Clinical features and diagnosis of peripheral lymphedema

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INTRODUCTION

Lymphedema is defined as the abnormal accumulation of interstitial fluid and fibroadipose tissues resulting from injury, infection, or congenital abnormalities of the lymphatic system. Lymphedema is classified as primary or secondary depending on etiology and presentation.

The etiology, risk factors, clinical manifestations, classification, diagnosis, and differential diagnosis of lymphedema will be reviewed here. The prevention and treatment of lymphedema, the operative management of primary and secondary lymphedema, and an overview of the pathophysiology and etiology of generalized edema are presented separately. (See "Clinical staging and conservative management of peripheral lymphedema" and "Surgical treatment of primary and secondary lymphedema" and "Pathophysiology and etiology of edema in adults" and "Pathophysiology and etiology of edema in children".)

NORMAL LYMPHATIC SYSTEM AND LYMPHEDEMA

Lymph flow takes place in a low-pressure system. Uptake of interstitial fluid begins in lymphatic capillaries and pre-collectors that abut the interstitial space. The process is facilitated by skeletal muscle contraction in the extremity. The initial lymphatics merge into vessels of increasing caliber that are partially surrounded by a specialized smooth muscle layer that, upon contraction, promotes peristaltic movement of the lymph fluid toward the systemic circulation. In addition, lymphatic collectors have unidirectional valves that prevent retrograde flow.

The lymph draining from both lower extremities, the gastrointestinal tract, and the left upper body (upper extremity, chest wall, upper back, shoulder, and breast) enter the venous circulation through the thoracic duct, which opens into the venous angle between the left subclavian vein and left internal jugular vein (figure 1) [1]. The lymph draining from the right upper body drains into the right lymphatic duct via a similar right-sided venous angle.

In the extremities, the superficial lymphatic system drains the skin and subcutaneous tissue and drains into the deep system that then drains into the lymph nodes in the axilla or pelvis [1,2].

Lymphedema — Lymphedema occurs when the lymphatic load exceeds the transport capacity of the lymphatic system, which causes filtered fluid to accumulate in the interstitium [3]. This imbalance between interstitial fluid production and transport may be due to congenital malformation of the lymphatic system, or damage to lymphatic vessels or lymph nodes leading to a reduction in the numbers of lymph channels or obstruction of the available channels. Persistent accumulation of lymphatic fluid promotes proliferation of adipocytes and deposition of collagen fibers in the extracellular matrix and around capillary and collecting lymphatics.

Lymphedema is a low-output failure of the lymphovascular system (ie, lymph transport is reduced). It is important to note that the rate of capillary filtration is normal in patients with lymphedema, in contrast to those with generalized edematous states, for which intact lymphatics are overwhelmed by an excessive amount of capillary infiltrate (ie, high-output failure of the lymphatics) [4]. In some cases where high-output failure of the lymphatic system is chronic (eg, recurrent infection, thermal burns, chronic venous insufficiency), a mixed form of edema/lymphedema can develop. (See "Pathophysiology and etiology of edema in adults".)

Classification

Primary — Lymphedema without an inciting factor, termed primary lymphedema, is generally due to a congenital or inherited condition associated with pathologic development of the lymphatic vessels. Primary lymphedema often presents in childhood, but later presentations in adulthood also occur.

Primary lymphedema is classified by the age at onset. Congenital lymphedema is defined by swelling that is present at birth or up to two years postnatally. Lymphedema praecox typically arises during puberty or pregnancy with onset prior to age 35 years, and lymphedema tarda presents with an onset after age 35. Conditions associated with primary lymphedema in children are discussed separately. (See "Pathophysiology and etiology of edema in children", section on 'Primary lymphedema'.)

Primary lymphedema more frequently involves the lower limbs and has an increased incidence in females [4]. Primary lymphedema does occur in upper extremity, and in one small series of 60 patients, the incidence was higher in males (2:1 male: female) [5]. The mean age at diagnosis was 38 years (range, 3 to 82 years), and the majority of cases were not associated with a recognized genetic condition.

Secondary — Lymphedema that occurs as the result of other conditions or treatments is termed secondary lymphedema. Secondary causes of lymphedema include cancer and cancer treatment, infection, inflammatory disorders, obesity, and chronic forms of lymphatic overload (eg, chronic venous insufficiency, trauma/burns). These are discussed in detail below. (See 'Epidemiology and risk factors' below.)

EPIDEMIOLOGY AND RISK FACTORS

Estimates of the prevalence of lymphedema range widely and depend upon age, gender, and etiology [6-10]. Worldwide, the most common cause of lymphedema is filariasis, due to infection by the nematode *Wuchereria bancrofti* [9]. In the developed world, the majority of cases of lymphedema are secondary and due to malignancy or its treatment [8,11-13]. However, other etiologies contribute as well, including primary causes, trauma, and the sequelae of severe chronic venous insufficiency.

Risk factors for lymphedema include certain hereditary syndromes and other genetic mutations, malignancy and its treatments, older age, obesity, autoimmune diseases, and inflammatory arthritis. Some of these factors (older age, obesity) contribute to an increased likelihood of worsening symptoms in patients already affected with lymphedema [14-16]. (See 'Inflammatory disorders' below and 'Obesity' below.)

Cancer and cancer treatment — Cancer-associated lymphedema can occur in several ways:

- Obstruction of lymphatic channels or nodes – Tumor compression of lymphatic channels or nodes can result in the development of lymphedema.
- Infiltration of lymphatic vessels – Tumor cells can infiltrate the lymphatic channels (also called lymphangitic carcinomatosis).
- Lymphatic dissection/lymphadenectomy – Disruption or removal of lymph nodes at the time of surgery can increase the risk of lymphedema in patients with cancer.
- Regional lymph node irradiation can destroy lymphatic channels, decreasing lymphatic transport. However, radiation therapy alone is rarely enough to result in development of

lymphedema.

- Medication effects [17].

