

## Approach to Leg Edema of Unclear Etiology

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**A common challenge for primary care physicians is to determine the cause and find an effective treatment for leg edema of unclear etiology. We were unable to find existing practice guidelines that address this problem in a comprehensive manner. This article provides clinically oriented recommendations for the management of leg edema in adults. We searched on-line resources, textbooks, and MEDLINE (using the MeSH term, “edema”) to find clinically relevant articles on leg edema. We then expanded the search by reviewing articles cited in the initial sources. Our goal was to write a brief, focused review that would answer questions about the management of leg edema. We organized the information to make it rapidly accessible to busy clinicians. The most common cause of leg edema in older adults is venous insufficiency. The most common cause in women between menarche and menopause is idiopathic edema, formerly known as “cyclic” edema. A common but under-recognized cause of edema is pulmonary hypertension, which is often associated with sleep apnea. Venous insufficiency is treated with leg elevation, compressive stockings, and sometimes diuretics. The initial treatment of idiopathic edema is spironolactone. Patients who have findings consistent with sleep apnea, such as daytime somnolence, loud snoring, or neck circumference >17 inches, should be evaluated for pulmonary hypertension with an echocardiogram. If time is limited, the physician must decide whether the evaluation can be delayed until a later appointment (eg, an asymptomatic patient with chronic bilateral edema) or must be completed at the current visit (eg, a patient with dyspnea or a patient with acute edema [ $<72$  hours]). If the evaluation should be conducted at the current visit, the algorithm shown in Figure 1 could be used as a guide. If the full evaluation could wait for a subsequent visit, the patient should be examined briefly to rule out an obvious systemic cause and basic laboratory tests should be ordered for later review (complete blood count, urinalysis, electrolytes, creatinine, blood sugar, thyroid stimulating hormone, and albumin). (J Am Board Fam Med 2006;19:148–60.)**

Edema is defined as a palpable swelling caused by an increase in interstitial fluid volume. The most likely cause of leg edema in patients over age 50 is venous insufficiency. Venous insufficiency affects up to 30% of the population,<sup>1,2</sup> whereas heart failure affects only approximately 1%.<sup>3,4</sup> The most likely cause of leg edema in women under age 50 is idiopathic edema, formerly known as cyclic ede-

ma.<sup>5</sup> Most patients can be assumed to have one of these diseases unless another cause is suspected after a history and physical examination. However, there are at least 2 exceptions to this rule: pulmonary hypertension and early heart failure can both cause leg edema before they become clinically obvious in other ways.

### Classification

There are 2 types of leg edema: venous edema and lymphedema. Venous edema consists of excess low-viscosity, protein-poor interstitial fluid resulting from increased capillary filtration that cannot be accommodated by a normal lymphatic system.<sup>6</sup> Lymphedema consists of excess protein-rich interstitial fluid within the skin and subcutaneous tissue resulting from lymphatic dysfunction.<sup>7</sup> A third type, lipidema, is more accurately considered a form of fat maldistribution rather than true edema.<sup>8</sup>

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**Table 1. Common Causes of Leg Edema in the United States**

Unilateral		Bilateral	
Acute (<72 hours)	Chronic	Acute (<72 hours)	Chronic
Deep vein thrombosis	Venous insufficiency		Venous insufficiency Pulmonary hypertension Heart failure Idiopathic edema Lymphedema Drugs Premenstrual edema Pregnancy Obesity

**Diagnosis**

The differential diagnosis of edema is presented in Tables 1 through 3. Figures 1 through 5 provide an algorithm for diagnostic evaluation.

**History**

Key elements of the history include

- What is the *duration* of the edema (acute [ $<72$  hours] vs. chronic)? If the onset is acute, deep vein thrombosis should be strongly considered.<sup>6,9-11</sup> The 72-hour cutoff is commonly cited<sup>9-11</sup> but arbitrary and not well supported with evidence. Deep vein thrombosis should be con-

sidered in patients presenting after 72 hours with otherwise consistent findings.

- Is the *edema* painful? Deep vein thrombosis and reflex sympathetic dystrophy are usually painful.<sup>10,12</sup> Chronic venous insufficiency can cause low-grade aching. Lymphedema is usually painless.<sup>9,10,12-15</sup>
- What *drugs* are being taken? Calcium channel blockers, prednisone, and anti-inflammatory drugs are common causes of leg edema.<sup>9,14,16,17</sup> Other drugs that may cause edema are listed in Table 4.
- Is there a history of *systemic disease* (heart, liver, or kidney disease)?
- Is there a history of pelvic/abdominal *neoplasm* or *radiation*?

**Table 2. Less Common Causes of Leg Edema in the United States**

Unilateral		Bilateral	
Acute (<72 hours)	Chronic	Acute (<72 hours)	Chronic
Ruptured Baker's cyst	Secondary lymphedema (tumor, radiation, surgery, bacterial infection)	Bilateral deep vein thrombosis	Renal disease (nephrotic syndrome, glomerulonephritis)
Ruptured medial head of gastrocnemius	Pelvic tumor or lymphoma causing external pressure on veins	Acute worsening of systemic cause (heart failure, renal disease)	Liver disease
Compartment syndrome	Reflex sympathetic dystrophy		Secondary lymphedema (secondary to tumor, radiation, bacterial infection, filariasis) Pelvic tumor or lymphoma causing external pressure Dependent edema Diuretic-induced edema Dependent edema Preeclampsia Lipidema <sup>8</sup> Anemia

