15

I have a patient with edema. How do I determine the cause?

CHIEF COMPLAINT

PATIENT 1

Mrs. V is 62-year-old woman with leg edema for the past 2 weeks.

What is the differential diagnosis of edema? How would you frame the differential?

CONSTRUCTING A DIFFERENTIAL DIAGNOSIS

Edema is defined as an increase in the interstitial fluid volume and is generally not clinically apparent until the interstitial volume has increased by at least 2.5–3 L. It is useful to review some background pathophysiology before discussing the differential diagnosis:

A. Distribution of total body water

1. 67% intracellular; 33% extracellular

2. Extracellular water: 25% intravascular; 75% interstitial

B. Regulation of fluid distribution between the intravascular and interstitial spaces

1. There is constant exchange of water and solutes at the arteriolar end of the capillaries

2. Fluid is returned from the interstitial space to the intravascular space at the venous end of the capillaries and via the lymphatics.

3. Movement of fluid from the intravascular space to the interstitium occurs through several mechanisms

a. Capillary hydrostatic (hydraulic) pressure pushes fluid out of the vessels

b. Interstitial oncotic pressure pulls fluid into the interstitium

c. Capillary permeability allows fluid to escape into the interstitium

4. Movement of fluid from the interstitium to the intravascular space occurs when opposite pressures predominate

a. Intravascular (plasma) oncotic pressure from plasma proteins pulls fluid into the vascular space

b. Interstitial hydrostatic pressure pushes fluid out of the interstitium

5. In skeletal muscle, the capillary hydrostatic pressure and the intravascular oncotic pressure are the most important.

6. There is normally a small gradient favoring filtration out of the vascular space into the interstitium; the excess fluid is removed via the lymphatic system.

C. Edema formation occurs when there is

1. An increase in capillary hydrostatic pressure (for example, increased plasma volume due to renal sodium retention)

2. An increase in capillary permeability (for example, burns, angioedema)

3. An increase in interstitial oncotic pressure (for example, myxedema)

4. A decrease in plasma oncotic pressure (for example, hypoalbuminemia)

5. Lymphatic obstruction

Although it is possible to construct a pathophysiologic framework (Figure 15–1) for the differential diagnosis of edema, it is more useful clinically to combine anatomic, pathophysiologic, and organ/system frameworks:

A. Generalized edema due to a systemic cause and manifested by bilateral leg edema, with or without presacral edema, ascites, pleural effusion, pulmonary edema, periorbital edema

1. Cardiovascular

a. Systolic or diastolic dysfunction, or both

b. Constrictive pericarditis

c. Pulmonary hypertension

2. Hepatic (cirrhosis)

3. Renal

a. Advanced renal failure of any cause

b. Nephrotic syndrome

4. Anemia

The most common systemic causes of edema are cardiac, renal, and hepatic diseases as well as anemia.

5. Nutritional deficiency

6. Medications

a. Antidepressants: Monoamine oxidase inhibitors

b. Antihypertensives

(1) Calcium channel blockers, especially dihydropyridines

(2) Direct vasodilators (hydralazine, minoxidil)

(3) β-Blockers

c. Hormones

(1) Estrogens/progesterones

(2) Testosterone

(3) Corticosteroids

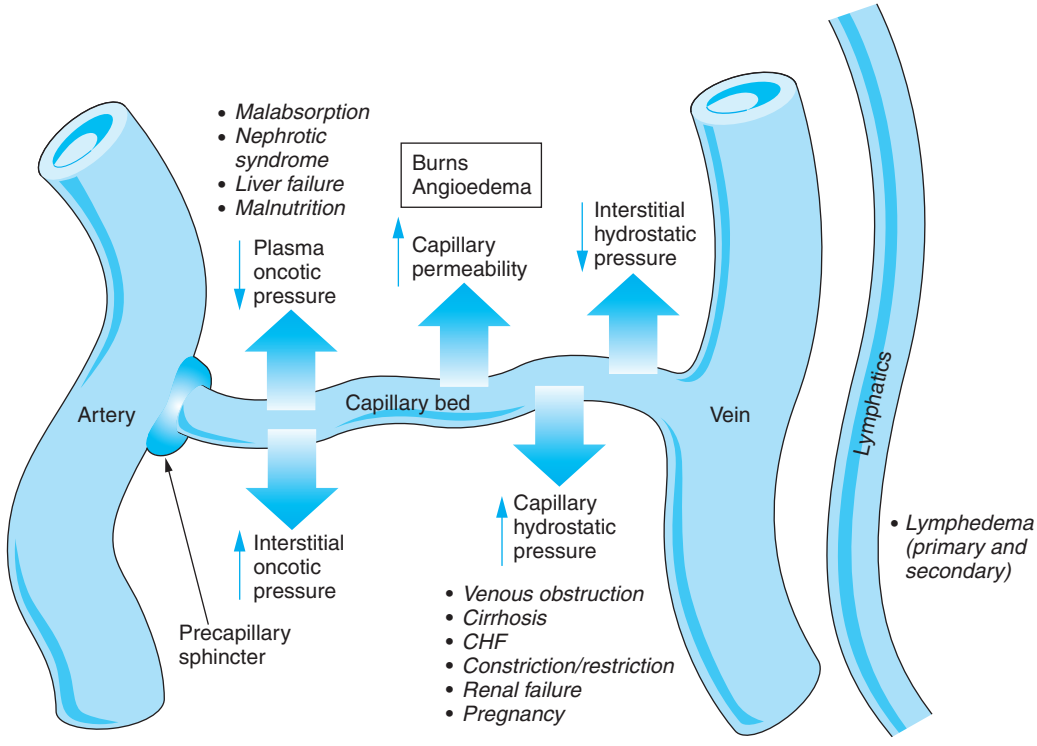


Figure 15–1. Pathophysiology of edema. (Adapted with permission from Cho S et al. Peripheral edema. Am J Med. 2002;V113:581. Copyright © 2002 *Excerpta Medica,* Inc.)

d. Nonselective nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors

e. Rosiglitazone, pioglitazone

8. Refeeding edema

9. Myxedema

B. Limb edema due to a venous or lymphatic cause, manifested by unilateral or bilateral edema

1. Venous disease

a. Obstruction

(1) Deep venous thrombosis (DVT) (see Chapter 14, Dyspnea for a full discussion of lower extremity DVT)

(2) Lymphadenopathy

(3) Pelvic mass

b. Insufficiency

2. Lymphatic obstruction (lymphedema)

a. Primary (idiopathic, often bilateral)

(1) Congenital

(2) Lymphedema praecox (onset in puberty) or tarda (onset after age 20)

b. Secondary (more common, generally unilateral)

(1) Neoplasm

(2) Surgery (especially, following mastectomy)

(3) Radiation therapy

(4) Miscellaneous (tuberculosis, recurrent lymphangitis, filariasis)

C. Localized edema

1. Burns

2. Angioedema, hives

3. Trauma

4. Cellulitis, erysipelas

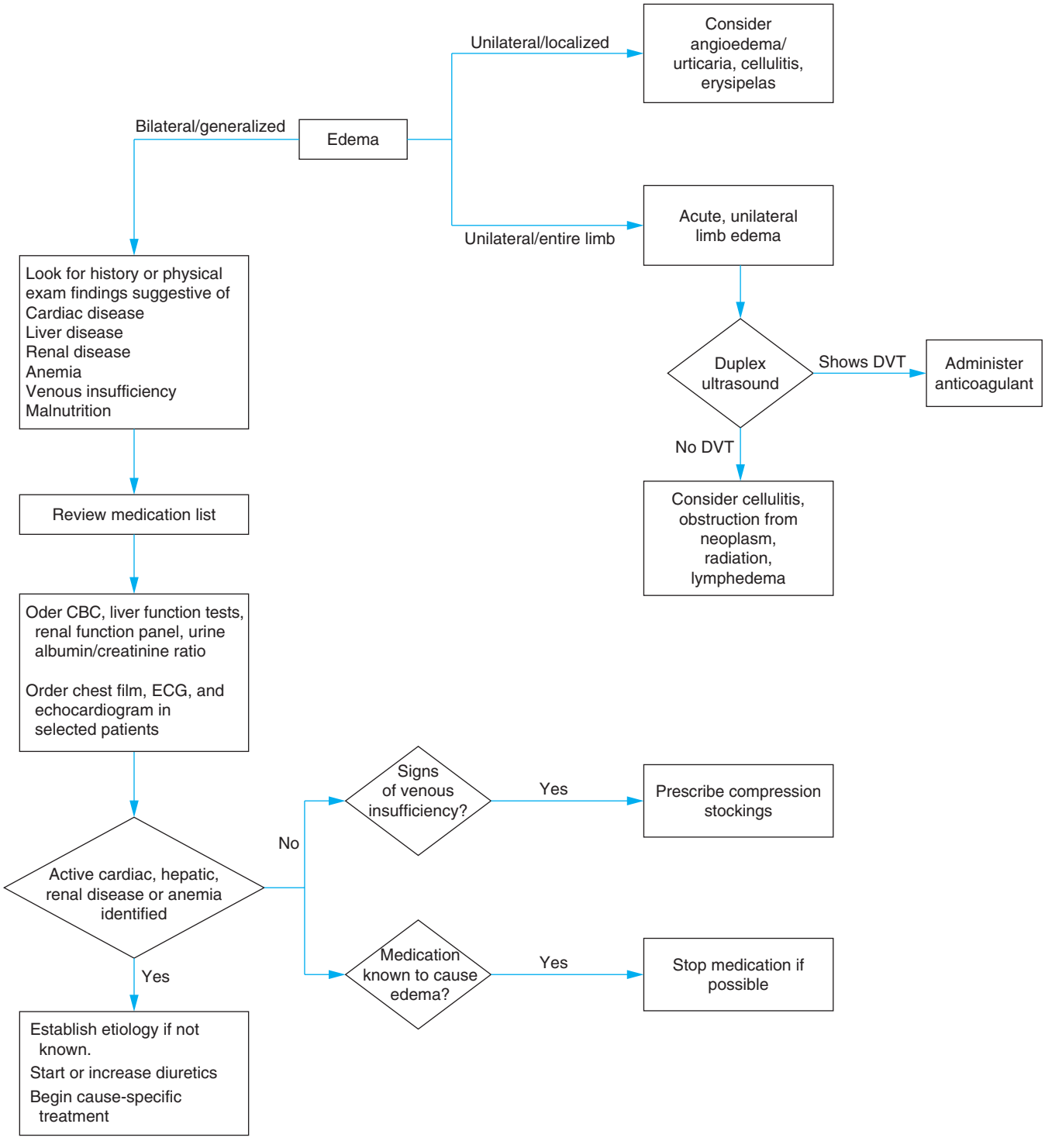
Figure 15–2 outlines the diagnostic approach to edema.