The most common cancer-associated with lymphedema is breast cancer related to lymphatic dissection [11-13,18,19]. In a systematic review that included 72 studies (n = 29,612 women), the pooled incidence of upper extremity lymphedema for breast cancer survivors was 17 percent [19]. The greatest incidence was within the first two years following the cancer diagnosis. It is estimated that nearly three fourths of women who will develop lymphedema after axillary lymph node dissection (ALND) do so within three years of surgery. The incidence varied based on the mode of diagnosis. Based on clinical diagnosis, limb measurements, and self-assessment, the incidence was 13, 15, and 20 percent, respectively. (See 'Diagnosis' below.)

Other malignancies are also associated with an increased risk of lymphedema [10,13,20]. In a meta-analysis, the overall incidence of lymphedema in nonbreast malignancies was 16 percent [11]. The incidence of lymphedema associated with specific malignancies was reported as follows:

- Sarcoma – 30 percent
- Lower extremity melanoma – 28 percent
- Gynecologic cancer – 20 percent
- Genitourinary cancer – 10 percent
- Head and neck cancer – 3 percent

Lymphadenectomy — Lymphadenectomy is perhaps the strongest predictor of lymphedema, and it is associated with an increased risk of lymphedema regardless of the cancer type. It is the primary cause of lymphedema in patients with breast cancer, prostate cancer, endometrial cancer, cervical cancer, and melanoma [1,20-22]. (See "Endometrial carcinoma: Staging and surgical treatment", section on 'Lymph node evaluation' and "Management of locally advanced cervical cancer" and "Radical prostatectomy for localized prostate cancer", section on 'Pelvic lymph node dissection'.)

The greatest risk factor for arm lymphedema following treatment for breast cancer is axillary node dissection. Fortunately, contemporary treatment of breast cancer does not mandate axillary node dissection in women with a clinically node-negative axilla. Instead, many women undergo sentinel lymph node biopsy (SLNB), which is associated with a significant reduction in lymphedema [23]. (See "Overview of sentinel lymph node biopsy in breast cancer".)

Risk factors for lymphedema supported by the best evidence following surgery for breast cancer include [19]:

- Axillary node dissection (hazard ratio [HR] 2.5-2.6)
- Increasing number of axillary nodes removed (HR 1.2)
- Mastectomy rather than wide local excision (odds ratio [OR] 2.7-7.4)
- Higher body mass index (HR 1.4)

Racial and ethnic differences in the incidence of breast-cancer associated lymphedema have been reported. An increased risk has persisted despite adjustment for other factors such as obesity and extent of lymph node dissection [24-26]. In one review of 31,274 women, included were 1767 (5.6 percent) Black participants, 27,856 (89.1 percent) White participants, and 1651 (5.3 percent) participants of other or unknown race [25]. The five-year risk of lymphedema was 6.8 percent in White participants undergoing SLNB, 8.8 percent in Black participants undergoing SLNB, 12.2 percent in White participants undergoing ALND, and 18.0 percent in Black participants undergoing ALND. In a prospective review, on multivariable analysis, Black race or Hispanic ethnicity (compared with White race) were independently associated with an increased risk of breast cancer-related lymphedema (OR 3.88, 95% CI 2.14-7.08 and OR 3.01, 95% CI 1.10-7.62, respectively) [24]

Beyond lymphadenectomy, the likelihood of developing lymphedema following surgery is related to other factors such as [11]:

- Increasing body mass index (BMI) (see 'Obesity' below)
- Extent of primary surgery
- Tumor location
- Delayed wound healing
- Postoperative infection
- Postoperative hematoma or seroma

Radiation therapy — The increased risk for lymphedema in patients treated with radiation therapy is best illustrated in breast cancer patients. In a systematic review, there was a significantly higher rate of lymphedema among women who underwent surgery plus axillary radiation therapy compared with surgery alone (41 versus 17 percent) [27].

Radiation therapy is an additive risk factor for those who have undergone axillary node dissection [27-29]. In one report, the incidence of subjective lymphedema was significantly higher with axillary node dissection plus radiation as compared with axillary node dissection alone (7 versus 38 percent) [29]. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)

Women undergoing breast-conserving therapy are also at risk for lymphedema following adjuvant radiation therapy. In a retrospective review involving 1497 women (75 percent with node-negative breast cancer), the reported incidence of lymphedema was 7 percent [30]. For women treated with supraclavicular, axillary, and internal mammary radiation therapy, the incidences were 10, 15, and 8 percent. Factors significantly associated with an increased risk of lymphedema included:

- Pathologically involved nodes (11 versus 6 percent, if nodes were negative)
- Removal of more than 14 nodes at surgery (9.5 versus 6 percent)
- Presence of extracapsular extension (13.4 versus 6.9 percent)
- Grade 2 or 3 breast tumor (11 versus 3 percent)
- Administration of adjuvant chemotherapy (10.5 versus 7 percent)

Infection — Infectious causes of lymphedema are more common in tropical and subtropical regions. Parasitic infections can result in lymphatic obstruction, and filariasis is the most common cause of this worldwide. (See "Lymphatic filariasis: Epidemiology, clinical manifestations, and diagnosis", section on 'Lymphedema'.)

Beyond parasitic infections, recurrent skin infections (eg, cellulitis, erysipelas), lymphadenitis, and tuberculosis may also be complicated by the development of lymphedema [31]. (See "Clinical staging and conservative management of peripheral lymphedema", section on 'Skin infection' and "Cellulitis and skin abscess: Epidemiology, microbiology, clinical manifestations, and diagnosis".)

Inflammatory disorders — Lymphedema is also associated with inflammatory disorders, such as arthritis, dermatitis, and sarcoidosis. Upper or lower extremity lymphedema, which can be unilateral or bilateral, is a rare extraarticular manifestation of inflammatory joint disease and is most often reported in patients with rheumatoid arthritis or psoriatic arthritis [32-38].

