepatic portosystemic shunt (TIPS) procedure. If an experienced interventional radiologist is not available to perform TIPS, refer the patient for emergent surgery.

TIPS: A stent is used to artificially connect the portal and hepatic veins, which decreases portal venous pressure.

Balloon tamponade: An inflated balloon exerts pressure on the bleeding varices, which controls bleeding. Associated with numerous complications, so this is used only as a temporizing measure before TIPS or surgery; always intubate before tamponade.

Bleeding gastric varices: Endoscopic hemostasis is not recommended (high failure rate). Treat with octreotide and balloon tamponade followed by TIPS or surgery.

ANSWERS TO CASE 52:

What are the causes of mildly elevated amino transaminases (AST and ALT <250 U/L)?

Amino transaminases (AST and ALT) are markers of hepatocellular injury. Causes of mildly elevated amino transaminases are listed in (Table 52-1). Approximately 4% of asymptomatic patients with mildly elevated amino transaminases do not have any underlying abnormality (false-positive). A list of laboratory abnormalities in patients with liver disease follows:

- LFTs: Includes amino transaminases (AST and ALT), GGT, alkaline phosphatase, total bilirubin, serum albumin, and prothrombin time (PT).

- Amino transaminases: Markers of hepatocellular injury; ALT is more specific for liver injury but AST is more sensitive. The extent of elevation does not correlate with prognosis.

- Alkaline phosphatase: Marker of cholestasis (extrahepatic or intrahepatic bile duct obstruction). Damage to other organs such as bone, muscle, and heart can also elevate alkaline phosphatase.

- GGT: ↑ in GGT correlates with ↑ in alkaline phosphatase. GGT is specific to the liver, so ↑ GGT confirms that the source of ↑ alkaline phosphatase is the liver and not other organs.

- Bilirubin: Both hepatocellular injury and bile duct obstruction can elevate serum bilirubin, so this test does not help distinguish between the two diagnoses. When serum bilirubin is >2 mg/dL, patients become jaundiced (yellow discoloration of skin, mucous membranes, and sclera).

- Serum albumin: The liver produces albumin. Chronic liver disease leads to decreased albumin production and subsequent hypoalbuminemia.

- PT: The liver produces clotting factors. Liver dysfunction can lead to prolonged PT within hours. Vitamin K does not correct the PT.

- ↑ Amino transaminases > ↑ alkaline phosphatase indicates hepatocellular injury.

- ↑ Alkaline phosphatase > ↑ amino transaminases indicates bile duct obstruction.

- Alcoholic liver disease: Suspect when AST/ALT ratio >2 and GGT >90 U/L. Transaminases are usually <500 U/L.

- Wilson's disease: Suspect when AST/ALT ratio >2.

- Amino transaminases > 1000 U/L: Indicates acute viral hepatitis, medication-induced liver injury, or shock-induced liver injury.

- Other possible laboratory abnormalities in patients with liver disease:

- Hyponatremia in patients with ascites

- Complete blood count (CBC): Patients with advanced liver disease may have anemia, thrombocytopenia, leukopenia, neutropenia. Patients with alcoholic liver disease may have increased mean red cell volume.

Table 52–1. Causes of mildly elevated amino transaminases in adults

Common hepatocellular causes	1. Alcoholic liver disease 2. Chronic hepatitis B and C infection 3. Nonalcoholic steatohepatitis (NASH) 4. Hereditary hemochromatosis
-------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------

Uncommon hepatocellular causes	<ol style="list-style-type: none"> 1. Autoimmune hepatitis 2. Wilson's disease 3. α-1-antitrypsin deficiency
Nonhepatic causes	<ol style="list-style-type: none"> 1. Medications or herbal supplements 2. Strenuous exercise 3. Hypothyroidism or hyperthyroidism 4. Celiac sprue 5. Hemolysis 6. Adrenal insufficiency

What is the next step in management of this asymptomatic patient with elevated amino transaminases?

No specific clues regarding the underlying cause are evident on history and physical exam, so the next step is to screen for common hepatocellular causes. Order the following tests at this time:

- Hepatitis B and C serologies: The initial test for chronic hepatitis B infection is hepatitis B surface antigen (HBsAg). The initial test for hepatitis C is hepatitis C antibody.
- Hemochromatosis screening: Order serum ferritin and transferrin saturation (serum iron/total iron binding capacity).
- Serum albumin and PT to screen for chronic liver disease (see the list of laboratory abnormalities above).

Viral hepatitis serologies, iron studies, serum albumin, and PT are normal.

What is the next step in management?

Consider a period of alcohol abstinence and weight loss. Recheck serum amino transaminases in 3 to 6 months or sooner if the patient develops symptoms. If amino transaminases are still elevated, obtain right upper quadrant (RUQ) ultrasound to evaluate for nonalcoholic steatohepatitis.