1

Mrs. V was well until a couple of months ago when she began feeling a bit more tired than usual, despite continuing to sleep well. She has had no shortness of breath or chest pain. She has noted intermittent vague abdominal pain, not related to eating, position, or bowel movements. She has been a bit constipated and feels bloated. Over the last 2 weeks, she has noted swelling in her feet and lower legs and has not been able to wear her regular shoes. As she tells you this, you note that she is wearing house slippers, and that her socks have produced a significant indentation above her ankles.

Her past medical history is notable for hypertension and diabetes, both well controlled. She had a blood transfusion during a cholecystectomy 25 years ago. Her current medications include hydrochlorothiazide, lisinopril, rosiglitazone, simvastatin, and aspirin. She has no history of heart or kidney disease, or tobacco or alcohol use.

At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?



DVT, deep venous thrombosis.

Figure 15–2. Diagnostic approach: edema.

PRIORITIZING THE DIFFERENTIAL DIAGNOSIS

Even before examining Mrs. V, you can see that she has significant bilateral leg edema, a pivotal point in her presentation. Although there are some local diseases that can present with bilateral leg edema, the first step in such patients is always to look for systemic causes. While the history and physical are often not sensitive or specific enough to make a diagnosis, they are a good starting point for organizing the differential. So the first question to ask is, "Does Mrs. V have any signs or symptoms pointing to a cardiac, hepatic, or renal cause of her edema?" The answers to this question would be additional pivotal points. Mrs. V's history of a blood transfusion puts her at risk for chronic hepatitis and cirrhosis, and her vague abdominal complaints raise the possibility of ascites, more commonly seen with cirrhosis than heart failure (HF) or renal failure. She is certainly at risk for both cardiac and renal disease because of her history of hypertension and diabetes. While most patients with heart failure complain of shortness of breath, some describe only fatigue. Medication should be considered as a cause, since rosiglitazone frequently causes edema; hypothyroidism does not cause pitting edema, and so is not likely. Finally, although it is uncommon for obstruction to cause bilateral edema, you should think about ovarian cancer causing malignant ascites and venous obstruction, either via extrinsic compression or due to associated DVT formation. Table 15–1 lists the differential diagnosis.

Table 15–1. Diagnostic hypotheses for Mrs. V

Diagnostic Hypotheses	Clinical Clues	Important Tests
Leading Hypothesis		
Cirrhosis	Hepatitis risk factors Ascites Spider angiomata Gynecomastia Normal or low JVP Splenomegaly	Ultrasound Bilirubin Liver enzymes Prothrombin time Albumin Liver biopsy
Active Alternatives—Must Not Miss		
Heart failure	Cardiovascular risk factors Dyspnea Elevated JVP Crackles S_3	ECG Chest radiograph Echocardiogram
Renal disease (insufficiency or nephrotic syndrome)	Malaise Nausea Dyspnea Edema	BUN/creatinine Urinalysis Albumin/creatinine ratio
Active Alternatives—Most Common		
Medication	History	History
Other Hypotheses		
Ovarian cancer	Abdominal pain or bloating Increased abdominal girth Family history	Transvaginal ultrasound CA-125

JVP, jugular venous pressure.

Always look for systemic causes of edema in patients with bilateral leg edema.

In general, Mrs. V appears fatigued. Her BP is 100/60 mm Hg, pulse is 92 bpm, and RR is 16 breaths per minute. Sclera are anicteric, jugular venous pressure is normal, and lungs are clear. On cardiac exam, she has a normal S_1 and S_2, a soft S_4, and no S_3 or murmurs. Her abdomen is slightly distended, but soft and nontender; there is a fluid wave. Her liver is not enlarged, but the spleen is palpable. Rectal exam shows hemorrhoids and guaiac-negative stool. She has 2+ edema bilaterally.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Cirrhosis

Textbook Presentation

Patients with cirrhosis can be asymptomatic or have mild symptoms, such as fatigue. Some patients have the classic manifestations of portal hypertension: ascites, edema, variceal bleeding, encephalopathy, or hypersplenism.

Disease Highlights

A. Etiology

1. Most common causes

- **a.** Alcohol
- **b.** Chronic hepatitis B or C
- **c.** Nonalcoholic fatty liver disease (NAFLD)
- **d.** Hemochromatosis
- **e.** Primary or secondary biliary cirrhosis

2. Less common causes

- **a.** Drugs and toxins (isoniazid, methotrexate, amiodarone)
- **b.** Autoimmune hepatitis
- **c.** Genetic metabolic diseases (Wilson, α_1-antitrypsin deficiency, glycogen storage diseases, porphyria)
- **d.** Infections (schistosomiasis, echinococcosis, brucellosis)
- **e.** Cardiac

The 2 most common causes of cirrhosis in the United States are alcoholic liver disease and chronic hepatitis C.

B. Pathophysiology

1. Advanced fibrosis, or cirrhosis, causes architectural distortion of the hepatic vasculature, leading to shunting of the blood coming into the liver via the portal vein directly to the hepatic vein outflow system, which causes

- **a.** Impaired hepatocyte function due to loss of normal sinusoids

b. Increased intrahepatic resistance, or portal hypertension

c. Increased risk of hepatocellular carcinoma due to increased regenerative activity

2. Consequences of cirrhosis and portal hypertension include

a. Formation of portosystemic collaterals (ie, varices)

b. Splanchnic vasodilation

c. Renal vasoconstriction and hypoperfusion of the kidneys, causing salt and water retention

d. Increased cardiac output

e. Decreased production of albumin and clotting factors

f. Increased capillary hydrostatic pressure resulting in ascites; hypoalbuminemia and salt and water retention also contribute to ascites formation

C. Prognosis

1. Risk factors for developing cirrhosis in patients with hepatitis C include age over 50, regular alcohol consumption, and male sex; for those with NAFLD, risk factors include older age, obesity, insulin resistance, hypertension, and hyperlipidemia.

2. Decompensation rates are 4%/year for hepatitis C cirrhosis and 10%/year for hepatitis B; patients with alcoholic cirrhosis who continue to drink decompensate rapidly.

3. 5-year mortality approaches 85% after decompensation if transplantation is not performed.

4. The Childs-Pugh-Turcotte classification of cirrhosis severity predicts prognosis (see Chapter 17, GI Bleeding).

Evidence-Based Diagnosis

A. Cirrhosis is a pathologic diagnosis definitively made only by examining the entire liver at autopsy or after liver transplantation.

B. The traditional gold standard is percutaneous liver biopsy, although due to sampling error, the sensitivity has been reported to be as low as 70–80%.

C. The clinical presentation is variable, making clinical diagnosis difficult.

1. Patients may have physical findings suggestive of chronic liver disease (see below), constitutional symptoms, asymptomatic liver enzyme or radiologic abnormalities, manifestations of portal hypertension (see below), or no symptoms at all. Cirrhosis is sometimes diagnosed at autopsy in patients in whom the disease never manifested.