The mechanism of lymphedema associated with rheumatoid arthritis is not known, but inflammatory synovitis leading to fibrosis of lymph vessels has been proposed [39]. In some patients, the lymphedema improves with effective treatment of the arthritis [37-39]. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis", section on 'Lymphatic obstruction'.)

A similar clinical appearance is seen as a result of extensive tenosynovitis in patients with psoriatic arthritis [36]. (See "Clinical manifestations and diagnosis of psoriatic arthritis".)

Obesity — Obesity is an independent risk factor for lymphedema, particularly in cancer survivors. As an example, in a study of 137 women treated for breast cancer, women with a BMI

(kg/m^2) >30 had an increased risk of lymphedema compared with women with BMI (kg/m^2) <25 (OR 2.93, 95% CI 1.03-8.31) [40].

Morbid obesity is associated with a clinical entity called massive localized lymphedema [41-44]. This typically presents as a painless and longstanding lesion of the thigh. Pathologically, it is characterized by dermal thickening and an ill-defined, unencapsulated, large mass (figure 2) [42,44]. Morbid obesity (BMI >59) has also been shown to result in spontaneous development of lower extremity lymphedema [45].

Hereditary syndromes — Approximately 1/6000 will develop primary lymphedema [7]. The incidence of primary lymphedema in those attending lymphedema clinics ranges from 8 percent among all newly diagnosed patients to 28 percent of those with non-cancer-related disease [22]. Certain congenital conditions and other genetic mutations are associated with primary lymphedema in children. (See "Pathophysiology and etiology of edema in children", section on 'Primary lymphedema'.)

Other causes — Other causes of peripheral lymphedema are uncommon in resource abundant nations.

Podoconiosis is a form of lower extremity lymphedema that occurs after chronic exposure to mineral particles (silicone, aluminum, and other metals) in red clay volcanic soil. Podoconiosis, similar to filariasis, is a tropical lymphedema with distribution in tropical Africa, Central America, and India. It is estimated that 5 to 10 percent of barefoot populations in these regions are affected by podoconiosis. Ethiopia and Cameroon have the highest number of affected individuals (500,000 to 1,000,000 patients) [46]. Interestingly, genetic susceptibility has been shown to play a role in development of podoconiosis, and it is associated with human leukocyte antigen (HLA) variants [47]. Podoconiosis can be eliminated by wearing shoes; however, affordability of footwear or unwillingness to wear them remain barriers to use in some endemic areas [48].

CLINICAL FEATURES

A system to identify lymphedema in those at risk should be implemented. Among breast cancer patients, an algorithm for recognition has been suggested to identify and treat patients to minimize the progression of lymphedema [49].

History and physical — A careful medical history is important in the evaluation of the patient with suspected lymphedema [2,13]. Components of the history that should be addressed include the age of onset, areas of involvement, associated symptoms, progression of symptoms

(eg, pain, swelling, tightness), past medical history (eg, infections, radiation therapy), surgical history, travel history, and family history. Any inciting medications should be noted. Some patients may have a history of diuretic use, which is generally ineffective for lymphedema treatment. (See 'Epidemiology and risk factors' above and "Pathophysiology and etiology of edema in adults", section on 'Drug-induced edema'.)

The onset of lymphedema is usually insidious. For patients who had previously undergone a lymph node dissection and/or radiation, lymphedema is typically characterized by slowly progressive ipsilateral swelling of an arm following axillary node dissection or a leg following inguinal node dissection [2]. Affected patients may initially experience aching pain in the affected limb. A feeling of heaviness, tightness, and discomfort commonly accompanies swelling. The swelling may first be apparent only in the proximal portion of the limb, or it can affect only a portion of the distal limb, including the digits. It may also include the corresponding quadrant of the trunk. As an example, a patient with breast cancer may complain of swelling over the ipsilateral breast and/or upper chest wall. In chronic lymphedema, large amounts of subcutaneous tissue may form, the genesis of which is incompletely understood. Patients may develop a restricted range of motion in the affected limb as a result of the increased weight, which may limit their ability to perform activities of daily living (ADLs) and affect body image.

The physical exam should evaluate the vascular system, skin, and soft tissue and include palpation of the lymph nodes. Two thirds of cases of lymphedema are unilateral, although the laterality depends on the precipitating event [50]. As an example, an axillary node dissection will increase the risk of lymphedema in the ipsilateral upper extremity while a pelvic node dissection increases the risk of bilateral lower extremity edema.

At onset, swelling in the affected limb is typically characterized as "soft" and "pitting." Pitting reflects movement of the excess interstitial water in response to pressure. Testing for pitting involves applying firm pressure to the edematous tissue for at least five seconds. If an indentation remains after the pressure is released, pitting edema is present. Pitting is variable in patients with lymphedema and is generally absent with progressive lymphedema. With worsening lymphedema, dermal thickening becomes clinically apparent and the skin becomes dry and firm with less pitting due to cutaneous fibrosis and adipose deposition. The overlying skin of the affected limb also becomes hyperkeratotic, which can lead to verrucous and vesicular skin lesions.

A positive Stemmer sign is indicative of lymphedema [51]. It is characterized by a thickened skin fold at the base of the second toe or second finger. The examiner's inability to lift the skin of the affected limb compared with the contralateral limb is a positive sign. It is also described as

difficulty lifting the skin of the dorsum of the fingers or toes of the affected limb [52]. A positive Stemmer sign can be found in any stage of lymphedema. While it is possible to have a false negative Stemmer sign, a false positive sign is rare.

If primary lymphedema is suspected, evaluation should include documentation of any physical signs or congenital anomalies associated with an inherited condition. Examples include:

- Short stature (Turner syndrome)
- Port wine stains or hemangiomas (Klippel-Trenaunay-Weber syndrome)
- Shield chest (Turner syndrome, Noonan syndrome)

Extremity measurements — Limb volume can be measured by the water displacement method or estimated by taking several circumferential measurements at standard distances [53-55]. In our practice, we use optoelectronic volumetry to document limb volume (eg, Perometer). Methods to obtain clinical measurements are reviewed below. Measurements of limb volume can aid the diagnosis of lymphedema and can also be used to monitor any changes during therapy [56]. (See "Clinical staging and conservative management of peripheral lymphedema".)