**Table 3. Rare Causes of Leg Edema in the United States**

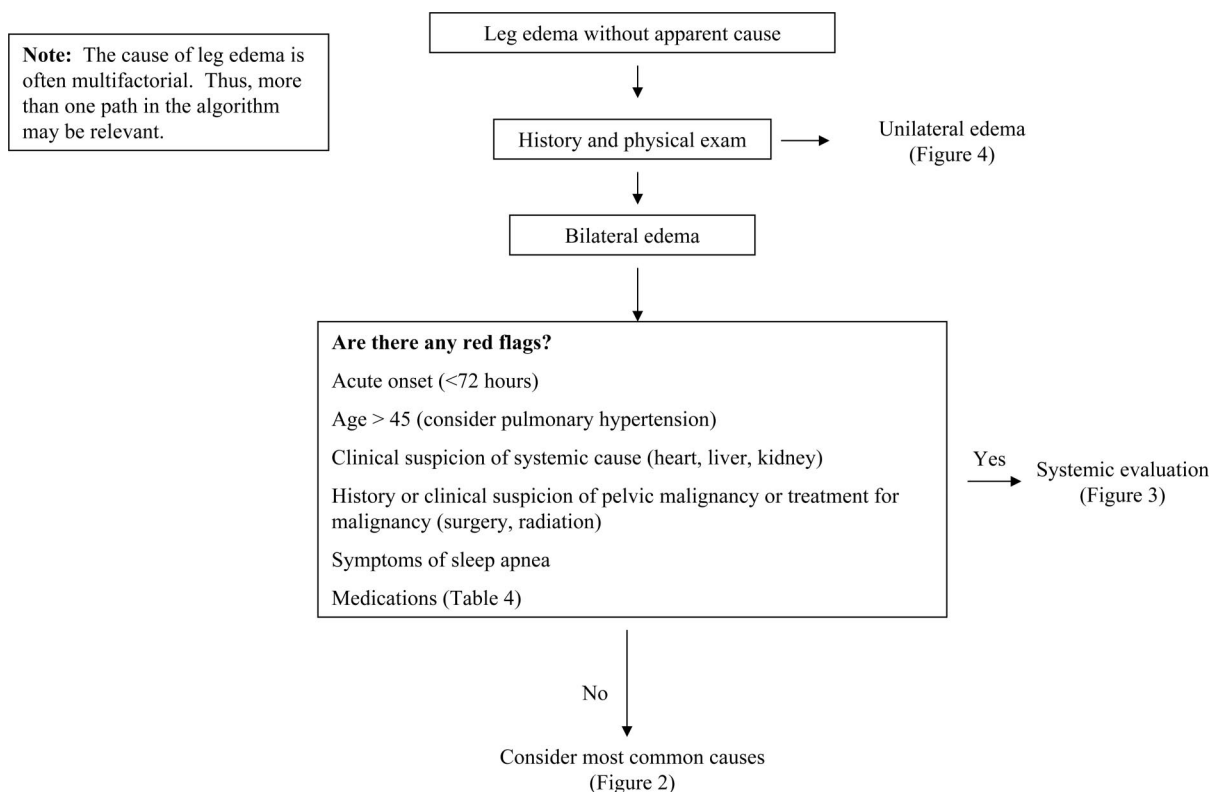
Unilateral		Bilateral	
Acute (<72 hours)	Chronic	Acute (<72 hours)	Chronic
	Primary lymphedema (congenital lymphedema, lymphedema praecox, lymphedema tarda)		Primary lymphedema (congenital lymphedema, lymphedema praecox, lymphedema tarda)
	Congenital venous malformations		Protein losing enteropathy, malnutrition, malabsorption
	May-Thurner syndrome (iliac-vein compression syndrome) <sup>51</sup>		Restrictive pericarditis
			Restrictive cardiomyopathy
			Beri Beri
			Myxedema

- Does the edema *improve overnight*? Venous edema is more likely than lymphedema to improve overnight.<sup>13</sup>
- Is there a history consistent with *sleep apnea*? Sleep apnea can cause pulmonary hypertension, which is a common cause of leg edema.<sup>4</sup> Findings that may increase suspicion of sleep apnea include loud snoring or apnea noted by the sleep partner, daytime somnolence, or a neck circumference >17 inches.

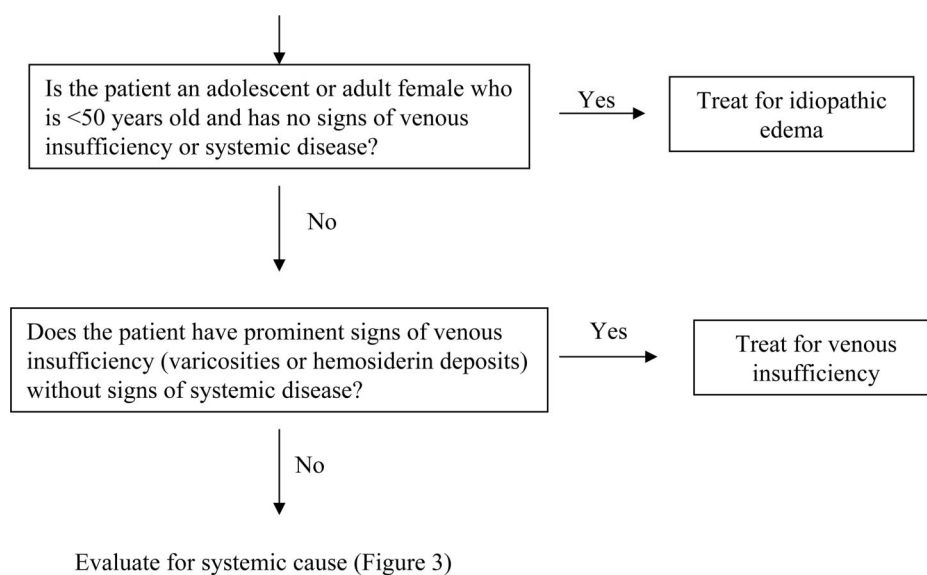
**Physical Examination**

Key elements of the physical examination include

- Body mass index. Obesity is associated with sleep apnea and venous insufficiency.<sup>18-20</sup>
- Distribution of edema: *unilateral* leg edema is generally due to a local cause such as deep vein thrombosis, venous insufficiency, or lymphedema. *Bilateral* edema can be due to a local cause or systemic disease, such as heart failure or kid-



**Figure 1. Algorithm for leg edema.**



**Figure 2. Common causes.**

ney disease. *Generalized* edema is due to systemic disease. The dorsum of the foot is spared in lipidema but prominently involved in lymphedema.<sup>8</sup>

- Tenderness: deep vein thrombosis and lipidema are often tender. Lymphedema is usually nontender.
- Pitting: deep vein thrombosis, venous insufficiency, and early lymphedema usually pit. Myxedema and the advanced fibrotic form of lymphedema typically do not pit.<sup>9,12,14,21</sup>
- Varicose veins: leg varicosities are often present in patients with chronic venous insufficiency, but venous insufficiency can occur without varicose veins.<sup>10</sup>
- Kaposi-Stemmer sign: inability to pinch a fold of skin on the dorsum of the foot at the base of the second toe is a sign of lymphedema.<sup>15,22</sup>
- Skin changes: a warty texture (hyperkeratosis) with papillomatosis and brawny induration are characteristic of chronic lymphedema.<sup>9,14</sup> Brown hemosiderin deposits on the lower legs and ankles are consistent with venous insufficiency. Reflex sympathetic dystrophy initially leads to warm tender skin with increased sweating. Later the skin is thin, shiny, and cool. In the chronic stage, the skin becomes atrophic and dry with flexion contractures.
- Signs of systemic disease: findings of heart failure (especially jugular venous distension and lung crackles) and liver disease (ascites, spider heman-