2. Physical findings associated with chronic liver disease include

a. Spider angiomata

b. Palmar erythema

c. Dupuytren contracture (alcoholic cirrhosis only)

d. Gynecomastia

e. Testicular atrophy

f. Jaundice

g. Ascites

h. Peripheral edema

i. Hepatomegaly

j. Splenomegaly

k. Caput medusae

l. None of these are sensitive or specific enough to diagnose cirrhosis, although multiple findings in combination do increase the pretest probability of cirrhosis.

3. Patients who show manifestations of portal hypertension (see below) are assumed to have cirrhosis.

D. Several noninvasive models and techniques have been developed to predict cirrhosis *in patients with chronic hepatitis C*, although they are not currently used in place of biopsy.

1. Ultrasound-based elastography, which measures mean hepatic stiffness (sensitivity 87%, specificity 91% for cirrhosis; sensitivity 70% and specificity 84% for advanced fibrosis)

2. AST (SGOT) to platelet ratio index (APRI)

a. $$\frac{(\text{AST level/Upper limit of normal AST}) \times 100}{\text{platelet count}}$$

b. For APRI > 0.5, the sensitivity is 81% and specificity 50% for significant fibrosis

c. For APRI > 1, the sensitivity is 76% and specificity 71% for cirrhosis

3. Fibrotest is a commercial product that combines the results of several assays into a predictive score.

a. It has a sensitivity of 75% and specificity of 85% for significant fibrosis.

b. It is 95% accurate in identifying patients with minimal or no fibrosis.

E. Test characteristics of ultrasound to diagnose cirrhosis are variable (LR+, 2.5–11.6; LR–, 0.13–0.73).

F. MRI has sensitivity and specificity as high as 93% and 82%, respectively.

Treatment

The treatment of cirrhosis depends on the underlying cause. Treatments for selected causes of cirrhosis are discussed in Chapter 22, Jaundice and Abnormal Liver Enzymes.

Manifestations of Portal Hypertension

Once it has been determined that the patient probably or definitively has cirrhosis, it is important to determine the specific cause of the cirrhosis (see Chapter 22, Jaundice and Abnormal Liver Enzymes) and to determine whether the patient has manifestations of portal hypertension: variceal bleeding, ascites and its complications, hepatic encephalopathy, and hypersplenism.

1. Variceal Bleeding

See Chapter 17, GI Bleeding.

2. Ascites

Textbook Presentation

The patient complains of an inability to fasten her pants due to increasing abdominal girth, sometimes accompanied by dyspnea and edema.

Disease Highlights

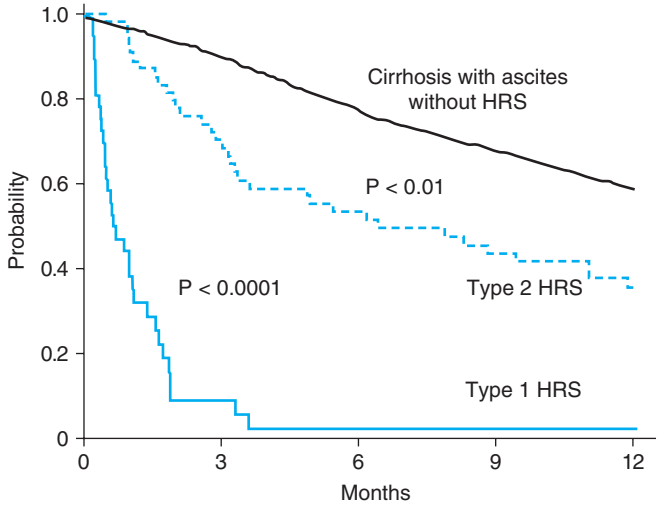
A. Epidemiology

1. Ascites develops over 5 years in 30% of patients with compensated cirrhosis, defined as the absence of manifestations of portal hypertension.

2. 1-year survival rates drop significantly once ascites develops.

B. Complications of ascites

1. Respiratory compromise due to compression of lung volumes
2. Hepatorenal syndrome (HRS)
   a. Diagnostic criteria
      (1) Cirrhosis with ascites
      (2) Serum creatinine > 1.5 mg/dL
      (3) Serum creatinine stays above 1.5 mg/dL after at least 2 days of diuretic withdrawal and volume expansion with albumin
      (4) Absence of shock
      (5) No current or recent treatment with nephrotoxic drugs
      (6) Absence of parenchymal kidney disease (< 500 mg/day of proteinuria, < 50 RBC/hpf, abnormalities on renal ultrasound)
   b. Clinical syndromes
      (1) Acute renal failure (type 1 HRS): serum creatinine doubles or increases to > 2.5 mg/dL in less than 2 weeks
      (2) Refractory ascites (type 2 HRS): serum creatinine 1.25–2.5 mg/dL with a steady or slowly progressive course
   c. Incidence in patients with cirrhosis and ascites is 18% at 1 year and 39% at 5 years
   d. The prognosis is poor (Figure 15–3)
   e. Precipitants of type 1 HRS include bacterial infections (especially spontaneous bacterial peritonitis), GI bleeding, alcoholic hepatitis, overdiuresis, and large volume paracentesis.



Salerno: Gut, Volume 56(9). September 2007.1310–1318

Figure 15–3. Survival in hepatorenal syndrome. (Reproduced, with permission, from Salerno F et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007 Sep; 56(9):1310–18.)

   f. HRS is due to peripheral vasodilation which causes decreased systemic vascular resistance, resulting in renal arteriolar vasoconstriction, decreased renal blood flow, and a reduced glomerular filtration rate (GFR).
   g. Treatment of HRS
      (1) Liver transplantation is the definitive treatment for both types of HRS.
      (2) There are limited data regarding the use of transvenous intrahepatic portosystemic shunts (TIPS) and vasopressin derivatives to treat type 1 HRS.
      (3) The treatment of refractory ascites will be discussed below.
3. Spontaneous bacterial peritonitis (SBP)
   a. Prevalence of 10–30% in hospitalized cirrhotic patients, with 1-year recurrence rate of 70% and mortality rate of about 20%; 96% of patients with SBP have a Childs-Pugh-Turcotte grade of B or C
   b. Overgrowth of intestinal bacterial and increased intestinal permeability lead to movement of bacteria into mesenteric lymph nodes; the bacteria can then enter the systemic circulation and colonize the ascitic fluid.
   c. The 3 most common isolates are *Escherichia coli, Klebsiella pneumoniae,* and pneumococci.
   d. Symptoms include fever (50–75% of patients), abdominal pain (27–72%), chills (16–29%), nausea/vomiting (8–21%), mental status changes (up to 50%), and decreased renal function (33%); about 13% of patients are asymptomatic.
   e. Risk factors for SBP include ascitic fluid total protein level ≤ 1 g/dL, upper GI bleeding, prior episode of SBP
   f. Diagnosis of SBP
      (1) Criteria for performing a diagnostic paracentesis in patients with cirrhosis and ascites:
         (a) Admission to the hospital
         (b) Change in clinical status (fever, abdominal pain, mental status changes, ileus, septic shock)
         (c) Development of leukocytosis, acidosis, or renal failure
         (d) Active GI bleeding
      (2) Always inoculate blood culture tubes at the bedside to maximize yield of ascitic fluid cultures.
      (3) Interpretation of ascitic fluid cell counts and cultures (Table 15–2)

Consider secondary peritonitis if more than 1 organism is cultured from the ascitic fluid.

      (4) Other ascitic fluid findings that increase the likelihood of SBP included WBC count > 1000 cells/mcL (LR+ = 9.1), pH < 7.35 (LR+ = 9.0), and blood-ascitic fluid pH gradient ≥ 0.1 (LR+ = 11)
   g. Treatment of SBP
      (1) Empiric treatment should be started prior to return of culture results
      (2) IV cefotaxime is the best-studied antibiotic for SBP; amoxicillin-clavulanic acid has also been studied.

Table 15–2. Interpretation of ascitic fluid results.

Condition	Polymorphonuclear Count (cells/mcL)	Culture Results
Spontaneous bacterial peritonitis	≥ 250	Single organism
Culture-negative neutrophilic ascites	≥ 250	Negative
Monomicrobial nonneutrocytic bacterascites	< 250	Single organism
Secondary bacterial peritonitis	≥ 250	Polymicrobial
Polymicrobial bacterascites	< 250	Polymicrobial

(3) Intravenous albumin has been shown to reduce mortality and development of renal impairment.

(4) All patients who recover from SBP should receive secondary prophylaxis with oral norfloxacin.

(5) Since 2-year survival after SBP is only about 30%, liver transplantation should be considered in patients who recover from SBP.

Evidence-Based Diagnosis

A. Physical exam: See Chapter 22, Jaundice and Abnormal Liver Enzymes

B. Peritoneal fluid analysis

1. Serum-ascites albumin gradient

a. In portal hypertension, ascites occurs due to transudation, without changes in permeability that would allow albumin to leak into the ascitic fluid.

b. Therefore, the albumin content of ascitic fluid is low relative to serum.

c. This is in contrast to exudative types of ascites, such as ascites from infection or malignancy, in which albumin can leak into the ascitic fluid.

d. A serum-ascites albumin gradient (serum albumin-ascitic fluid albumin) of ≥ 1.1 mg/dL has a LR+ of 4.6 for the diagnosis of ascites due to portal hypertension; a serum ascites-albumin gradient of < 1.1 mg/dL has a LR− of 0.06 for the diagnosis of portal hypertension.