Limb circumference — Circumferential measurements on the affected and contralateral arm are a simple and inexpensive method to estimate edema. It is possible to estimate volume by the measurement of limb circumference, and data suggest that circumferential measurements correlate well with volume measurements by water displacement [53-55].

Measurements can be taken at any point in the upper or lower extremity, as long as the clinician is using anatomic landmarks to reproduce the measurements. The measurements can be used to classify lymphedema severity using the American Physical Therapists Association classification system. (See 'Clinical severity' below.)

Simplified measurements in the extremity can be made at four points in both the affected and contralateral extremities with the limb in a relaxed position [57]:

- For the upper extremity:
  - At the metacarpal-phalangeal joints (if edematous)
  - Around the wrist
  - 10 cm below to the olecranon process
  - 10 cm above to the olecranon process

- In the lower extremity
  - At the metatarsal-phalangeal joints (if edematous)
  - 2 cm superior to the medial malleolus
  - 10 cm above the superior pole of the patella
  - 10 cm below the inferior pole of the patella

A difference of more than 2 cm between the affected and contralateral arm is considered clinically significant. Changes in circumference may be more difficult to detect in obese patients. In addition, in the upper extremity, they are subject to variation due to differences in muscle mass as a result of hand dominance and shifting of fluid proximally or distally due to arm positioning and/or compression.

Limb volume — Limb volume can be estimated from limb circumference measurements or determined through water displacement, optoelectronic volumetry, or calculation of limb volume using the truncated cone formula.

- Water displacement – Water displacement detects changes in volume of less than 1 percent. For patients with limb lymphedema, volume difference of 200 mL or more between the affected and opposite limbs is typically considered as a cutoff point to define lymphedema [29,53,55]. This method is the usual method to measure extremity lymphedema in clinical trials. Traditional volumeters are cumbersome because they are large, expensive, and prone to leakage. However, an alternative, homemade, and smaller device has been developed that is as accurate and is suitable for home or office use (figure 3 and table 1) [58].

- Optoelectronic volumetry – Volume can also be assessed utilizing infrared, optoelectronic measurements. This technique uses infrared beams to scan the limb and calculate a volume. The optoelectronic volumetry method is more reliable than water displacement volumetry for the measurement of upper extremity lymphedema [59,60].

- Limb volume calculation with the truncated cone formula – In this technique, upper or lower limb measurements are performed at 4 cm intervals beginning at the wrist and ankle, respectively. The measurements are then converted to volume using the truncated cone formula [61].

DIAGNOSIS

A history and physical examination with typical clinical features consistent with lymphedema and asymmetric limb measurements can usually establish a diagnosis of lymphedema. We reserve additional imaging for cases in which the history and physical do not yield a definitive diagnosis, or in cases where lymphatic obstruction (eg, due to tumor) is suspected. (See 'Further evaluation' below.)

The presence of lymphedema is usually suggested by the following findings (see 'Epidemiology and risk factors' above and 'Clinical features' above):

- The edema is typically localized and characterized by slowly progressive ipsilateral (unilateral) swelling of an upper extremity following axillary node dissection or lower extremity following inguinal node dissection [2].
- A history of cancer treatment or trauma. Cancer treatments include surgery, lymph node dissection or removal (eg, axillary, inguinal lymph nodes), and radiation therapy.
- The absence of a cause of generalized edema (eg, heart failure, nephrotic syndrome). Occasional patients have both lymphedema and generalized edema, such as cancer patients with an established diagnosis of heart failure who have undergone a lymphadenectomy, or the patient with obesity and longstanding chronic venous insufficiency. In these settings, lymphedema is suggested by asymmetry of the limbs.
- The presence of cutaneous and subcutaneous thickening, which is seen in severe lymphedema [52].
- Nonpitting edema is suggestive of lymphedema; however, the presence of pitting does **not** exclude lymphedema, since, as noted above, pitting is present in early stages of lymphedema.

Clinical severity — Several classification systems are used to describe the severity of lymphedema as mild (grade or stage I), moderate (grade or stage II), or severe (grade or stage III), based on the physical condition of the extremity (eg, limb girth, limb volume, skin changes). These are useful for guiding treatment. Clinical classification systems are discussed separately. (See "Clinical staging and conservative management of peripheral lymphedema", section on 'Clinical classification'.)

Differential diagnosis — The differential diagnosis of lymphedema is broad and differentiated by the distribution of the edema. (See "Clinical manifestations and evaluation of edema in adults".)

The main conditions associated with peripheral edema that might be confused with lymphedema are listed below.

- **Chronic venous insufficiency** – Lymphedema shares many clinical features with chronic venous insufficiency (CVI). Lymphedema is distinguished from CVI by an absence of typical varicose veins, an absence of characteristic skin change distribution (ie, brawny discoloration at the medial ankle in CVI), and alleviation of symptoms and reduction of swelling with limb elevation. Duplex ultrasound will demonstrate typical findings of venous valvular insufficiency. However, a subset of patients with longstanding and severe chronic venous insufficiency may develop concurrent lymphedema. (See "Clinical manifestations of lower extremity chronic venous disease" and 'Epidemiology and risk factors' above.)

- **Acute deep venous thrombosis** – Classic symptoms of a deep venous thrombosis (DVT) include acute swelling, pain, and erythema involving one limb. The onset of edema and the associated symptoms (eg, acute erythema, calf pain) readily distinguish DVT from lymphedema. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

- **Post-thrombotic syndrome** – Post-thrombotic syndrome (PTS) is the development of chronic venous symptoms and/or signs secondary to DVT. These include pain, venous dilation, edema, pigmentation, skin changes, and venous ulcers. A prior history of DVT can distinguish this condition from lymphedema. (See "Post-thrombotic (postphlebitic) syndrome".)