The patient quits alcohol and loses 10 lbs with diet and exercise. Six months later, AST is 200 and ALT is 210 U/L. The patient is still asymptomatic. RUQ ultrasound is unrevealing.

What is the next step in management?

At this stage, order the following tests to screen for nonhepatic as well as uncommon hepatocellular causes of elevated amino transaminases:

- Serum creatine kinase or aldolase to screen for muscle injury.
- Thyroid function tests to screen for thyroid disorders.
- Antiendomysial and antitissue transglutaminase to screen for celiac sprue.
- Serum protein electrophoresis (SPEP) to screen for autoimmune hepatitis (AIH).
- Serum ceruloplasmin to screen for Wilson's disease if patient is <40 years old.
- α -1 Antitrypsin phenotype.

If these tests are all unrevealing, perform liver biopsy.

In asymptomatic patients, close observation rather than liver biopsy is sufficient if these tests are all negative and amino transaminases are elevated less than two-fold.

ANSWERS TO CASE 53:

What is the most likely diagnosis?

Aminotransferase values >1000 U/L indicate medication-induced liver injury, acute viral hepatitis, or shock (ischemic hepatitis). This patient has not recently taken any medications and does not have any signs of shock, so the most likely cause is acute viral hepatitis.

Serum IgM anti-hepatitis A virus (HAV) is positive; hepatitis B serologies and hepatitis C antibodies are negative.

What is the diagnosis?

The patient has hepatitis A virus (HAV) infection. HAV spreads via the fecal–oral route and is commonly acquired by consuming contaminated food and water. This condition is infrequent in the United States, but it is common in many developing countries such as Mexico. Patients typically develop symptoms within 15 to 30 days of exposure.

- Serum IgM HAV: Positive as soon as symptoms begin and usually disappears in 3 to 6 months. Sometimes, serum IgM can stay positive for a prolonged period, so positive IgM HAV does not always indicate acute infection.

- Serum IgG HAV: Appears after a month of illness and persists for decades.

What treatment is recommended?

Treatment is supportive because the illness is usually acute and self-limited. Patients do not progress to chronic hepatitis or cirrhosis.

Hepatitis E virus (HEV): Rare in the United States, so a diagnostic test (IgM HEV) is not routinely available. Spread via the fecal-oral route. Infection is acute and self-limiting except in pregnant women (10% to 20% mortality from acute liver failure).

The patient lives with his wife and stepmother. None of them have been vaccinated against HAV.

Is any therapy recommended to prevent HAV in close personal contacts?

Administer a single dose of HAV immunoglobulin (passive prophylaxis) as well as HAV vaccine (active prophylaxis) to close household and sexual contacts.

Consider HAV immunoglobulin but not HAV vaccine for persons who have had infrequent contact with the patient. Administer immunoglobulin no later than 2 weeks after the last known exposure.

Postexposure prophylaxis is not necessary for people who have received at least one dose of HAV vaccine at least 1 month prior to exposure.

ANSWERS TO CASE 54:

What is the most likely cause of cirrhosis?

Skin hyperpigmentation, diabetes, and cirrhosis are the classic triad of hereditary hemochromatosis (“bronze diabetes”). This autosomal recessive condition is caused by a mutation in the HFE gene that leads to increased intestinal iron absorption. Clinical manifestations are caused by excessive iron deposition in liver (leads to cirrhosis), skin (leads to skin hyperpigmentation), pancreas (leads to diabetes), heart (leads to dilated cardiomyopathy), joints (leads to arthritis), and other organs.

What diagnostic tests are indicated?

Obtain serum iron, total iron binding capacity, and serum ferritin. If serum iron/TIBC (transferrin saturation) is >0.45 and serum ferritin is elevated, perform genetic testing and liver biopsy to confirm the diagnosis.

First-degree relatives of hereditary hemochromatosis patients are usually screened with iron studies and genetic testing. As a result, 75% of patients are asymptomatic at diagnosis.

How is hereditary hemochromatosis treated?

Both symptomatic and asymptomatic patients should undergo repeated phlebotomy (blood removal) to remove excess iron.

ANSWERS TO CASE 55:

What is the diagnosis?

The patient with a family history of liver disease, $AST > ALT$, and decreased ceruloplasmin (<20 mg/dL) most probably has Wilson's disease. Patients with this autosomal recessive condition have defective biliary excretion of copper. Clinical manifestations result from deposition of excess copper in the liver, brain, eyes, and other organs.

- Liver: Clinical findings range from asymptomatic increase in amino transaminases to acute liver failure to cirrhosis.

- Brain: Clinical findings range from asymptomatic to psychiatric abnormalities to Parkinsonian symptoms (due to basal ganglia deposits).