2. Ascitic fluid total protein

a. Also based on the principle that ascites due to cirrhosis is transudative and should have a low protein content relative to serum

b. Using a cut point of 2.5 mg/dL of ascitic fluid total protein to distinguish an exudate from a transudate had an accuracy of only 56%.

Serum-ascites albumin gradient is the best test for distinguishing between ascites due to portal hypertension and ascites due to other causes.

Treatment

A. Sodium restriction (sodium intake < 2 g/d) is commonly recommended, but there are no clinical trials showing that it leads to improved outcomes; fluid restriction of 1000–1500 mL/day is recommended if the serum sodium is < 130 mEq/L.

B. Spironolactone is the diuretic of choice to treat the aldosterone driven salt and water retention seen in cirrhosis.

1. 75% of patients respond

2. Furosemide or other loop diuretics can be added in patients who do not respond to spironolactone alone; 90% of patients respond to sodium restricted diets, spironolactone, and loop diuretics.

3. In order to avoid hypovolemia and renal impairment, the rate of weight loss should not exceed 0.5 kg/d in the absence of peripheral edema or 1 kg/d in the presences of edema.

Aspirin and NSAIDs blunt the natriuretic effect of diuretics and should be avoided in patients with ascites.

C. Large volume paracentesis with volume expansion (dextran or albumin) for patients unresponsive to diuretics

D. TIPS

1. Creates a shunt between the high-pressure portal vein and the low-pressure hepatic vein, leading to improved hemodynamics and a decrease in ascites

2. Complications include bleeding, shunt stenosis or thrombosis, right-sided heart failure, and encephalopathy in 30% of patients.

E. Liver transplantation

F. When should ascites be treated with measures beyond sodium restriction?

1. Not in grade 1 ascites (detectable only by ultrasound)

2. Grade 2 (moderate) and grade 3 (severe) ascites are generally treated due to patient discomfort and respiratory compromise.

a. Grade 2 should be treated with diuretics.

b. Grade 3 should be treated with paracentesis, followed by diuretics.

3. Refractory ascites (ascites not responsive to maximal tolerated medical therapy) should be treated with repeated paracentesis or TIPS, or both.

3. Encephalopathy

Textbook Presentation

The classic presentation of hepatic encephalopathy is a patient with known cirrhosis who has mental status changes or is in a coma.

Disease Highlights

A. Present in 50–70% of patients with chronic liver disease

B. The clinical manifestations range from subtle abnormalities detectable only on neuropsychological testing to coma (Table 15–3).

C. Can be precipitated by a wide variety of insults including

1. Increased ammonia production due to

a. Excess dietary protein

Table 15–3. Grading system for hepatic encephalopathy.

Grade	Level of Consciousness	Clinical Symptoms	Neurologic Signs	EEG Abnormalities
0	Normal	None	None	None
Subclinical	Normal	Normal	Abnormal neuropsychological testing	None
1	Sleep-wake reversal, restlessness	Forgetfulness, agitation, irritability, mild confusion	Tremor, apraxia, incoordination	Present
2	Lethargy, slow responses	Disorientation, amnesia, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive reflexes	Present
3	Somnolence, confusion	Disorientation, aggressive behavior	Asterixis, hyperactive reflexes, positive Babinski sign, muscle rigidity	Present
4	Coma	Unresponsive	Decerebration	Present

b. Constipation
c. GI bleeding
d. Infection
e. Azotemia
f. Hypokalemia
g. Systemic alkalosis

2. Reduced metabolism of toxins because of hepatic hypoxia due to
a. Dehydration
b. Arterial hypotension
c. Anemia

3. Increased central nervous depressant effect with use of benzodiazepines or other psychoactive drugs

4. Reduced metabolism of toxins because diversion of portal blood, due to surgical or intrahepatic shunts

Always look for the underlying cause of worsening hepatic encephalopathy.

Evidence-Based Diagnosis

A. There is some correlation between the degree of elevation of ammonia (either arterial or venous) and the severity of the encephalopathy, but the ammonia level cannot be used to determine the presence or absence of hepatic encephalopathy.

B. Diagnosis is based on history and exclusion of other causes of encephalopathy in a patient with significant liver dysfunction.

Treatment

A. Treatment focuses on reduction of intestinal production of ammonia.

B. Lactulose removes both dietary and endogenous sources of ammonia through its cathartic action; it also lowers pH, which reduces the population of urease-producing bacteria, and traps ammonia as ammonium ions in the gut lumen.

1. Frequently used in clinical practice, although most studies showing an improvement in encephalopathy are of poor quality

2. Daily dose should be titrated to result in 2–4 soft stools/day.

3. Complications include hypovolemia and hypernatremia.

C. Antibiotics reduce the population of urease-producing bacteria.

1. Rifaximin may be superior to lactulose.

2. Neomycin is equivalent to lactulose but has the potential to cause ototoxicity and nephrotoxicity with long-term use.

D. Consideration of liver transplantation is indicated in patients with hepatic encephalopathy.

4. Hypersplenism

Textbook Presentation

Cytopenias are found on routine blood testing in a patient with cirrhosis.

Disease Highlights

A. Splenomegaly is found in 36–92% of patients with cirrhosis; 11–55% have the clinical syndrome of hypersplenism, defined as the presence of leukopenia or thrombocytopenia (or both) with splenomegaly.

B. There is a rough correlation between spleen size and degree of decrease in blood cells.

C. Blood cell abnormalities in liver disease

1. Thrombocytopenia is due to platelet sequestration in the spleen, impaired bone marrow production, and decreased platelet survival.

2. Leukopenia is due to sequestration in the spleen and is rare compared with thrombocytopenia (1 series found 64% of cirrhotic patients had thrombocytopenia, but only 5% had leukopenia).

3. Although not part of the syndrome of hypersplenism, anemia often occurs in patients with cirrhosis and is due to increased destruction in the spleen as well as iron or folate deficiency; there is also reduced erythropoietin production.

Evidence-Based Diagnosis

A. Hypersplenism is a clinical syndrome without a specific set of diagnostic criteria.

B. Hypersplenism is manifested by splenomegaly and a significant reduction in 1 or more cellular elements of the blood, in the presence of normal or hypercellular bone marrow.

Treatment

A. Treatment is usually not necessary.

B. Splenectomy or partial splenic embolization is sometimes done for severe thrombocytopenia with bleeding complications.

C. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin are rarely used.

D. TIPS does not correct thrombocytopenia.

MAKING A DIAGNOSIS

1

Initial laboratory test results follow: WBC, 9700/mcL; Hgb, 10.5 g/dL; Hct, 31%; MCV, 86 mcm^3; platelet, 123,000 mcL; electrolytes normal; BUN, 8 mg/dL; creatinine, 0.4 mg/dL; glucose, 97 mg/dL; albumin, 2.1 g/dL; alkaline phosphatase, 95 units/L; total bilirubin, 1.2 mg/dL; ALT, 102 units/L; AST, 66 units/L; PT/PTT normal; urinalysis, 2+ protein with no cells or casts.

Have you crossed a diagnostic threshold for the leading hypothesis, cirrhosis and portal hypertension? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Mrs. V's physical exam suggests that she has splenomegaly, ascites, and edema, without pulmonary findings or an elevated jugular venous pressure, making HF unlikely. Her laboratory results are notable for elevation of transaminases and hypoalbuminemia—all consistent with chronic liver disease. However, the findings of proteinuria and hypoalbuminemia are also consistent with nephrotic syndrome.

Alternative Diagnosis: Nephrotic Syndrome

Textbook Presentation

Patients with nephrotic syndrome classically have edema (often periorbital), hypertension, hypoalbuminemia, hyperlipidemia, and at least 3.5 g/24 hour of proteinuria.

Disease Highlights

A. Etiology

1. Primary glomerular diseases
   a. Etiology uncertain but probably immune mediated
   b. Most common pathologies found in adults are membranous and focal glomerulosclerosis (33% each)
   c. Less common pathologies found in adults are minimal change disease (15%), IgA nephropathy (10%), and membranoproliferative glomerulonephritis (2–5%)
2. There are many systemic diseases associated with nephrotic syndrome
   a. Diabetes is the most common cause in the United States.
   b. Systemic lupus erythematosus (SLE) generally causes an inflammatory nephritis, but sometimes a noninflammatory, membranous pathology.
   c. Amyloidosis and multiple myeloma should be considered in patients over 40.
   d. Infections commonly associated with nephrotic syndrome include HIV, hepatitis B, hepatitis C, syphilis, and malaria.
   e. Malignancies, especially lung, breast, and colon cancer, and Hodgkin lymphoma are associated with nephrotic syndrome; occasionally nephrotic syndrome is the presentation of the malignancy
   f. Many drugs, including NSAIDs, captopril, and heroin, can cause nephrotic syndrome.