- **Limb hypertrophy** – Several syndromes are characterized by limb size discrepancies that may be due to hypertrophy of the soft tissue and bones (ie, Klippel-Trenaunay syndrome), or overgrowth of body parts in a disproportionate fashion (ie, Proteus syndrome), that may affect one or more limbs [62,63]. These syndromes are associated with other clinical manifestations, such as capillary malformations, which may help to distinguish them from lymphedema. (See "Capillary malformations (port wine birthmarks) and associated syndromes".)

- **Lipedema** – Lipedema is a rare adipose disorder characterized as the abnormal deposition of fat with associated edema [64-66]. A pedigree analysis suggests it is inherited as an X-linked dominant or autosomal dominant condition [67]. It occurs almost exclusively in women. Patients with lipedema may have family members who also have abnormal patterns of fat deposition but will generally not have a history of lymph node resection or trauma as seen with lymphedema. Patients with lipedema may complain of pain and tenderness and sustain easy bruising. Elevating the limbs has no effect on limbs with

lipedema. The feet are usually not involved with lipedema, but the feet may or may not be involved in lymphedema. Physical examination will help differentiate lipedema from lymphedema; patients with lipedema will not generally have pitting edema while lymphedema may have pitting edema. If a question remains, imaging studies may help (algorithm 1). Patients with lipedema usually have normal lymphatic function, whereas patients with lymphedema may have dermal backflow and lack of uptake in lymph nodes. (See "Diagnosis and management of lipedema" and 'Imaging the lymphatic system' below.)

- **Myxedema** – Myxedema results from infiltration of the skin by glycosaminoglycans with associated water retention leading to nonpitting edema. (See "Clinical manifestations of hypothyroidism", section on 'Skin'.)

- **Tumor** – Following treatment of cancer, an onset several years after the primary surgery without obvious trauma may be indicative of tumor, which always needs to be evaluated. In particular, recurrence of the breast cancer in the axillary area or the development of lymphangiosarcoma should be excluded [68-70].

FURTHER EVALUATION

Imaging can be helpful to distinguish lymphedema from nonlymphatic causes of edema if the diagnosis of lymphedema is not immediately apparent based upon history, physical examination, and extremity measurements. We recommend duplex ultrasound for all patients with new-onset extremity swelling. Ultrasound can be used to exclude other etiologies in the differential diagnosis (eg deep venous thrombosis [DVT], venous insufficiency) but also directly aids in the diagnosis by identifying a mass that might be the cause of lymphatic compression, identifying tissue alterations, and demonstrating live nematodes in scrotal filariasis [3]. Patients in endemic areas should be tested for filarial infection.

Imaging the lymphatic system — Imaging modalities that have been used in the diagnostic evaluation of lymphedema include lymphoscintigraphy, computed tomography (CT), magnetic resonance (MR) imaging/MR lymphography, and indocyanine green (ICG) lymphangiography. Unfortunately, all of these imaging studies suffer from a lack of standardized techniques, resulting in variable results. The protocols used for lymphoscintigraphy, in particular, can be highly variable. Nevertheless, in centers that specialize in lymphatic disorders, protocols that use varying techniques can depict the specific lymphatic dysfunction.

Lymphoscintigraphy images the flow of macromolecules and interstitial fluid from the skin to the lymph nodes, particularly in the extremities [2,71]. Subcutaneous or intradermal radioactive tracers are injected in the web space of the extremities, and imaging is performed 30 to 120 minutes after injection. The patient then performs a stress activity (such as walking, massage, or squeezing a ball for approximately 20 minutes), which is followed by repeat imaging. Criteria for impaired lymphatic function for qualitative lymphoscintigraphy include delayed, asymmetric, or absent visualization of the regional lymph nodes and dermal backflow. Quantitation of regional lymph node accumulation of the tracer appears to be more sensitive than qualitative lymphoscintigraphy (100 versus 70 percent in a series of 219 patients with secondary or primary lymphedema) [72]. All cases missed with qualitative lymphoscintigraphy were mild grade I disease. ICG lymphangiography is one technique in which a near-infrared dye (indocyanine green) is injected intradermally. The dye is bound by albumin after injection, and uptake is therefore restricted to the lymphatics. The lymphatic vasculature can then be directly imaged with specialized sensors. Lymphatic vessel anatomy, leaking, pumping capacity, and dermal reflux can all be seen. This is currently an off-label use of ICG; nevertheless, many lymphatic surgeons rely on ICG imaging for preoperative analysis and staging of lymphedema [73,74].

More commonly available imaging techniques, including CT and MR imaging, can demonstrate accumulation of fluid within soft tissues of the extremity with good sensitivity [50,75]. In one study of 55 patients who underwent both CT and lymphoscintigraphy, CT had a sensitivity and specificity of 93 and 100 percent [75]. Major CT findings for patients with lymphedema were skin thickening (95 percent), subcutaneous edema accumulation (95 percent), and a honeycombed appearance (41 percent). For demonstrating the lymphatic channels, MR has many advantages; however, the injected contrast material taken up by the lymphatics is also taken up by nearby veins. The lymphatics are typically beaded in appearance in comparison with the veins and have a higher signal intensity, but judgment is needed to distinguish them. Specialized MR techniques are being developed to exclude venous uptake, but these are not widely available [76].

Genetic testing — For patients diagnosed with primary lymphedema or suspected of lymphedema tarda, referral to a medical geneticist or genetic counselling service is suggested for evaluation of the family history and recommendations for further workup [77]. (See "Genetic testing".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Lymphedema".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Peripheral lymphedema after cancer treatment (The Basics)")
- Beyond the Basics topics (see "Patient education: Lymphedema after cancer surgery (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Lymphedema** – Lymphedema is a progressive disorder of the lymphatic system that results in the accumulation of interstitial fluid and fibroadipose tissue. (See 'Introduction' above and 'Normal lymphatic system and lymphedema' above.)
- **Classification**
  - Primary lymphedema often results from genetic or inherited conditions that impair lymphatic vessel development or function. (See 'Primary' above and "Pathophysiology and etiology of edema in children", section on 'Primary lymphedema'.)
  - Secondary lymphedema is due to underlying disease, infection, or iatrogenic injury to the lymphatic system. In the United States, nearly all cases of lymphedema are secondary to malignancy or cancer therapy. The most common cause of lymphedema

worldwide is filariasis, secondary to infection by the nematode *Wuchereria bancrofti*. (See 'Normal lymphatic system and lymphedema' above and 'Epidemiology and risk factors' above.)

