Approach to Leg Edema of Unclear Etiology

John W. Ely, MD, MSPH, Jerome A. Osberoff, MD, M. Lee Chambliss, MD, MSPH, and Mark H. Ebell, MD, MS

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, load 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, whereas heart failure affects only approximately 1%. The most likely cause of leg edema in women under age 50 is idiopathic edema, formerly known as cyclic edema. 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. Lymphedema consists of excess protein-rich interstitial fluid within the skin and subcutaneous tissue resulting from lymphatic dysfunction. A third type, lipedema, is more accurately considered a form of fat maldistribution rather than true edema.
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.6,9–11 The 72-hour cutoff is commonly cited9–11 but arbitrary and not well supported with evidence. Deep vein thrombosis should be considered in patients presenting after 72 hours with otherwise consistent findings.
- Is the edema painful? Deep vein thrombosis and reflex sympathetic dystrophy are usually painful.10,12 Chronic venous insufficiency can cause low-grade aching. Lymphedema is usually painless.9,10,12–15
- What drugs are being taken? Calcium channel blockers, prednisone, and anti-inflammatory drugs are common causes of leg edema.9,14,16,17 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 1. Common Causes of Leg Edema in the United States

<table>
<thead>
<tr>
<th></th>
<th>Unilateral</th>
<th>Bilateral</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Acute (&lt;72 hours)</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td>Deep vein thrombosis</td>
<td>Venous insufficiency</td>
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<tr>
<td></td>
<td>Venous insufficiency</td>
<td>Chronic</td>
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<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Idiopathic edema</td>
<td>Lymphedema</td>
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<tr>
<td></td>
<td>Drugs</td>
<td>Drugs</td>
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<td></td>
<td>Premenstrual edema</td>
<td>Pregnancy</td>
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<td></td>
<td>Pregnancy</td>
<td>Obese</td>
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Table 2. Less Common Causes of Leg Edema in the United States

<table>
<thead>
<tr>
<th></th>
<th>Unilateral</th>
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<tbody>
<tr>
<td></td>
<td>Acute (&lt;72 hours)</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td>Ruptured Baker’s cyst</td>
<td>Bilateral deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Secondary lymphedema (tumor, radiation,</td>
<td>Renal disease (nephrotic syndrome,</td>
</tr>
<tr>
<td></td>
<td>surgery, bacterial infection)</td>
<td>glomerulonephritis)</td>
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<tr>
<td></td>
<td>Ruptured medial head of gastrocnemius</td>
<td>Acute worsening of systemic cause</td>
</tr>
<tr>
<td></td>
<td>Pelvic tumor or lymphoma causing external</td>
<td>(heart failure, renal disease)</td>
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<tr>
<td></td>
<td>pressure on veins</td>
<td></td>
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<tr>
<td></td>
<td>Compartment syndrome</td>
<td>Reflex sympathetic dystrophy</td>
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http://www.jabfm.org
Does the edema improve overnight? Venous edema is more likely than lymphedema to improve overnight.13
Is there a history consistent with sleep apnea?
Sleep apnea can cause pulmonary hypertension, which is a common cause of leg edema.4 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.

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

<table>
<thead>
<tr>
<th>Unilateral Acute (&lt;72 hours)</th>
<th>Unilateral Chronic</th>
<th>Bilateral Acute (&lt;72 hours)</th>
<th>Bilateral Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lymphedema (congenital lymphedema, lymphedema praecox, lymphedema tarda)</td>
<td></td>
<td>Primary lymphedema (congenital lymphedema, lymphedema praecox, lymphedema tarda)</td>
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<tr>
<td>Congenital venous malformations</td>
<td></td>
<td>Protein losing enteropathy, malnutrition, malabsorption</td>
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<tr>
<td>May-Thurner syndrome (iliaic-vein compression syndrome)</td>
<td></td>
<td>Restrictive pericarditis</td>
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<td></td>
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<td>Restrictive cardiomyopathy</td>
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<td>Beri Beri</td>
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<tr>
<td></td>
<td></td>
<td>Myxedema</td>
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**Physical Examination**
Key elements of the physical examination include
- Body mass index. Obesity is associated with sleep apnea and venous insufficiency.18–20
- 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.**
ney disease. Generalized edema is due to systemic disease. The dorsum of the foot is spared in lipidema but prominently involved in lymphedema.8

- Tenderness: deep vein thrombosis and lipidema are often tender. Lymphedema is usually non-tender.
- Pitting: deep vein thrombosis, venous insufficiency, and early lymphedema usually pit. Myxedema and the advanced fibrotic form of lymphedema typically do not pit.9,12,14,21
- Varicose veins: leg varicosities are often present in patients with chronic venous insufficiency, but venous insufficiency can occur without varicose veins.10
- 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.15,22
- Skin changes: a warty texture (hyperkeratosis) with papillomatosis and brawny induration are characteristic of chronic lymphedema.9,14 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 hemangioenas, 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.14 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%).23
- 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.5 However, tests to confirm idiopathic edema have been described and may be helpful in difficult cases (Table 5).12,24

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Figure 2. Common causes.
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. However, an elevated D-dimer should be followed up with a Doppler examination because false positive D-dimers are common. The variability among laboratory assays has been problematic, but a recent systematic review recommended the rapid quantitative ELISA as the most useful test.