B. Clinical consequences

1. Primary sodium retention by the kidney causes edema and hypertension.
2. Albumin excretion leads to hypoalbuminemia, which also contributes to edema formation.
3. Alterations in lipoprotein production and catabolism lead to elevations of low-density lipoprotein and sometimes triglycerides.
4. Immunoglobulin excretion causes increased susceptibility to infection.
5. Thromboembolic complications
   a. Due to increased procoagulatory factors and fibrinogen, altered fibrinolytic system, urinary loss of antithrombin III, and increased platelet activity
   b. The annual incidence of venous thromboses (eg, renal vein thrombosis, pulmonary embolism, DVT) is 1.02%, with an annual incidence of 1.48% for arterial thromboembolism (ATE); in the first 6 months after diagnosis, the incidence for venous thromboembolism (VTE) is 9.85% and for ATE 5.52%.
      (1) Risk factors for VTE include serum albumin < 2.0–2.5 mg/dL, protein excretion > 8 g/24 h; GFR and traditional risk factors predict ATE
      (2) The role of prophylactic anticoagulation is unclear, but it should be considered in high-risk patients.

Evidence-Based Diagnosis

A. Nephrotic syndrome is defined by the presence of urinary protein excretion of at least 3.5 g/24 hours, measured with either a 24-hour specimen or a spot albumin/creatinine ratio > 3000–3500 mcg/mg.

B. Laboratory evaluation should include

1. CBC
2. Comprehensive metabolic panel (renal and liver function, including serum albumin)
3. Fasting glucose and HbA_{1c}
4. Antinuclear antibody (ANA)
5. HIV
6. Hepatitis B serology (surface antigen, core antibody)
7. Hepatitis C antibody
8. Serum and urine protein electrophoresis

C. Renal biopsy is often necessary.

Treatment

A. Loop diuretics are used to treat the edema; high doses are often needed due to the primary sodium retention by the kidney.

B. ACE inhibitors reduce proteinuria in both hypertensive and normotensive patients.

1. The antiproteinuric effect becomes maximal in 28 days.

2. The effect can be increased by a low-salt diet, diuretic treatment, or both.

3. Proteinuria is further reduced when an angiotensin receptor blocker is added to the ACE inhibitor.

C. Corticosteroids and other immunosuppressives are used in selected patients.

CASE RESOLUTION

1

Mrs. V's hepatitis C antibody is positive, with negative hepatitis B serologies. Her total cholesterol is 145 mg/dL, and her 24-hour urinary protein excretion is 1.4 g. An abdominal CT scan demonstrates a small, nodular liver; splenomegaly; and ascites. You schedule an esophagogastroduodenoscopy to screen for varices, start spironolactone because of the discomfort she is having from the edema, and refer her to a hepatologist.

CHIEF COMPLAINT

PATIENT 2

Mrs. E is a 62-year-old woman with a long history of hypertension that is well controlled with hydrochlorothiazide, atenolol, and amlodipine. She comes in today with a new complaint of swelling in her legs and feet for several weeks. It is generally most noticeable late in the day and is often absent when she first gets up in the morning. She has no history of liver or kidney disease or alcohol use. She has no chest pain and no shortness of breath, although notes she finds it tiring to climb stairs or walk more than a few blocks. She smoked a few cigarettes a day for 20 years, but quit 20 years ago.

Her physical exam is notable for a BMI of 38, clear lungs, an S_4 with no S_3 or murmurs, and a normal abdomen. Her legs show 1+ edema to the knees bilaterally. She has a long-standing goiter that is unchanged from previous exams. It is difficult to identify her jugular venous pressure due to the shape of her neck.

At this point, what is the leading hypothesis, what are the active alternatives, and is there a must not miss diagnosis? Given this differential diagnosis, what tests should be ordered?

PRIORITIZING THE DIFFERENTIAL

Once again, given the pivotal finding of bilateral edema, the first step is to look for systemic causes, focusing first on cardiac, hepatic, and renal causes. Mrs. E's long-standing history of hypertension raises the possibility of diastolic dysfunction, and the lack of physical exam findings does not rule this out. There are no clinical clues to suggest liver or kidney disease, but these are easy to test for and should always be ruled out. Amlodipine commonly causes edema, but she has taken it for years without symptoms. "Dependent edema," edema that is worsened by standing and improves or resolves with leg elevation, is consistent with, but not specific for, venous insufficiency. A final consideration would be pulmonary hypertension. Patients with pulmonary hypertension commonly complain of dyspnea in addition to edema, and the tired feeling she experiences with exertion could represent dyspnea. Additionally, she is overweight, putting her at risk for obstructive sleep apnea and consequent pulmonary hypertension. Table 15–4 lists the differential diagnosis.

2

Initial laboratory test results include BUN, 15 mg/dL; creatinine, 0.9 mg/dL; albumin/creatinine, ratio 5 mcg/mg; normal liver enzymes, albumin, and prothrombin time.

The ECG and chest radiograph are normal. An echocardiogram shows normal left ventricle size and function, elevated pulmonary pressures consistent with moderate pulmonary hypertension (estimated mean PAP 40 mm Hg), mild tricuspid regurgitation, and normal right ventricular size and function.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

There is no evidence of renal disease, liver disease, or diastolic dysfunction. However, the echocardiogram shows the somewhat unexpected finding of pulmonary hypertension. This necessitates revising the original set of diagnostic hypotheses: the leading hypothesis is now pulmonary hypertension, and venous insufficiency is the remaining active alternative.

Leading Hypothesis: Pulmonary Hypertension

Textbook Presentation

Patients commonly complain of long-standing dyspnea that progresses over months or years. Syncope, exertional chest pain, and edema occur with more severe pulmonary hypertension and impaired right heart function.

Disease Highlights

A. Definition

1. The normal mean pulmonary artery pressure (PAP) is 12 mm Hg.

Table 15–4. Diagnostic hypotheses for Mrs. E.

Diagnostic Hypotheses	Clinical Clues	Important Tests
Leading Hypothesis		
Diastolic dysfunction	History of hypertension Dyspnea Edema Elevated JVP S_3	Echocardiogram
Active Alternatives—Most Common		
Venous insufficiency	Dependent edema Varicose veins Typical skin changes (see description below)	Physical exam Duplex ultrasound
Active Alternatives—Must Not Miss		
Renal and liver disease	See Table 15–1	See Table 15–1
Other Hypotheses		
Pulmonary hypertension	Dyspnea, often long-standing Edema Syncope	Echocardiogram Right heart catheterization

JVP, jugular venous pressure.

2. Pulmonary hypertension is defined as a mean PAP > 25 mm Hg, with a mean pulmonary arterial occlusion pressure < 15 mm Hg; severe pulmonary hypertension is defined as a mean PAP of at least 50 mm Hg.

B. Pathophysiology: the increased pulmonary vascular resistance is due to 3 factors:

1. Vascular remodeling with vascular inflammation and endothelial cell proliferation

2. Platelet dysfunction and thrombosis

3. Vasoconstriction due to 2 factors

a. Endothelial dysfunction resulting in overproduction of vasoconstrictors such endothelin-1 and underproduction of vasodilators such as nitric oxide, prostacyclin, and vasoactive intestinal peptide

b. Abnormal voltage-gated potassium channels

C. The clinical classification was revised in 2003 and is organized using a pathophysiologic framework

1. Pulmonary arterial hypertension (PAH)

a. Idiopathic PAH

b. Familial PAH

c. PAH associated with

(1) Collagen vascular disease (especially scleroderma, SLE, and mixed connective tissue disease)

(2) Congenital systemic-pulmonary shunts

(3) Portal hypertension (1–6% of patients)

(4) HIV infection (0.5% of patients)

(5) Drugs or toxins (dexfenfluramine or fenfluramine containing appetite suppressants, amphetamine, methamphetamine, cocaine)

d. PAH associated with significant venous or capillary involvement (pulmonary veno-occlusive disease or capillary hemangiomatosis)

2. Pulmonary hypertension with left heart disease (ventricular, atrial, valvular)

3. Pulmonary hypertension associated with lung disease or hypoxemia

a. Chronic obstructive pulmonary disease

b. Interstitial lung disease

c. Sleep disordered breathing

d. Alveolar hypoventilation

e. Chronic exposure to high altitude

4. Pulmonary hypertension due to chronic thromboembolic disease (proximal or distal pulmonary arteries)

5. Miscellaneous (sarcoidosis; compression of pulmonary vessels due to adenopathy, tumor, fibrosing mediastinitis)

Evidence-Based Diagnosis

A. History

1. In 1 series of patients with PAH, initial symptoms included dyspnea (60%), fatigue (19%), chest pain (7%), syncope (8%), edema (3%).

2. At the time these patients were given the diagnosis of PAH and were enrolled in the study, 98% had dyspnea, 73% fatigue, 47% chest pain, 36% syncope, 37% edema, and 33% palpitations.