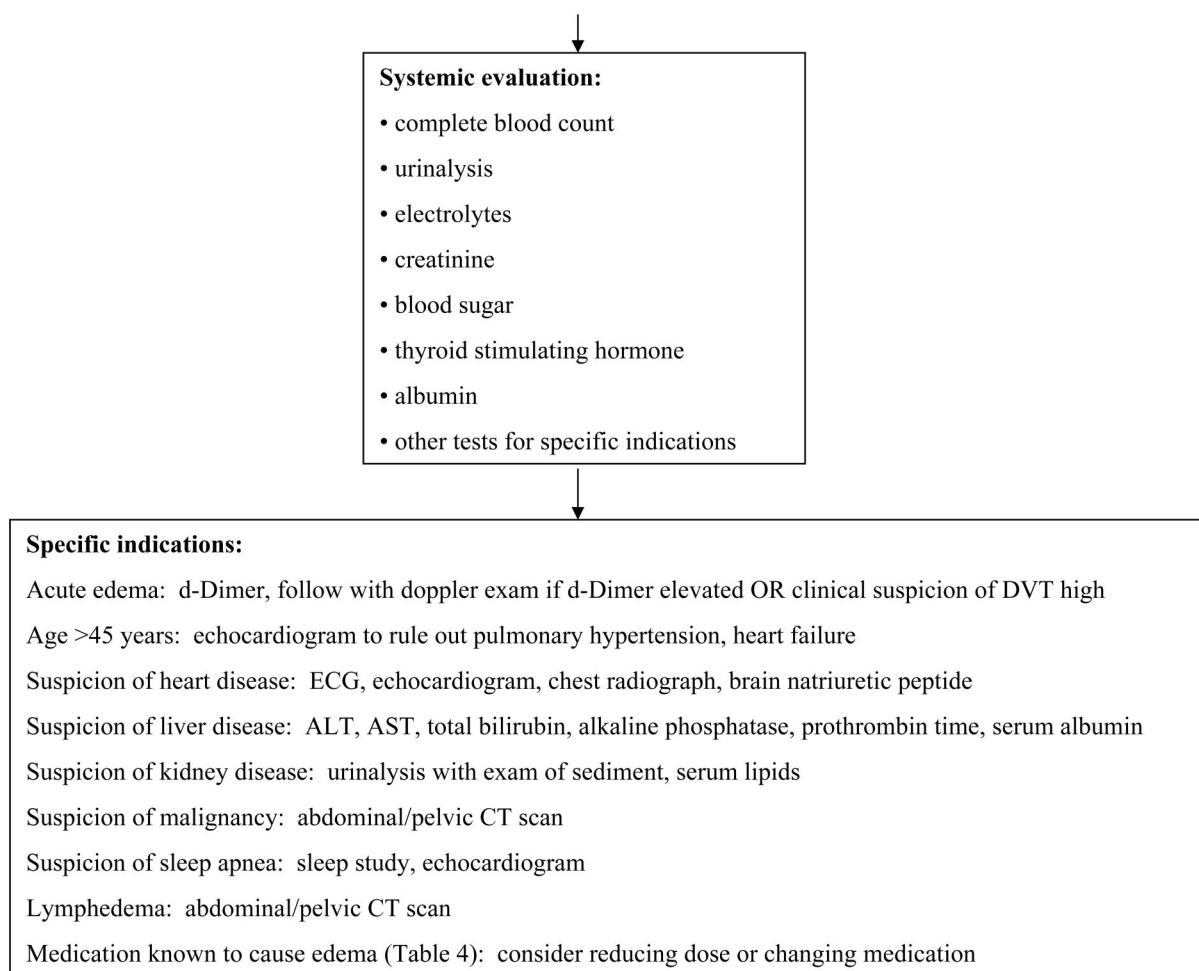
giomas, and jaundice) may be helpful in detecting a systemic cause.

### Diagnostic Studies

#### Laboratory Tests

Most patients over age 50 with leg edema have venous insufficiency, but if the etiology is unclear, a short list of laboratory tests will help rule out systemic disease: complete blood count, urinalysis, electrolytes, creatinine, blood sugar, thyroid-stimulating hormone, and albumin. A serum albumin below 2 g/dL often leads to edema and can be caused by liver disease, nephrotic syndrome, or protein-losing enteropathy.<sup>14</sup> Additional tests are indicated depending on the clinical presentation:

- Patients who may have a *cardiac etiology* should have an electrocardiogram, echocardiogram, and chest radiograph. Dyspneic patients should have a brain natriuretic peptide (BNP) determination to help detect heart failure. The BNP is most helpful for ruling out (rather than ruling in) heart failure because the sensitivity is high (90%).<sup>23</sup>
- *Idiopathic edema* can be diagnosed in young women without further testing if there is no reason to suspect another etiology based on history and physical examination.<sup>5</sup> However, tests to confirm idiopathic edema have been described and may be helpful in difficult cases (Table 5).<sup>12,24</sup>



**Figure 3. Systemic evaluation.**

- In patients with *acute edema* (<72 hours), a normal D-dimer will essentially rule out deep vein thrombosis if the clinical suspicion is low because false negative D-dimers are rare.<sup>25-27</sup> However, an elevated D-dimer should be followed up with a Doppler examination because false positive D-dimers are common.<sup>28</sup> The variability among laboratory assays has been problematic, but a recent systematic review recommended the rapid quantitative ELISA as the most useful test.<sup>25</sup>
- Patients with possible *nephrotic syndrome* should have serum lipids in addition to the basic laboratory studies listed above.