- **Clinical features** – Symptoms of peripheral lymphedema include extremity swelling, skin changes, limb pain and discomfort, restricted range of motion, and nonpitting edema. (See 'Clinical features' above.)

- **Diagnosis** – The diagnosis of lymphedema can be made by history, physical exam, and extremity measurements comparing the affected with the unaffected limb. While imaging of the lymphatic system is usually not necessary to confirm the diagnosis of lymphedema, imaging can be helpful to distinguish lymphedema from nonlymphatic causes of edema. (See 'Diagnosis' above and 'Imaging the lymphatic system' above and 'Further evaluation' above.)

- **Differential diagnosis** – The differential diagnosis of lymphedema includes chronic venous insufficiency, acute deep venous thrombosis, post-thrombotic syndrome, limb hypertrophy, lipedema, peripheral edema due to other systemic illness, drug-induced edema, and tumor. (See 'Differential diagnosis' above.)

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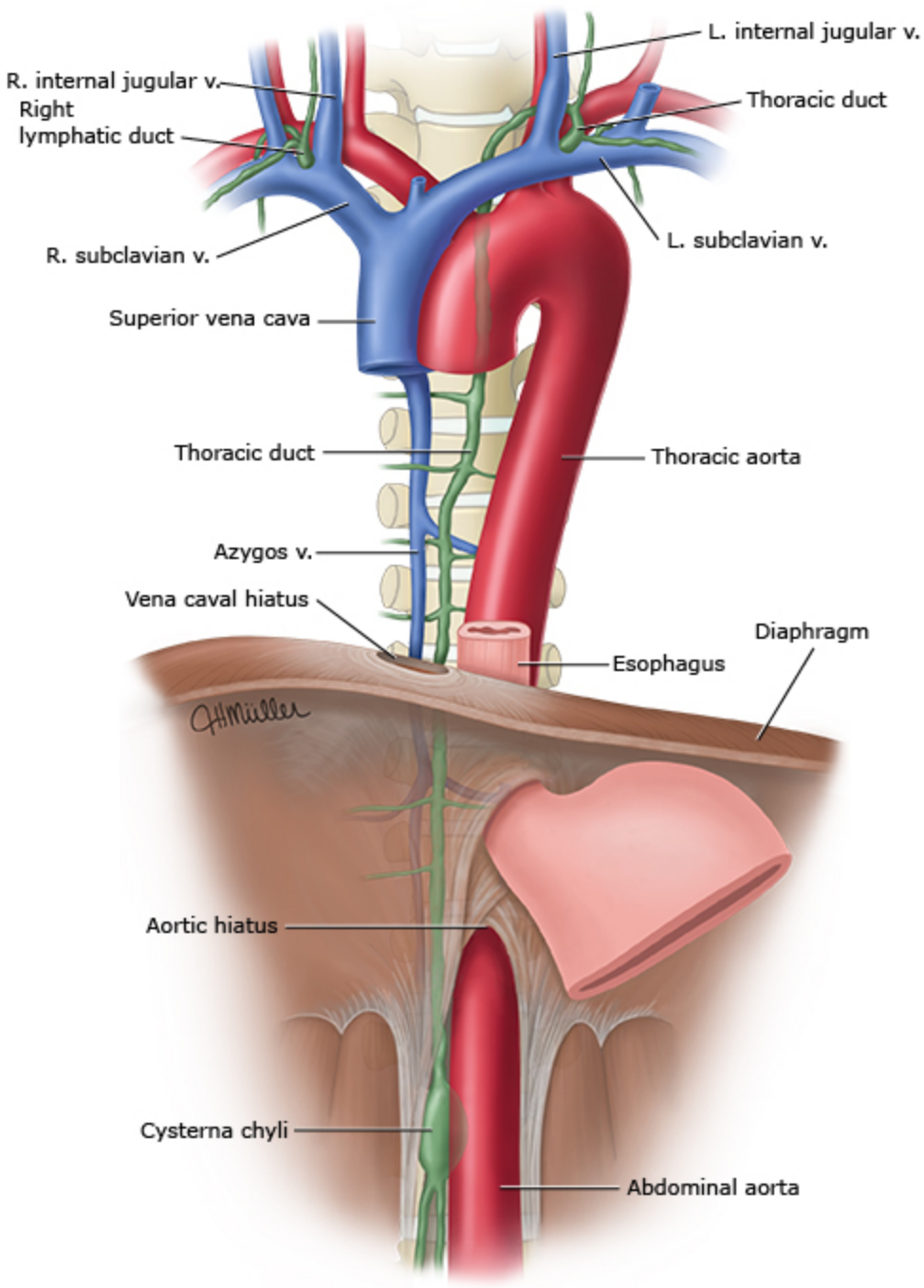
Topic 755 Version 55.0