B. Physical exam

1. Characteristic findings include

a. An accentuated pulmonary component of S_2

b. Sustained left lower parasternal movement

c. An early systolic click

d. Increased jugular a and v waves

e. Tricuspid regurgitation murmur

f. Hepatojugular reflux

g. Pulsatile liver

h. Elevated jugular venous pressure

i. Edema

2. Sustained left lower parasternal movement for detecting a mean PAP > 50 mm Hg: sensitivity, 71%; specificity, 80%; LR+, 3.6; LR–, 0.4

3. A palpable P_2 for detecting a mean PAP > 50 mm Hg (studied in patients with mitral stenosis): sensitivity, 96%; specificity, 73%; LR+, 3.6; LR–, 0.05

C. ECG

1. Expected findings include right axis deviation, right ventricular hypertrophy, and P-pulmonale pattern (right atrial enlargement).

2. Not sensitive or specific enough to diagnosis pulmonary hypertension (sensitivity, 51%; specificity, 86%; LR+, 3.6; LR–, 0.56)

D. Chest film

1. Expected findings include enlargement of pulmonary arteries and right ventricular enlargement.

2. Not sensitive or specific enough to diagnose pulmonary hypertension (sensitivity, 46%; specificity, 63%)

E. Transthoracic echocardiogram

1. Most common noninvasive way to estimate pulmonary pressure
2. Echocardiogram estimates often correlate fairly well with invasively determined PAPs, but differences as large as 38 mm Hg have been reported in individual patients.
3. Sensitivity ranges from 79% to 100%.
4. Specificity ranges from 60% to 98%.

F. Right heart catheterization is the gold standard for diagnosing pulmonary hypertension, and all patients with suspected pulmonary hypertension need a right heart catheterization to confirm the finding.

Treatment

A. Depends on underlying etiology

B. Correct underlying cause when possible

1. For obstructive sleep apnea, administer continuous positive airway pressure.
2. For chronic thromboembolism, begin anticoagulation and consider thromboendarterectomy.
3. For valvular disease, replace the valve.
4. For congenital heart disease, repair surgically.
5. For left ventricular dysfunction, optimize medical regimen.

C. Oxygen therapy for patients with hypoxemia (PO_2 < 55 mm Hg at rest, oxygen saturation < 85% with exercise)

D. Most patients require loop diuretics.

E. Most medication trials showing improvement in hemodynamics and/or exercise capacity have included patients with idiopathic, fenfluramine-associated, and connective tissue disease–associated pulmonary hypertension

1. Currently available drugs include oral endothelin antagonists such as bosentan, oral phosphodiesterase-5 inhibitors such as sildenafil, and prostacyclins such as epoprostenol (parenteral) or iloprost (inhaled).
2. Calcium blockers are effective in a few patients.

MAKING A DIAGNOSIS

2

Mrs. E has a normal physical exam, ECG, and chest radiograph, normal right ventricular function on echocardiogram, and the isolated finding of moderately elevated PAP seen on an echocardiogram. The echocardiogram estimate of PAP alone is not specific enough to make the diagnosis of pulmonary hypertension, and Mrs. E has no other findings supporting the diagnosis of pulmonary hypertension. Furthermore, Mrs. E's dyspnea is minimal, suggesting that she has neither significant pulmonary hypertension nor pulmonary disease.

You explain the puzzling finding to Mrs. E. She does not want to undergo a right heart catheterization to verify the PAP. She reports that she is able to walk a mile every morning without shortness of breath, and that her edema is most noticeable when she has been on her feet for a long time.

Have you crossed a diagnostic threshold for the leading hypothesis, pulmonary hypertension? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Alternative Diagnosis: Venous Insufficiency

Textbook Presentation

Venous insufficiency can be asymptomatic or manifested just by small visible, but nonpalpable veins. In more severe cases, the patient has large varicose veins and skin changes ranging from edema to fibrosing panniculitis to ulceration. Symptoms include leg fullness or heaviness, aching leg pain, and nocturnal leg cramps.

Disease Highlights

A. Anatomy (Figure 15-4)

1. The superficial saphenous veins join the deep system at the knee (popliteal vein) and the groin (femoral vein).
2. Perforating veins directly connect the saphenous veins and the deep veins at various points along their parallel courses.
3. Valves within the veins prevent reflux back toward the feet.

B. Pathophysiology and epidemiology

1. Chronic venous disease is due to venous hypertension caused by reflux through incompetent valves, venous outflow obstruction, or lack of calf muscle pumping due to obesity or immobility.

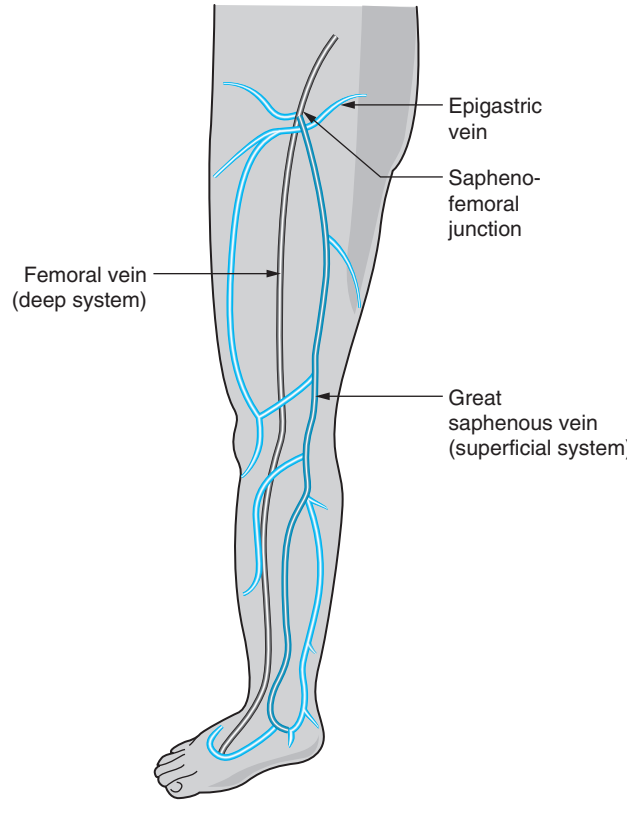


Figure 15–4. Anatomy of the superficial venous system.

   a. Reflux occurs in the superficial system in about 45% of patients, both the superficial and deep systems in about 40%, and in the deep system only in the remainder of patients
   b. Prolonged standing leads to marked increases in venous pressure in all people; while those with competent valves quickly lower the venous pressure with walking, individuals with incompetent valves have only slight decreases in pressure with walking.
2. Varicose veins are found in 25–33% of women and 10–20% of men.
3. Prevalence of skin changes is 3–11%; prevalence of skin ulcers is 0.3–1%.
4. Risk factors for venous insufficiency include advancing age, obesity, a history of phlebitis or venous thrombosis, serious leg trauma, pregnancy, prolonged standing, and greater height.
5. Postthrombotic syndrome (venous insufficiency after a DVT) occurs in 35–69% of patients at 3 years and in 49–100% of patients at 5–10 years; incidence is reduced to 8% if patients are treated with adequate anticoagulation, early mobilization, and long-term use of compression stockings.

C. Classification
1. Class 1: telangiectasias or reticular veins (nonpalpable subdermal veins up to 4 mm in diameter)
2. Class 2: varicose veins (palpable, subcutaneous veins > 4 mm in diameter)
3. Class 3: edema without skin changes
   a. Initially present just at the end of day but can become persistent and massive
   b. Can be unilateral initially
   c. Often begins around medial malleolus
4. Class 4: skin changes
   a. Pigmentation due to breakdown of extravasated RBCs
   b. Stasis dermatitis: itching, weeping, scaling, erosions, and crusting
   c. Lipodermatosclerosis or fibrosing panniculitis
      (1) Induration initially at medial ankle, spreading circumferentially round the entire leg, up to mid calf
      (2) The skin is heavily pigmented and fixed to subcutaneous tissues, with brawny edema above the fibrosis and in the foot below
      (3) High risk for cellulitis
5. Classes 5 and 6: healed or nonhealed ulcers
   a. Usually low on the medial ankle or along the path of the long or short saphenous vein
   b. Never above the knee or on the forefoot
   c. Chronic and recurrent, often lasting for months or even years

Evidence-Based Diagnosis

A. Diagnosis is often made based on the appearance of the leg.
B. Venography is the gold standard.
C. Duplex ultrasonography is the best noninvasive test.
1. Should be done if the diagnosis is in doubt (especially to rule out DVT), in patients with atypical symptoms or presentations, or if surgery is being considered
2. For diagnosing valvular incompetence, the sensitivity is 84%, specificity is 88%, LR+ = 7, and LR− = 0.18.
3. For diagnosing severe venous insufficiency, the sensitivity is 77%, specificity is 85%, LR+ = 5.1, and LR− = 0.26.

D. Because many patients have both arterial and venous insufficiency, concurrent arterial disease must be ruled out with the ankle brachial index (ABI).