- Eye: Copper deposits form a golden-brown band near the limbus (Kayser-Fleischer ring).

What are the next diagnostic steps?

Perform a slit-lamp examination (to detect Kayser-Fleischer rings) and measure 24-hour urinary copper excretion (increased in Wilson's disease). Perform liver biopsy if diagnostic tests are inconclusive.

In practice, the diagnosis of Wilson's disease is challenging because ceruloplasmin levels are often normal and Kayser-Fleischer rings are often absent.

How is Wilson's disease treated?

First-line therapy is lifelong copper chelation using penicillamine or trientine. Add zinc to the regimen if the patient does not respond adequately to first-line agents. Zinc can also be used as monotherapy for patients who cannot tolerate first-line medications.

Screen all first-degree relatives with liver function tests (LFTs) and serum ceruloplasmin.

ANSWERS TO CASE 56:

What is the most likely cause of his symptoms?

The patient most likely has hepatic encephalopathy, which can present with a spectrum of neurological and psychiatric abnormalities in patients with advanced liver disease. Symptoms can range from subclinical to severe cognitive impairment and coma. Onset can be acute (precipitated by infection or electrolyte/metabolic abnormality) or gradual. Sleep derangements (insomnia or hypersomnia) are a common early feature. As encephalopathy worsens, patients develop signs such as fetor hepaticus, asterixis, and hypo- or hyperactive reflexes.

What causes hepatic encephalopathy in patients with cirrhosis?

Decreased metabolic function of the liver leads to numerous metabolic derangements that contribute to development of this complication. Decreased metabolism of ammonia is the most clearly defined abnormality.

What is the next step in management?

The characteristic signs, symptoms, and laboratory evidence of decreased hepatic synthetic function (decreased albumin, increased PT) are sufficient to establish the diagnosis of hepatic encephalopathy. CT scan of the head is only indicated if the diagnosis is in question.

How is hepatic encephalopathy treated?

- First-line therapy: Administer lactulose and correct any underlying infections, hypovolemia, electrolyte, or metabolic abnormalities (in this case, hypokalemia).
- Second-line therapy: If mental status does not improve within 48 hours, consider ornithine-aspartate (increases hepatic ammonia metabolism) or sodium benzoate (increases ammonia excretion).
- Chronic therapy: After the acute episode of HE resolves, continue lactulose.

Neomycin and other antibiotics are commonly used as second-line agents for hepatic encephalopathy, but evidence for their effectiveness is lacking.

Lactulose: Gut flora metabolize lactulose (a disaccharide) to short-chain fatty acids. Short-chain fatty acids reduce colon pH. Lower colon pH prevents ammonium metabolism to ammonia, which leads to trapping of ammonium in the gut.

ANSWERS TO CASE 57:

This man has abnormal liver function tests which indicate hepatic failure; the hypoproteinaemia has caused the ascites and ankle swelling. The number of spider naevi is more than the accepted normal of three. The cause is likely to be alcohol as it is a common cause of this problem, he is at increased risk through his work in the catering business. His symptoms of morning nausea and vomiting are typical, and this would account for his cushingoid appearance (alcohol increases adrenocorticotrophic hormone (ACTH) secretion) and the macrocytosis on the blood film (due to dietary folate deficiency and a direct toxic action on the bone marrow by alcohol). However his alcohol intake is too low to be consistent with the diagnosis of alcoholic liver disease. When the provisional diagnosis is discussed with him though, he eventually admits that his alcohol intake has been at least 40-50 units per week for the last 20 years and has increased further during the last year after his marriage had ended, the reason for this being his drinking.

The slight reductions in the sodium and urea reflect a chronic reduced intake of salt and protein; the rise in bilirubin is insufficient to cause jaundice.

Further investigations are the measurement of hepatitis viral serology, which was negative, and an ultrasound of the abdomen. This showed a slight reduction in liver size, and an increase in splenic length of 2-3 cm. There was no evidence of a hepatoma. These findings indicate that portal hypertension has developed. A liver biopsy, performed to confirm the diagnosis, assess the degree of histological damage and exclude other pathology, showed changes of cirrhosis.

The crucial aim in management is to impress upon the patient the necessity to stop drinking

alcohol, in view of the degree of liver damage, the presumed portal hypertension and the risk of oesophageal varices and bleeding, and to effect this by his attending an alcohol addiction unit. In the short term he should also improve his diet to increase his protein intake. Diuretics could be used to reduce his oedema, but it should be remembered that they could cause postural hypotension more easily against this background.

His attendance at the addiction unit was fitful, he continued to drink heavily and he died 1 years later as a result of a second bleed from oesophageal varices.

Clinical pearls

- > Patients who drink excessive amounts of alcohol will often disguise this fact in their history.
- > Alcoholic liver disease has a poor prognosis if the alcohol intake is not terminated.