#### *Imaging Studies*

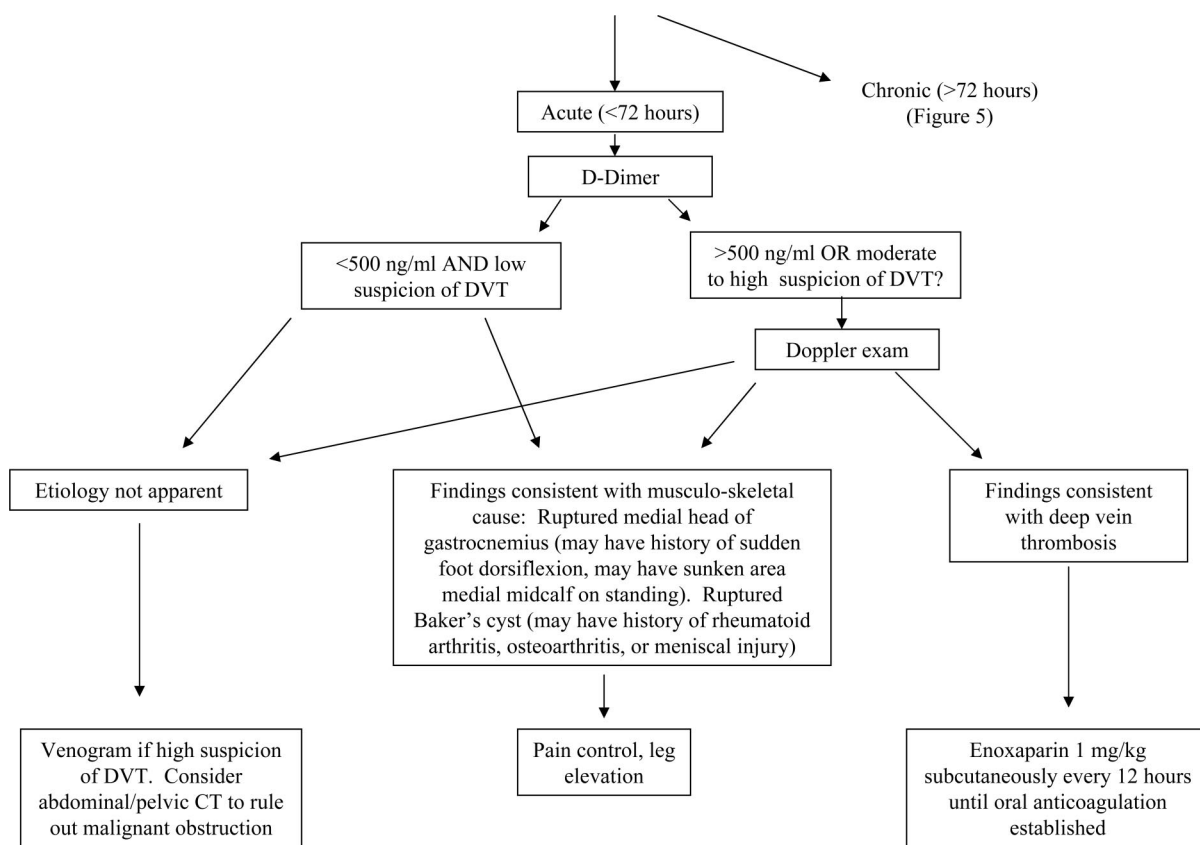
Patients over age 45 with edema of unclear etiology should have an echocardiogram to rule out pulmonary hypertension.<sup>4</sup> Lymphoscintigraphy can be helpful to distinguish lymphedema from venous

edema and to determine the cause of lymphedema. Lymphoscintigraphy is performed by injecting a radioactive tracer into the first web space and monitoring lymphatic flow with a gamma camera.<sup>13</sup>

#### **Common Causes of Leg Edema**

##### *Venous Insufficiency*

Venous insufficiency is characterized by chronic pitting edema, often associated with brown hemosiderin skin deposits on the lower legs. The skin changes can progress to dermatitis and ulceration, which usually occur over the medial malleoli. Other common findings include varicose veins and obesity. Most patients are asymptomatic but a sensation of aching or heaviness can occur.<sup>2</sup> The diagnosis is usually made clinically but can be confirmed with a Doppler study.<sup>2,29</sup> Although chronic venous insufficiency is thought to result from previous deep vein thrombosis, only one third



**Figure 4. Unilateral edema.**

of patients will give that history.<sup>2</sup> “Dependent edema” is a variant of venous insufficiency and often occurs in patients following stroke who sit in wheelchairs for long periods.

#### Heart Failure

Patients with congestive heart failure complain of dyspnea, dependent edema, and fatigue. On physical examination they may have elevated jugular venous pressure, basilar crackles on chest auscultation, gallop rhythm, and pitting edema. In one study, BNP was found to be helpful in diagnosing heart failure among dyspneic patients.<sup>23</sup> Using a cutoff value of 100 pg/mL, this test had a sensitivity of 90% and specificity of 76% when compared with a clinical diagnosis by 2 independent cardiologists.<sup>23</sup>