Treatment

A. Compression stockings are the most important treatment modality.
1. Have been shown to reduce risk of postthrombotic syndrome, to accelerate ulcer healing, and to prevent recurrent ulceration
2. Classified into several grades, based on degree of compression at the ankle
   a. 20–30 mm Hg: for patients with varicose veins, edema, leg fatigue (Classes 2 and 3)
   b. 30–40 mm Hg: for patients with severe varicosities or moderate disease (Classes 4–6)
   c. 40–50 mm Hg: for patients with recurrent ulceration
3. Knee high stockings are better tolerated than thigh high stockings.
4. Compliance often poor due to skin irritation, discomfort, and difficulty putting on the stockings.

Compression stockings should not be used in patients with peripheral arterial disease or with invasive infection at an ulcer site.

5. Alternative ways to provide compression include elastic wraps and intermittent pneumatic compression pumps.
6. Ulcers should be covered with a dressing before putting on the compression device.

B. Diuretics are ineffective for the edema unless given with compression therapy.
C. Treatment of venous insufficiency ulcers
1. Occlusive dressing
2. Leg elevation and compression
3. Aspirin, 325 mg daily, might accelerate healing.
4. Pentoxifylline might accelerate healing.
5. Topical antibiotics have no role.
6. Systemic antibiotics indicated only if cellulitis or other invasive infection is present.

D. Interventional therapies
1. Sclerotherapy for spider veins, venous lakes, varicose veins 1–4 mm in diameter
2. Endovenous radiofrequency ablation and laser: alternative to vein stripping for great saphenous vein reflux
3. Iliac vein stenting for venous outflow abnormalities
4. Vein stripping and ligation

a. Usually involves removing the saphenous vein with high ligation of the saphenofemoral junction

b. Shown to result in significant improvement in symptoms in patients with Class 2–6 disease

c. Surgery plus compression is better than compression alone for preventing ulcer recurrence (12% combined therapy vs. 28% compression alone).

CASE RESOLUTION

2

You decide that Mrs. E's symptoms are more consistent with venous insufficiency than with pulmonary hypertension. Duplex ultrasonographic scans confirm valvular incompetence, and you recommend that Mrs. E wear compression stockings. She returns in 3 months reporting that she has no edema when she wears the stockings, and that she continues to walk 1 mile daily without any dyspnea.

CHIEF COMPLAINT

PATIENT 3

Mrs. K is a 64-year-old woman who had a right mastectomy 2 years ago for breast cancer. She was treated with adjuvant radiation therapy and has been taking tamoxifen since completing the radiation. She has had no evidence of recurrent disease but has had some right arm swelling for at least 18 months. She comes to see you now because 2 days ago the swelling of her right arm worsened, with associated pain and redness. This morning her temperature was 37.9°C.

At this point, what is the leading hypothesis, what are the active alternatives, and is there a must not miss diagnosis? Given this differential diagnosis, what tests should be ordered?

PRIORITIZING THE DIFFERENTIAL

Mrs. K has chronic lymphedema due to disruption of her lymphatic drainage by her previous surgery and radiation therapy. This is a pivotal point in her history since patients with lymphatic disruption and lymphedema are at high risk for skin and subcutaneous infections. Pathophysiologically, the edema found in cellulitis is due to a localized increase in capillary permeability due to inflammation; however, patients with underlying limb abnormalities will often present with more diffuse edema. The other primary consideration in *any* patient with unilateral limb swelling is DVT. Mrs. K has several risk factors for this, including history of cancer, possible venous scarring secondary to radiation, and use of tamoxifen (a drug associated with a relative risk for DVT of about 3). Table 15–5 lists the differential diagnosis.

Always think about DVT in a patient with unilateral limb swelling.

3

On physical exam, Mrs. K is clearly uncomfortable. Her temperature is 38.3°C, pulse 102 bpm, RR 16 breaths per minute, and BP 125/80 mm Hg. Her right upper arm and chest are bright red, hot, and tender. The border of the erythema is sharply demarcated, and the area of erythema feels indurated. She has eczema of all of her fingers, with multiple areas of cracked skin.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Cellulitis & Erysipelas

Textbook Presentation

A painful, red, hot, and swollen limb develops acutely in a patient with underlying venous or lymphatic disease.

Table 15–5. Diagnostic hypotheses for Mrs. K.

Diagnostic Hypotheses	Clinical Clues	Important Tests
Leading Hypothesis		
Cellulitis or erysipelas	Edema Erythema Pain Fever Entry site for infection Underlying venous insufficiency or lymphedema	Clinical exam
Active Alternative—Must Not Miss		
Upper extremity DVT	Unilateral arm/neck swelling Feeling of fullness or heaviness DVT risk factors (especially indwelling intravenous catheter)	Duplex ultrasound CT MRA Venography

DVT, deep venous thrombosis.

Disease Highlights

A. Definitions

1. Cellulitis is an infection of the dermis and subcutaneous tissue.

2. Erysipelas is a superficial cellulitis with prominent lymphatic involvement.

B. Cellulitis highlights

1. Risk factors for the development of cellulitis

a. Lymphedema

b. Peripheral edema

c. Venous insufficiency

d. Obesity

e. Diabetes

f. History of cellulitis

g. Breast cancer treatment

(1) Cellulitis of the ipsilateral arm is seen in women in whom lymphedema of the arm develops after mastectomy.

(2) Cellulitis of the ipsilateral breast is seen in women in whom localized lymphedema develops after lumpectomy, axillary node dissection, and radiation therapy.

2. Often an entry site for infection can be identified (leg ulcer, trauma, tinea pedis, eczema, subcutaneous abscess)

3. Clinical presentation

a. Presence of systemic symptoms (eg, fever, chills, myalgias) is unusual and suggest concomitant bacteremia or a more serious infection such as necrotizing fasciitis.

b. Physical findings

(1) Nonpalpable, confluent erythema with indistinct margins

(2) Generalized swelling

(3) Warmth and tenderness of involved skin

(4) Tender regional adenopathy sometimes found

(5) Lymphangitis and abscess formation sometimes seen

(6) In women who have been treated for breast cancer and have arm lymphedema, the humeral area of the ipsilateral extremity is most often involved, with extension to the shoulder and forearm.

(7) In breast cellulitis, the infection starts at the lumpectomy site and can extend to the remainder of the breast, the anterior shoulder, back, and ipsilateral upper extremity.

4. Microbiology

a. β-Hemolytic streptococci and *Staphylococcus aureus* are the most common organisms.

(1) Community-acquired methicillin-resistant *S aureus* (MRSA), usually the USA300 genotype, is increasingly common; it is now the most common pathogen cultured from skin and soft tissue infections in urban emergency departments

(2) The following groups are at risk for having community-acquired MRSA:

(a) Household contacts

(b) Soldiers

(c) Children

(d) Men who have sex with men

(e) Incarcerated persons

(f) Athletes

(g) Native Americans, Pacific Islanders

(h) Injection drug users

(i) Patients with a previous community-acquired MRSA infection

(3) Many patients with community-acquired MRSA have none of these risk factors

(4) Skin abscesses, often with central necrosis, are a very common manifestation of community-acquired MRSA; patients often think they have been bitten by a spider or other insect.

(5) Other manifestations include cellulitis, necrotizing pneumonia, pleural empyema, necrotizing fasciitis, septic thrombophlebitis, myositis, and severe sepsis

b. A variety of other organisms may be seen with specific exposures or sites of infection (Table 15-6)

C. Erysipelas highlights

1. Risk factors for development of erysipelas

Table 15–6. Microbiology of cellulitis.

Cellulitis Syndrome	Location/ Key Point	Likely Organisms
Periorbital	Periorbital	*Staphylococcus aureus,* pneumococcus, group A streptococcus (GAS)
Orbital	Emergent because of potential to affect oculomotor function and visual acuity	Staphylococcus, streptococcus
Perianal	Evaluate for underlying abscess	GAS
Breast cancer treatment	See text	Non-group A hemolytic streptococcus
Saphenous vein harvest	Ipsilateral leg	GAS or non-group A streptococcus
Injection drug use	Extremities, neck	Staphylococcus, streptococcus (groups A, C, F, G), gram-negative organisms, anaerobes
Crepitant cellulitis	Trunk, extremities; consider necrotizing fasciitis	GAS, anaerobes, *Clostridia*
Salt water exposure	Exposed body part	*Vibrio vulnificus*
Fresh water exposure	Exposed body part	*Aeromonas hydrophilia*
Hot tub exposure	Bathing suit distribution	*Pseudomonas aeruginosa*

a. Similar to those for cellulitis

b. Lymphedema and an identified portal of entry (primarily tinea pedis) are the 2 strongest risk factors in 1 study.

Always treat tinea pedis in a patient with cellulitis, erysipelas, or risk factors for developing those infections.

2. Clinical presentation

a. Sudden onset of fever (85% of patients), erythema, edema, and pain

b. Physical findings

(1) Palpable plaque of erythema that extends by 2–10 cm/day

(2) **Sharply demarcated border**

(3) Leg is the most common site (90%), then the arm (5%), and then the face (2.5%).