GRAPHICS

Anatomy of the thoracic duct

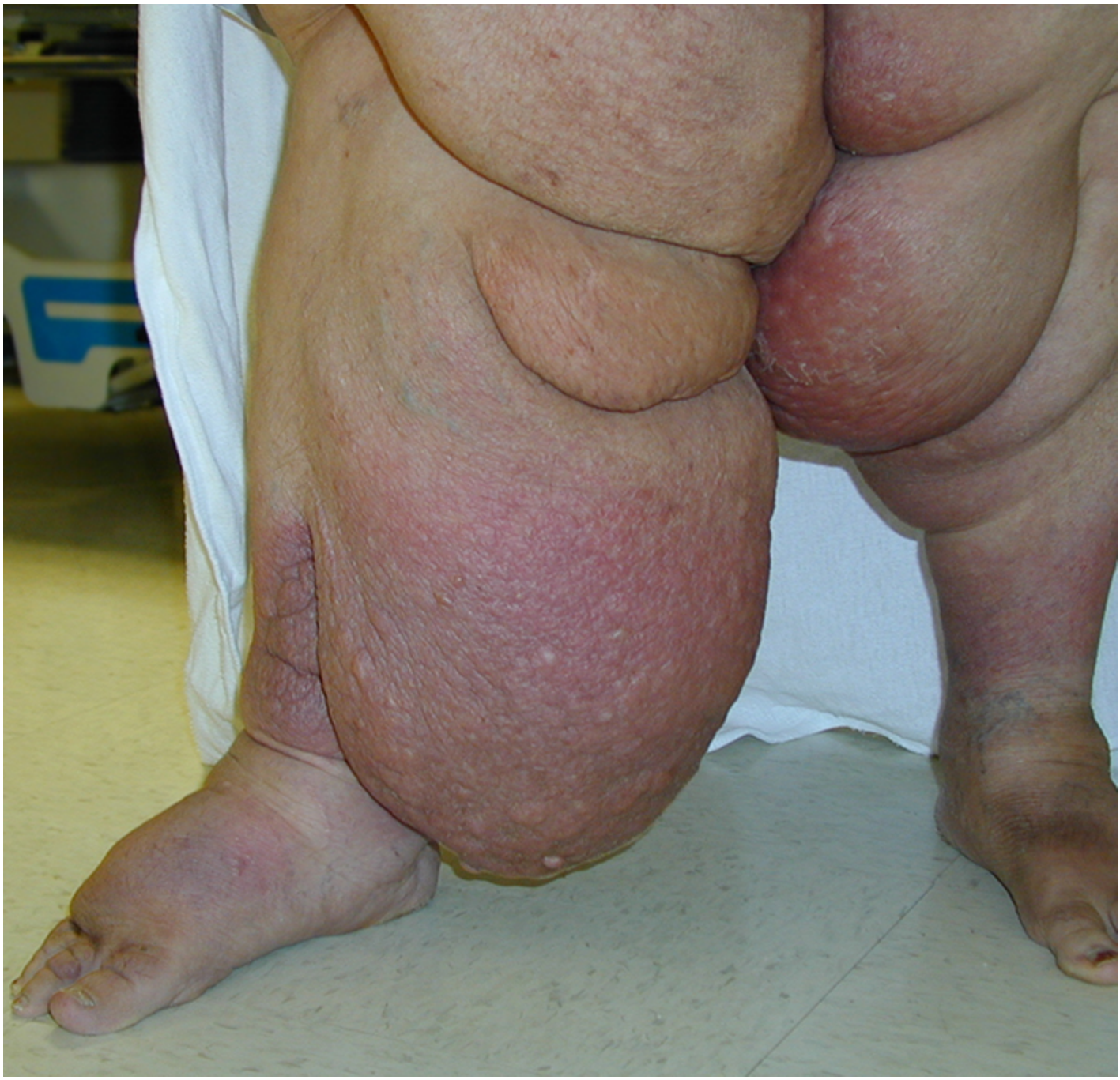


Course of the thoracic duct. Although wide anatomic variation exists, in most patients (40 to 60 percent), the left thoracic duct ascends from the cisterna chyli, which is a sac located just anterior to the first or second lumbar vertebra and which receives drainage from the intestinal and two lumbar lymphatic trunks. The thoracic duct passes through the aortic hiatus of the diaphragm into the posterior mediastinum continuing cephalad between the aorta and azygos vein until approximately the level of the fifth thoracic vertebra where it passes behind the esophagus. Below

the fifth thoracic vertebra, the thoracic duct is commonly a dual or plexiform duct but it becomes a single 2 to 3 mm duct above that level. The thoracic duct continues cephalad adjacent the esophagus passing posterior to the aortic arch and left subclavian artery. It then arches over the subclavian artery descending to empty either as a single (50 percent) or multiple lymphatic channels into the left subclavian vein near its confluence with the left internal jugular vein. A one-way valve at this location prevents blood from entering the thoracic duct. The right lymphatic duct drains into the right subclavian vein.