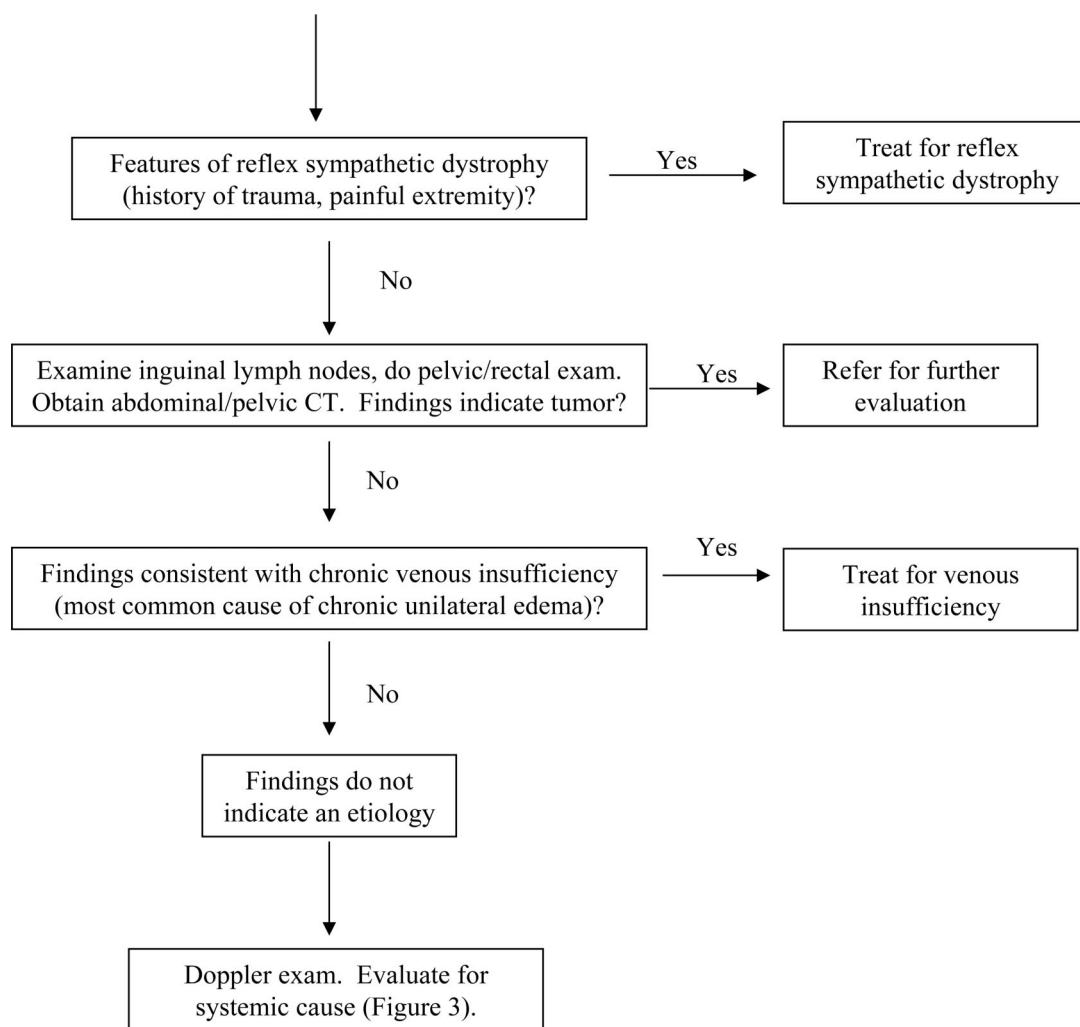
#### Pulmonary Hypertension

Pulmonary hypertension commonly results from sleep apnea, is under-recognized as a cause of edema,<sup>4</sup> and can be diagnosed by echocardiography. Other causes of pulmonary hypertension include left heart failure and chronic lung disease. In a

study of primary care patients, Blankfield and colleagues<sup>4</sup> obtained echocardiograms on 45 patients with edema. The initial clinical impression was venous insufficiency in 71% of these patients. However, the final impression was pulmonary hypertension (>40 mm Hg) in 20% and “borderline pulmonary hypertension” (31 to 40 mm Hg) in 22%. Only 22% of the patients were found to have venous insufficiency. This study was not designed to determine whether borderline pulmonary hypertension was the primary cause of edema or simply an incidental finding. Treating sleep apnea might improve the leg edema that results from pulmonary hypertension, but this also is unknown. Given these uncertainties, we recommend an echocardiogram in patients who are at risk for pulmonary hypertension and in patients over age 45 with leg edema of unclear etiology.

#### Drugs

Drugs that can cause edema are listed in Table 4. Calcium channel blockers and nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly



**Figure 5. Chronic unilateral edema.**

implicated.<sup>14</sup> The incidence of edema in patients taking NSAIDs is approximately 5%.<sup>17</sup> Up to 50% of patients on calcium-channel blockers develop

edema.<sup>13</sup> Dihydropyridines (amlodipine, nifedipine) may be more likely to induce edema than phenylalkylamines (verapamil) or benzothiazepines (diltiazem).<sup>14</sup>

**Table 4. Drugs That May Cause Leg Edema**<sup>9,12,14,16,17</sup>

Antihypertensive drugs
Calcium channel blockers
Beta blockers
Clonidine
Hydralazine
Minoxidil
Methyldopa
Hormones
Corticosteroids
Estrogen
Progesterone
Testosterone
Other
Nonsteroidal anti-inflammatory drugs
Pioglitazone, Rosiglitazone
Monoamine oxidase inhibitors

#### *Idiopathic Edema*

Idiopathic edema occurs only in menstruating women and is most common in the 20s and 30s. Synonyms include fluid-retention edema, orthostatic edema, cyclical edema, and periodic edema. However, the symptoms persist throughout the menstrual cycle, and idiopathic edema should be distinguished from premenstrual edema. Idiopathic edema leads to pathologic fluid retention in the upright position, and women typically notice a weight gain of >1.4 kg as the day progresses.<sup>30</sup> However, the weight gain may be as little as 0.7 kg.<sup>31</sup> Patients often complain of face and hand

**Table 5. Tests for Idiopathic Edema**<sup>12,30,31,52</sup>

Morning and Evening Weights: Patients should weigh themselves nude and with an empty bladder before food or fluids in the morning and at bedtime. A mean weight gain >0.7 kg is consistent with idiopathic edema.

Water Load Test: After avoiding diuretics for at least 10 days, the patient drinks 20 mL/kg body weight (maximum 1500 mL) uniced water over 20 minutes, sometime between 7:30 AM and 9:00 AM. The patient collects urine every hour, starting 1 hour before the oral fluid load and ending 4 hours after. On the first day, the patient should be walking slowly or standing during this 4-hour period. On the second day, the patient repeats the fluid load and urine collection, but should be recumbent during the 4-hour period. In patients with idiopathic edema, less than 55% of water load is excreted in the upright position and more than 65% in the recumbent position.

edema in addition to leg swelling.<sup>31</sup> Several confirmatory tests are available (Table 5), but the diagnosis is usually made clinically after ruling out systemic disease by history and physical examination.<sup>31</sup> The confirmatory tests in Table 5 are indicated only when there is significant doubt about the diagnosis. Obesity and depression can be associated with this syndrome, and diuretic abuse is common.<sup>14</sup>

#### *Lymphedema*

*Primary lymphedema* is a rare disorder that is divided into 3 types according to age of presentation.<sup>21</sup>

*Congenital lymphedema* may be present at birth or becomes manifest by age 2 years. The familial form of congenital lymphedema is an autosomal dominant disorder known as Milroy disease.

*Lymphedema praecox*, the most common form of primary lymphedema, has its onset between age 2 and 35 and has a female to male ratio of 10:1. Lymphedema praecox is usually unilateral and is limited to the foot and calf in most patients.<sup>32</sup> The familial form of lymphedema praecox is an autosomal dominant disorder known as Meige disease.

*Lymphedema tarda* presents after age 35.