(4) Regional adenopathy and lymphangitis sometimes seen

c. Recurrence rate of 10% at 6 months and 30% at 3 years is usually due to untreated local factors.

d. Patients should respond to antibiotic therapy in 24–72 hours.

3. Microbiology

a. Streptococci are the causative organisms in 90% of cases (group A in about 58–67% of cases caused by streptococci, group B in 3–9%, and group C or G in 14–25%)

b. *S aureus* is also found in 10% of cases, although it is unclear whether it is contributing to the infection or just colonizing.

Evidence-Based Diagnosis

A. Both cellulitis and erysipelas are clinical diagnoses.

B. Blood cultures are positive in 2–5% of patients.

C. Skin biopsy cultures are positive in 5-40% of patients, but are rarely necessary.

D. Aspiration of the leading edge of erythema is sometimes done, but the yield is low.

E. Toe web cultures are sometimes helpful in patients with tinea pedis.

F. If there is a skin abscess associated with the cellulitis, it should be drained and the fluid cultured.

Cultures are rarely helpful in cellulitis or erysipelas without an associated abscess.

Treatment

A. Cellulitis

1. Initial therapy is usually empiric.

2. Must cover staphylococcus and streptococcus

3. Purulent cellulitis is more likely to be caused by *S aureus;* nonpurulent cellulitis is often due to a combination of staphylococci and streptococci.

4. Because of the emergence of community-acquired MRSA, antibiotics previously used for cellulitis (such as cephalexin or dicloxicillin) may not be effective.

a. Local susceptibility patterns can guide choices.

b. Oral drugs to which community-acquired MRSA is commonly sensitive include clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines.

(1) Streptococci are often resistant to trimethoprim-sulfamethoxazole and tetracyclines.

(2) 10–20% of MRSA isolates that are sensitive to clindamycin, but resistant to erythromycin, develop inducible clindamycin resistance due to the presence of the *erm* gene.

(3) Clindamycin sensitive/erythromycin resistant isolates should undergo the "D-Zone Test" to look for inducible resistance (Figure 15–5).

5. A reasonable choice for cellulitis would be clindamycin or a β-lactam antibiotic (such as dicloxicillin or amoxicillin/clavulanate) plus trimethoprim-sulfamethoxazole.

6. Should treat for 10–14 days

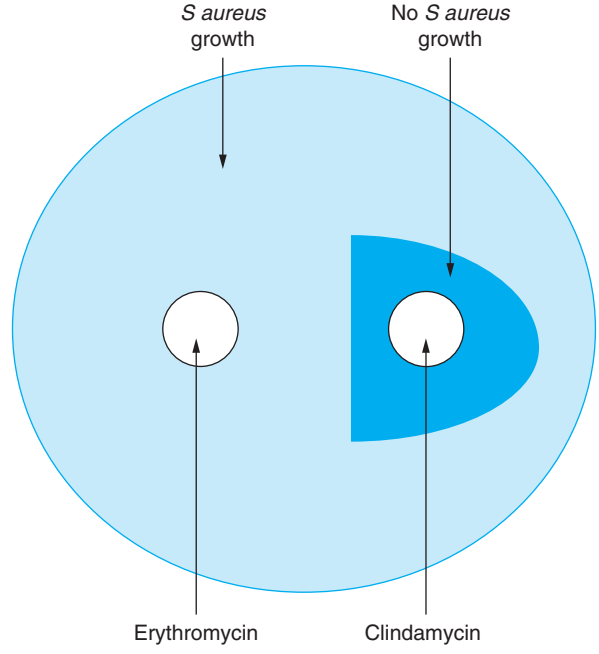
B. Erysipelas

1. Penicillin G or amoxicillin is effective in > 80% of patients with erysipelas.

2. Other drugs that have been studied include macrolides and fluoroquinolones

3. Should treat for 10–20 days

C. Uncomplicated, slowly progressive infection in a well-appearing patient can be treated with oral antibiotics if



When there is inducible clindamycin resistance, the zone of clindamycin inhibition is blunted on the side next to the erythromycin disk, resulting in a "D" shaped area of no growth surrounding the clindamycin disk. If there is no inducible resistance, the no growth area around the clindamycin disk will be a more symmetric circle

Figure 15–5. D-Zone test.

1. The patient has no GI upset
2. The limb can be elevated
3. Serial exams are feasible

D. Patients who appear ill, who have rapidly progressive infection, are immunocompromised, or who might not be able to follow treatment instructions should be admitted for IV antibiotics, generally including vancomycin.

E. Obtain infectious disease and surgical consultations for patients with rapidly progressive infections, especially if progression occurs while they are receiving appropriate antibiotics.

MAKING A DIAGNOSIS

3

Initial laboratory tests include the following: WBC 11,700/mcL, 83% PMNs, 10% basophils, 7% lymphocytes; Hgb, 13.5 g/dL; glucose, 88 mg/dL; creatinine, 0.8 mg/dL.

Have you crossed a diagnostic threshold for the leading hypothesis, cellulitis or erysipelas? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Alternative Diagnosis: Upper Extremity DVT (UEDVT)

Textbook Presentation

Patients can be asymptomatic, but generally arm, shoulder, or neck discomfort or fullness as well as arm swelling are the presenting symptoms.

Disease Highlights

A. Classification

1. Primary UEDVT (20% of cases)
   a. Idiopathic
   b. Effort thrombosis, also known as Paget-Schroetter syndrome
      (1) Occurs in young men after strenuous exercise, which causes microtrauma to the veins
      (2) May or may not find compression by hypertrophied muscles or a cervical rib
2. Secondary UEDVT (80% of cases) (Table 15–7)
   a. Indwelling central venous catheter–associated UEDVT (up to 70% of cases)
      (1) UEDVT occurs more often with large catheters than with smaller ones.
      (2) Risk increases with duration of catheter use, being negligible within 6 days and increasing significantly after 2 weeks.
      (3) Risk is higher with polyvinyl chloride-coated catheters than with silicone ones.
   b. Malignancy (> 40% of cases); patients with cancer and an indwelling catheter are at especially high risk.

Table 15–7. Risk factors for upper extremity deep venous thrombosis.

Risk Factor	Adjust Odds Ratio (95% CI)
Indwelling central venous catheter (CVC)	9.7 (7.8–12.2)
CVC plus inherited coagulation disorder	~30
Cancer	18.1 (9.4–35.1)
Metastatic vs localized cancer	11.5 (1.6–80.2)
Cancer plus CVC	43.6 (25.5–74.6)
Oral contraceptives plus factor V Leiden or prothrombin G20210A mutation	13.6 (2.7–67.3)
Upper extremity surgery	13.1 (2.1–80.6)
Upper extremity plaster cast	7.0 (1.7–29.5)

   c. Hypercoagulable states
   d. Other miscellaneous causes (surgery, infection, immobility, concurrent lower extremity DVT)

B. Sites

1. Subclavian in 18–69% of cases
2. Axillary in 5–42% of cases
3. Internal jugular in 8–29% of cases
4. Brachial in 4–13% of cases
5. Multiple veins are often involved, but bilateral UEDVT is rare.

C. Clinical features

1. Pain is present in ~40% of patients.
2. Edema is present ~80% of patients in some series, but patients with catheter-related UEDVT often do not have edema.
3. Patients may note numbness, heaviness, paresthesias, pruritus, and coldness.
4. Dilated cutaneous veins sometimes visible.

D. Complications

1. Pulmonary embolism occurs in up to 36% of cases and is more often seen with secondary UEDVT, especially catheter-related.

UEDVT can cause pulmonary embolism.

2. Recurrent thrombosis occurs in up to 10% of patients.
3. Postthrombotic syndrome is seen in up to 4–34% of patients in different series.

Evidence-Based Diagnosis

A. Venography is the gold standard.

B. Duplex ultrasonography is the most commonly used noninvasive test.

1. Disadvantages include a blind spot caused by the clavicle and difficulties interpreting the study if there are collateral veins.

2. Sensitivity ranges from 56% to 100%, and specificity from 94% to 100%
3. Magnetic resonance angiography and CT are sometimes done; sensitivity and specificity are unknown.

Treatment

A. Anticoagulation with heparin, followed by at least 3 months of warfarin; patients with cancer or chronic indwelling central venous catheters should receive anticoagulation therapy indefinitely.

B. Thrombolysis with or without stent placement is sometimes done, especially in patients who require permanent indwelling catheters.

CASE RESOLUTION

3

Mrs. K's presentation of a sharply demarcated, erythematous plaque, fever, and leukocytosis is diagnostic of erysipelas. The portal of entry is the eczematous, cracked skin on her hands. Although she has some risk factors for UEDVT, it is not necessary to test for it at this point. Because of the extent of infection, Mrs. K is admitted to the hospital and treated with IV cefazolin. One of 2 blood cultures grows group A β-hemolytic streptococci. She improves rapidly and is switched to oral penicillin and is discharged.

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