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. 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.

**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 maleoli. Other common findings include varicose veins and obesity. Most patients are asymptomatic but a sensation of aching or heaviness can occur. The diagnosis is usually made clinically but can be confirmed with a Doppler study. Although chronic venous insufficiency is thought to result from previous deep vein thrombosis, only one third
of patients will give that history. “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. 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.

**Pulmonary Hypertension**

Pulmonary hypertension commonly results from sleep apnea, is under-recognized as a cause of edema, 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 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
Implicated. The incidence of edema in patients taking NSAIDS is approximately 5%. Up to 50% of patients on calcium-channel blockers develop edema. Dihydropyridines (amlodipine, nifedipine) may be more likely to induce edema than phenylalkylamines (verapamil) or benzothiazepines (diltiazem).

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. However, the weight gain may be as little as 0.7 kg. Patients often complain of face and hand

### Table 4. Drugs That May Cause Leg Edema

<table>
<thead>
<tr>
<th>Antihypertensive drugs</th>
<th>Calcium channel blockers</th>
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<tbody>
<tr>
<td>Clonidine</td>
<td>Hydralazine</td>
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<tr>
<td>Minoxidil</td>
<td>Methyldopa</td>
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<tr>
<td>Corticosteroids</td>
<td>Estrogen</td>
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<tr>
<td>Progesterone</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Pioglitazone, Rosiglitazone</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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</tbody>
</table>

**Figure 5. Chronic unilateral edema.**
edema in addition to leg swelling. Several confirmatory tests are available (Table 5), but the diagnosis is usually made clinically after ruling out systemic disease by history and physical examination. 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.

**Lymphedema**

**Primary lymphedema** is a rare disorder that is divided into 3 types according to age of presentation.

- **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. 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). 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. 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). 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. However, the distinction cannot always be made because chronic venous insufficiency can lead to secondary lymphedema with abnormally delayed lymph drainage on lymphoscintigram.

**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.

**Pregnancy**

Increased venous pressure resulting from an enlarging uterus near term commonly leads to lower
extremity edema and varicosities. Edema is commonly present in patients with preeclampsia but is no longer considered a factor in making the diagnosis.36

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.2,37–40 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.2 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.41–44 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.45 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.2

Idiopathic Edema

Spironolactone is considered the drug of choice for idiopathic edema because of the secondary hyperaldosteronism found in patients with this disorder.31 The starting dose is 50 to 100 mg daily (maximum 100 mg, 4 times daily).30,46 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.30 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.31 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.”46–48 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.49 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 6. Strength of Evidence for Major Recommendations

<table>
<thead>
<tr>
<th>Diagnostic recommendations</th>
<th>Strength of Recommendation*</th>
</tr>
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<tbody>
<tr>
<td>Relative frequencies of causes of edema in Tables 1–31,4,53</td>
<td>C</td>
</tr>
<tr>
<td>Clinical findings that help distinguish venous edema, lymphedema, and lipidema8,9,11,12,21,22,24</td>
<td>C</td>
</tr>
<tr>
<td>Important components of the patient history2,9–12,24,25</td>
<td>C</td>
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<tr>
<td>Important components of physical exam2,9–12,22,24</td>
<td>C</td>
</tr>
<tr>
<td>Echocardiogram recommended in patients over age 454</td>
<td>C</td>
</tr>
<tr>
<td>Medications that cause edema4,13,14,16,17,28,55</td>
<td>C</td>
</tr>
<tr>
<td>Normal D-dimer rules out deep vein thrombosis23,56</td>
<td>B</td>
</tr>
<tr>
<td>Use of Doppler exam to confirm or rule out deep vein thrombosis25–59</td>
<td>B</td>
</tr>
</tbody>
</table>

* Strength of recommendation classified according to the 3-component SORT system61: A, denotes recommendation based on consistent and good-quality patient-oriented evidence61; B, denotes recommendation based on inconsistent or limited-quality patient-oriented evidence61; C, denotes recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.61
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.30,46

Lymphedema

Nonspecific treatment of lymphedema includes exercise, elevation, compressive garments, manual lymphatic drainage, intermittent pneumatic compression, and surgery (excisional procedures, microsurgery).13,21,33 Tinea pedis should be controlled, and prophylactic antibiotics may be indicated for recurrent cellulitis. Diuretics are generally not helpful.13 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.50 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.50 If anticoagulation is contraindicated, an inferior vena cava filter may be an option. Thrombolytic agents are generally reserved for patients with phlegmasia cerula 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.

We are indebted to focus groups of faculty and residents at the University of Iowa Department of Family Medicine and the Moses Cone Hospital Family Medicine Residency for extensive review and comments, which were audiotaped, transcribed, and used to revise the manuscript.

References


61. Ebell MH, Siwek J, Weiss BD. Strength of recom-