*Secondary lymphedema* is much more common than primary, and the cause is generally apparent from the history. The most common causes of leg lymphedema are tumor (eg, lymphoma, prostate cancer, ovarian cancer), surgery involving lymphatics, radiation therapy, and infection (bacterial infection or filariasis).<sup>21</sup> Chronic lymphedema is usually distinguished from venous edema based on characteristic skin changes, absence of pitting, and history of an inciting cause. The skin becomes thickened and darkened and may develop multiple projections called lymphostatic verrucosis.<sup>9</sup> The dorsum of the foot is prominently involved and may have a squared-off appearance. The examiner is unable to pinch a fold of skin on the dorsal aspect of the base of the second toe (Kaposi-Stemmer

sign).<sup>12,14,22</sup> However, early lymphedema may be difficult to distinguish from venous edema because pitting is present in both, and the skin changes are absent early in the course. If the distinction between early lymphedema and venous edema cannot be made clinically, lymphoscintigraphy may be indicated.<sup>33</sup> However, the distinction cannot always be made because chronic venous insufficiency can lead to secondary lymphedema with abnormally delayed lymph drainage on lymphoscintigram.<sup>15,34</sup>

#### *Deep Vein Thrombosis*

Deep vein thrombosis classically results in an acutely swollen, painful leg that may be discolored. However, the presentation can be more subtle with mild, painless, asymmetric edema. The physical examination is often unreliable and patients with acute edema usually require further evaluation, which may include a D-dimer determination and a Doppler study (Figures 1–5). Risk factors for deep vein thrombosis include cancer, immobilization (especially following surgery or an injury), and a hypercoagulable state.

#### *Obesity*

Obesity itself does not cause leg edema but obesity can lead to many other causes such as chronic venous insufficiency, lymphedema, idiopathic edema, and obstructive sleep apnea.

#### *Premenstrual Edema*

Most women experience some premenstrual edema and weight gain. The edema tends to be generalized, occurs a few days before the beginning of menses, and resolves during a diuresis that occurs with the onset of menses. The etiology is poorly understood.<sup>35</sup>

#### *Pregnancy*

Increased venous pressure resulting from an enlarging uterus near term commonly leads to lower



**Table 6. Strength of Evidence for Major Recommendations**

	Strength of Recommendation*
Diagnostic recommendations	
Relative frequencies of causes of edema in Tables 1–3 <sup>1,4,53</sup>	C
Clinical findings that help distinguish venous edema, lymphedema, and lipidema <sup>8,9,11,12,21,22,24</sup>	C
Important components of the patient history <sup>9–12,24,54</sup>	C
Important components of physical exam <sup>2,9–12,22,24</sup>	C
Echocardiogram recommended in patients over age 45 <sup>4</sup>	C
Medications that cause edema <sup>4,13,14,16,17,24,55</sup>	C
Normal D-dimer rules out deep vein thrombosis <sup>25,56</sup>	B
Use of Doppler exam to confirm or rule out deep vein thrombosis <sup>57–59</sup>	B
Treatment recommendations	
Diuretics to treat venous insufficiency <sup>2</sup>	C
Horse chestnut seed extract to treat venous insufficiency <sup>41–44</sup>	B
Compression stockings to treat venous insufficiency <sup>60</sup>	C
Diuretics to treat idiopathic edema <sup>5,31,46</sup>	C

\* Strength of recommendation classified according to the 3-component SORT system<sup>61</sup>: A, denotes recommendation based on consistent and good-quality patient-oriented evidence<sup>61</sup>; B, denotes recommendation based on inconsistent or limited-quality patient-oriented evidence<sup>61</sup>; C, denotes recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.<sup>61</sup>

extremity edema and varicosities. Edema is commonly present in patients with preeclampsia but is no longer considered a factor in making the diagnosis.<sup>36</sup>

## Treatment

### Venous insufficiency

Chronic venous insufficiency is treated with leg elevation and knee-high compression stockings that provide 30 to 40 mm Hg pressure at the ankle.<sup>2,37–40</sup> If arterial insufficiency is a concern, an ankle-brachial index should be performed because compression stockings are contraindicated in arterial insufficiency. Patients who are refractory to compression stockings may improve with intermittent pneumatic compression pumps.<sup>2</sup> Horse chestnut seed extract (300 mg, standardized to 50 mg of escin, twice a day) has been found to be effective in several studies and can be obtained in health food stores.<sup>41–44</sup> Horse chestnut seed extract contains escin, which inhibits the activity of elastase and hyaluronidase. These enzymes are thought to play a role in the pathophysiology of chronic venous insufficiency.<sup>45</sup> However, the benefits are modest and the agent has not gained widespread acceptance. Diuretics (eg, furosemide 20 to 40 mg once a day with supplemental potassium) can be used for short periods in severely affected patients. However, venous insufficiency is not a volume overload state, and long-term use of diuretics can lead to adverse metabolic complications.<sup>2</sup>

### Idiopathic Edema

Spirolactone is considered the drug of choice for idiopathic edema because of the secondary hyperaldosteronism found in patients with this disorder.<sup>31</sup> The starting dose is 50 to 100 mg daily (maximum 100 mg, 4 times daily).<sup>30,46</sup> If spironolactone is not effective, low doses of a thiazide diuretic (eg, hydrochlorothiazide, 25 mg daily) can be added with close monitoring of the serum potassium. It is best to avoid loop diuretics.<sup>30</sup> The diuretic should be given in the early evening because fluid retention is most noticeable at the end of the day. Other measures include intermittent recumbency, avoiding environmental heat, low salt diet, avoiding excessive fluid intake, and weight loss for obese patients.<sup>31</sup> It may be helpful to ask about depression, eating disorder, and surreptitious diuretic or laxative use. Compression stockings are usually not helpful and not tolerated. Many patients with idiopathic edema are already taking diuretics when first seen and may have “diuretic-induced edema.”<sup>46–48</sup> Chronic use of diuretics may lead to a state of mild hypovolemia with resulting stimulation of the renin-angiotensin-aldosterone system. When the diuretics are withdrawn, a rebound worsening of edema occurs and patients believe they must continue.<sup>49</sup> However, the treatment of suspected diuretic-induced edema is to withdraw diuretics for 3 to 4 weeks after warning the patient that her edema will probably worsen initially and reassuring her that the diuretic can

**Table 7. Frequently Asked Questions**

Question	Answer
Who needs a pelvic and rectal exam to rule out tumor?	We recommend a pelvic/rectal exam in patients who present with findings suspicious for tumor, such as unilateral edema, pelvic symptoms, or weight loss. We were unable to find evidence or published opinions on when the pelvic or rectal exam is indicated in patients with edema. The pelvic exam has poor sensitivity compared with computed tomography (CT) scan for detection of pelvic tumors that cause leg edema. However, information gained from this part of the exam may complement subsequent radiologic studies.
Who needs an abdominal/pelvic CT scan to rule out tumor?	An abdominal/pelvic CT scan should be considered in patients over 40 without an apparent cause for edema and in younger patients with suspicious findings (unilateral edema, pelvic signs or symptoms, weight loss). Patients over age 35 with undiagnosed lymphedema should have a CT scan. <sup>11</sup> Tumors commonly associated with leg edema include prostate cancer, ovarian cancer, and lymphoma. <sup>11,12</sup>
Who needs to be evaluated for a systemic cause, and what tests should be done?	It is reasonable to obtain a few basic tests in all patients with bilateral leg edema over age 45 because the tests are relatively few and inexpensive. The basic tests include a complete blood count, urinalysis, electrolytes, creatinine, blood sugar, thyroid-stimulating hormone, and serum albumin. An echocardiogram should be considered in patients over age 45, because pulmonary hypertension is a common cause of leg edema and is commonly missed. <sup>4</sup> Unilateral edema generally does not require a search for a systemic cause. A search for liver disease is unnecessary in the absence of ascites because leg edema is a late finding in patients with cirrhosis.
When should diuretics be used and when should they be avoided?	Loop diuretics (eg, furosemide, 40 mg daily) should be used in patients with edema secondary to heart failure or renal failure. <sup>62</sup> Patients with ascites and leg edema due to cirrhosis should be treated with spironolactone (starting with 50 mg daily) combined with furosemide (starting with 40 mg daily). <sup>63,64</sup> In patients with chronic venous insufficiency, diuretics should be used only after leg elevation and compression stockings have failed. At that point, they should be used sparingly and for brief periods. In patients with idiopathic edema who are taking diuretics, a 3 to 4 week trial off diuretics is indicated. In patients with idiopathic edema who are not already taking diuretics or those who fail to improve off diuretics, spironolactone and thiazides can be used. Long-term furosemide use in patients with idiopathic edema has been associated with impaired renal function. <sup>65</sup> Diuretics should be used rarely if at all in patients with lipidema, lymphedema, and deep vein thrombosis.

always be restarted. If the edema does not improve after 4 weeks, spironolactone can be initiated at a dose of 50 to 100 mg daily and increased to a maximum of 100 mg, 4 times daily.<sup>30,46</sup>

### **Lymphedema**

Nonspecific treatment of lymphedema includes exercise, elevation, compressive garments, manual lymphatic drainage, intermittent pneumatic compression, and surgery (excisional procedures, microsurgery).<sup>13,21,33</sup> Tinea pedis should be controlled, and prophylactic antibiotics may be indicated for recurrent cellulitis. Diuretics are generally not helpful.<sup>13</sup> Treatment of lymphedema is often disappointing, and psychosocial support is important in such patients.

### **Deep Vein Thrombosis**

An acute deep vein thrombosis is generally treated with low molecular weight heparin, such as enoxaparin 1 mg/kg/dose subcutaneously every 12 hours.<sup>50</sup> Warfarin can be initiated simultaneously

with heparin, starting with 5 to 10 mg daily for 2 days with subsequent dosage based on a target international normalized ratio range of 2.0 to 3.0. Heparin is continued for at least 5 days (10 days for severe iliofemoral thrombosis). When the international normalized ratio is between 2.0 and 3.0 for 2 days, the heparin can be withdrawn. A platelet count should be obtained on day 3 and day 10 of heparin therapy to rule out heparin-induced thrombocytopenia. The total duration of oral anticoagulation is reviewed elsewhere.<sup>50</sup> If anticoagulation is contraindicated, an inferior vena cava filter may be an option. Thrombolytic agents are generally reserved for patients with phlegmasia cerulea dolens, which is manifested by severe pain, bullae formation, and skin discoloration.

### **Summary and Recommendations**

- In the approach to leg edema of unclear etiology, the physician should first rule out lipidema (fat

maldistribution with sparing of feet) and lymphedema (marked foot and toe involvement, verrucous thickened skin, nonpitting when chronic) because subsequent evaluation and treatment are different for these disorders.

- If systemic disease is considered unlikely, the most common causes of bilateral leg edema are idiopathic edema (in young women) and chronic venous insufficiency (in older patients).
- In patients with chronic bilateral edema, the physician should consider the most common systemic causes (cardiac, renal, hepatic) and decide, based on history and physical examination, which of them need to be ruled out with further testing. Pulmonary hypertension is a common cause and should be suspected in patients who may have sleep apnea (eg, neck circumference >17 inches, loud snoring or apnea noted by sleep partner).
- If the patient presents with sudden onset (<72 hours) of leg swelling, a deep vein thrombosis should be ruled out using a Doppler examination.
- Evidence ratings for the major recommendations in this article are included in Table 6.

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## References

1. Menzoain JO, Doyle JE. Venous insufficiency of the leg. *Hosp Pract* 1989;24:109–16.
2. Alguire PC, Mathes BM. Chronic venous insufficiency and venous ulceration. *J Gen Intern Med* 1997;12:374–83.
3. Kannel WB. Epidemiological aspects of heart failure. *Cardiol Clin* 1989;7:1–9.
4. Blankfield RP, Finkelhor RS, Alexander JJ, et al. Etiology and diagnosis of bilateral leg edema in primary care. *Am J Med* 1998;105:192–7.
5. Streeten DH. Idiopathic edema. *Curr Ther Endocrinol Metab* 1997;6:203–6.
6. Gorman WP, Davis KR, Donnelly R. ABC of arterial and venous disease. Swollen lower limb-1: general assessment and deep vein thrombosis. *BMJ* 2000;320:1453–6.
7. Mortimer PS. Swollen lower limb-2: lymphoedema. *BMJ* 2000;320:1527–9.
8. Rudkin GH, Miller TA. Lipidema: a clinical entity distinct from lymphedema. *Plast Reconstr Surg* 1994;94:841–7.
9. Ciocon JO, Fernandez BB, Ciocon DG. Leg edema:

clinical clues to the differential diagnosis. *Geriatrics* 1993;48:34–40, 45.

10. Merli GJ, Spandorfer J. The outpatient with unilateral leg swelling. *Med Clin North Am* 1995;79:435–47.
11. Young JR. The swollen leg. Clinical significance and differential diagnosis. *Cardiol Clin* 1991;9:443–56.
12. Yale SH, Mazza JJ. Approach to diagnosing lower extremity edema. *Compr Ther* 2001;27:242–52.
13. Topham EJ, Mortimer PS. Chronic lower limb oedema. *Clin Med* 2002;2:28–31.
14. Cho S, Atwood JE. Peripheral edema. *Am J Med* 2002;113:580–6.
15. Tiwari A, Cheng KS, Button M, Myint F, Hamilton G. Differential diagnosis, investigation, and current treatment of lower limb lymphedema. *Arch Surg* 2003;138:152–61.
16. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. *Curr Cardiol Rep* 2002;4:479–82.
17. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002;89:18D–25D.
18. Padberg F Jr, Cerveira JJ, Lal BK, Pappas PJ, Varma S, Hobson RW 2nd. Does severe venous insufficiency have a different etiology in the morbidly obese? Is it venous? *J Vasc Surg* 2003;37:79–85.
19. L’Hermitte F, Behar A, Paries J, Cohen-Boulakia F, Attali JR, Valensi P. Impairment of lymphatic function in women with gynoid adiposity and swelling syndrome. *Metabolism* 2003;52:805–9.
20. Ageno W, Piantanida E, Dentali F, et al. Body mass index is associated with the development of the post-thrombotic syndrome. *Thromb Haemost* 2003;89:305–9.
21. Szuba A, Rockson SG. Lymphedema: classification, diagnosis, and therapy. *Vasc Med* 1998;3:145–6.
22. Stemmer R. Ein klinisches zeichen zur gruendung differential diagnose des lymphodem. [A clinical symptom for the early and differential diagnosis of lymphedema]. *German. Vasa* 1976;5:261–2.
23. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
24. Powell AA, Armstrong MA. Peripheral edema. *Am Fam Physician* 1997;55:1721–6.
25. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004;140:589–602.
26. Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003;108:313–8.

27. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost* 2002;87:7–12.
28. Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. *Am J Med* 2003;114:276–82.
29. Szendro G, Nicolaidis AN, Zukowski AJ, et al. Duplex scanning in the assessment of deep venous incompetence. *J Vasc Surg* 1986;4:237–42.
30. Marks AD. Intermittent fluid retention in women. Is it idiopathic edema? *Postgrad Med* 1983;73:75–83.
31. Streeten DH. Idiopathic edema. Pathogenesis, clinical features, and treatment. *Endocrinol Metab Clin North Am* 1995;24:531–47.
32. Rockson SG. Lymphedema. *Am J Med* 2001;110:288–95.
33. Mortimer PS. Managing lymphedema. *Clin Exp Dermatol* 1995;20:90–106.
34. Bull RH, Gane JN, Evans JE, Joseph AE, Mortimer PS. Abnormal lymph drainage in patients with chronic venous leg ulcers. *J Am Acad Dermatol* 1993;28:585–90.
35. Seippel L, Eriksson O, Grankvist K, von Shoultz B, Backstrom T. Physical symptoms in premenstrual syndrome are related to plasma progesterone and desoxycorticosterone. *Gynecol Endocrinol* 2000;14:173–81.
36. Zlatnik FJ. Hypertension in pregnancy. *The Iowa Perinatal Letter* 2004;25:5–9.
37. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997;349:759–62.
38. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med* 2001;161:2105–9.
39. Kolbach DN, Sandbrink MW, Hamulyak K, Neumann HA, Prins MH. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2004(1):CD004174.
40. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;141:249–56.
41. Rehn D, Unkauf M, Klein P, Jost V, Lucker PW. Comparative clinical efficacy and tolerability of oxerutins and horse chestnut extract in patients with chronic venous insufficiency. *Arzneimittelforschung* 1996;46:483–7.
42. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev* 2002(1):CD003230.
43. Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency. A criteria-based systematic review. *Arch Dermatol* 1998;134:1356–60.
44. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet* 1996;347:292–4.
45. Facino RM, Carini M, Stefani R, Aldini G, Saibene L. Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from *Hedera helix*, *Aesculus hippocastanum*, and *Ruscus aculeatus*: factors contributing to their efficacy in the treatment of venous insufficiency. *Arch Pharm (Weinheim)* 1995;328:720–4.
46. Kay A, Davis CL. Idiopathic edema. *Am J Kidney Dis* 1999;34:405–23.
47. MacGregor GA, Markandu ND, Roulston JE, Jones JC, de Wardener HE. Is “idiopathic” edema idiopathic? *Lancet* 1979;1:397–400.
48. Idiopathic edema: role of diuretic abuse. *Kidney Int* 1981;19:881–91.
49. Rose BD. Idiopathic edema. Available from UpToDate.com. Accessed on 26 February 2005.
50. Lip GYH, Hull RD. Treatment of deep vein thrombosis. Available from [www.UpToDate.com](http://www.UpToDate.com). Accessed on 5 November 2004.
51. Boyd DA. Unilateral lower extremity edema in May-Thurner syndrome. *Mil Med* 2004;169:968–71.
52. Streeten DHP. Orthostatic disorders of the circulation. New York: Plenum Press; 1987.
53. Coon WW, Willis PW 3rd, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation* 1973;48:839–46.
54. Rose BD. Approach to the adult with edema. Available from UpToDate.com. Accessed 11 October 2004.
55. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. *Pharmacotherapy* 2002;22:924–9.
56. Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: an overview. *Thromb Haemost* 1994;71:1–6.
57. Lensing AW, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989;320:342–5.
58. Mattos MA, Londrey GL, Leutz DW, et al. Color-flow duplex scanning for the surveillance and diagnosis of acute deep venous thrombosis. *J Vasc Surg* 1992;15:366–75; Discussion 375–6.
59. Monreal M, Montserrat E, Salvador R, et al. Real-time ultrasound for diagnosis of symptomatic venous thrombosis and for screening of patients at risk: correlation with ascending conventional venography. *Angiology* 1989;40:527–33.
60. Partsch H. Compression therapy of the legs. A review. *J Dermatol Surg Oncol* 1991;17:799–805.
61. Ebell MH, Siwek J, Weiss BD. Strength of recom-

- mendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Fam Pract* 2004;53:111–20.
62. Brater DC. Diuretic therapy. *N Engl J Med* 1998; 339:387–95.
  63. Such J, Runyon BA. Initial therapy of ascites in patients with cirrhosis. Available from UpToDate.com. Accessed on 27 September 2004.
  64. Fogel MR, Sawhney VK, Neal EA, Miller RG, Knauer CM, Gregory PB. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. *J Clin Gastroenterol* 1981;3(Suppl 1): 73–80.
  65. Shichiri M, Shiigai T, Takeuchi J. Long-term furosemide treatment in idiopathic edema. *Arch Intern Med* 1984;144:2161–4.