Graphic 57280 Version 9.0

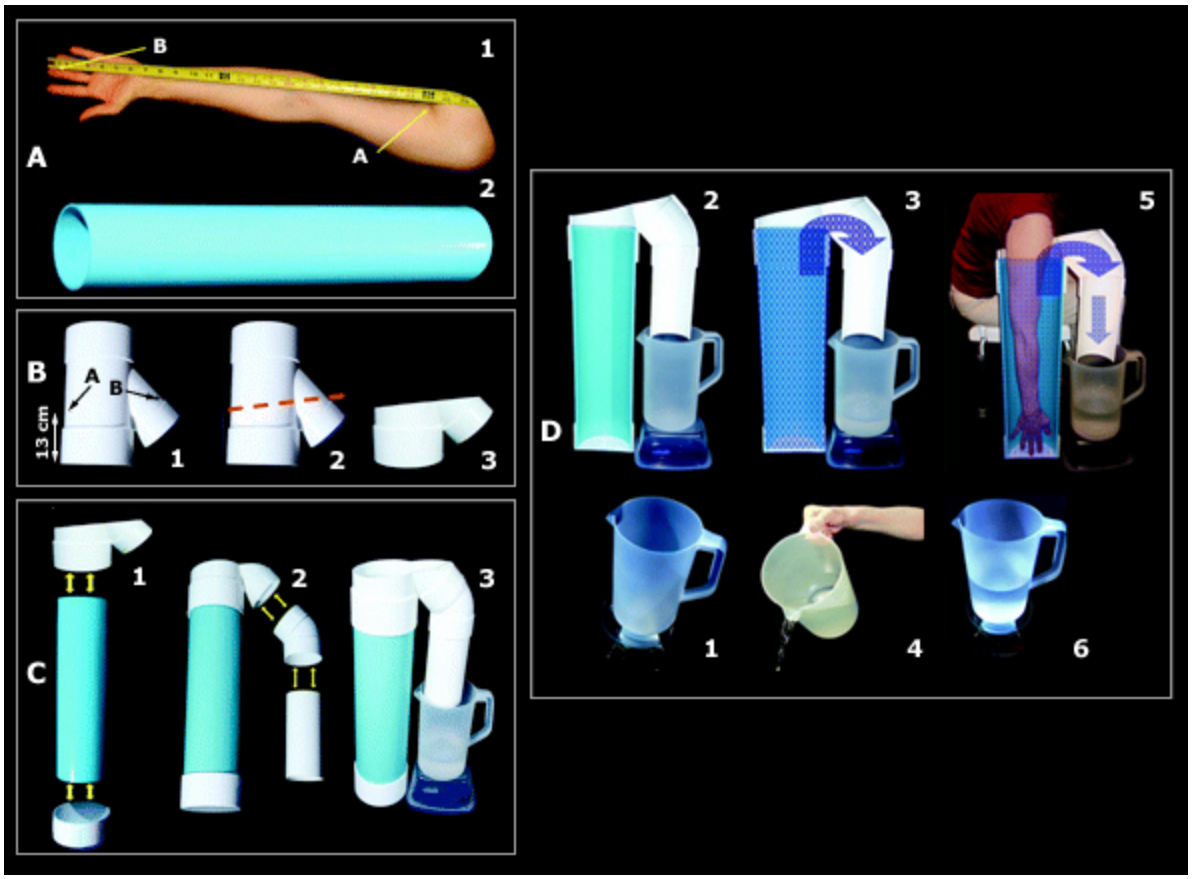
Severe combined chronic venous insufficiency and lymphedema



This patient had recurrent episodes of cellulitis requiring inpatient treatment. The mass on the medial aspe leg represents a focal form of lymphedema that is related to obesity. Surgical excision may be required in th of persistent or recurrent infection.

Graphic 104429 Version 2.0

How to construct and use a home arm volumeter



(A, B) Preparation of parts, (C) assembly, and (D) arm volume measurement procedure, including a longitudinal cross-section view.

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Graphic 54531 Version 1.0

Home arm volumeter instructions

I. How to construct a home arm volumeter
A. Parts. All parts are made of common polyvinyl chloride (PVC) piping used in plumbing. All parts are unthreaded. (Note: Phrases set in quotation marks in this section indicate the phrase to use when purchasing materials at the hardware store.)
one 6-inch (15-cm) internal diameter PVC pipe of approximately 1/4-inch (6-mm) standard thickness (called "6-inch Pipe"); length equal to arm length
one 4-inch (10-cm) internal diameter PVC pipe (called "4-inch Pipe"), 9 inches (23 cm) long
one asymmetric "Y" PVC all female connector (called "Asymmetric Y connector"; also called "Wye" in some plumbing catalogs), designed to connect two 6-inch and one 4-inch pipes
one PVC 45-degree elbow (called "Elbow") with one male and one female connecter end, designed to connect two 4-inch-diameter PVC pipes, also called a "45-degree 4-inch male-female PVC angle"
one 6-inch PVC cap (called "6 inch Cap")
PVC solvent glue
B. Assembly instructions.
1. Arm length
Determine arm length by measuring the arm from the inner fold of the armpit (anterior axillary fold; Point A) along the inside (anterior aspect) of the arm to the tip of the middle finger when the hand is outstretched in a taut position (Point B).
2. Cutting and gluing
Warning: It is dangerous to cut PVC pipe with a power saw and to handle PVC glue, which emits toxic vapors; these tasks should be left to a properly trained person.
Reference for metric equivalents: Conversion factor: 1 inch = 2.5 cm. Approximate equivalents: 1/4 inch = 6 mm; 4 inches = 10 cm; 5 inches = 13 cm; 6 inches = 15 cm; 9 inches = 23 cm.
a. Cut the 6-inch pipe to a length equal the length of the arm.
b. Cut the 4-inch pipe to a length of 9 inches (23 cm).
c. Cut the asymmetric Y-connector. Stand the asymmetric Y-connector with the 4-inch connector end facing down. Measure 5 inches (13 cm) up from the bottom of the 6-inch connector end and mark point A. Mark point B just above the ridge of the 4-inch connector end (Step 1). Cut across the asymmetric Y-connector in a straight line spanning from point A to point B (Step 2). File and sand the newly cut top edge to make a smooth, curved lip (Step 3).
d. Glue the 6-inch cap to one end of the 6-inch pipe to seal the bottom of the volumeter.
e. Glue the asymmetric Y-connector to the other end of the 6-inch pipe.
3. Fitting

Attach the 4-inch pipe to one end of the elbow and attach the elbow to the asymmetric Y-connector. The volumeter's spout is now in place. The spout also serves as a handle to lift, drag, or carry the volumeter.

C. Filing, sanding, cleaning, and disinfecting. Clean all parts before assembly. Carefully check the assembled volumeter, inside and out. File and sand any sharp edges or points. Clean and disinfect the volumeter using a bleach solution. Rinse thoroughly with water to remove any trace of bleach.

II. How to measure arm volume

A. Equipment

Home arm volumeter

Beverage pitcher (the pitcher does not need to have volume gradations because the water volume is measured by weighing)

Digital gram kitchen scale or postal scale (the scale should read up to 5000 grams, be accurate to 1 gram, and have a platform large enough to hold the pitcher. The display must be in grams [not ounces] because water weight in grams is equivalent to water volume in milliliters, which is the only way the water volume can be determined through weighing. The author strongly recommends that patients weigh the water and not use graduated containers, which are too imprecise and yield misleading volumetric readings.)

B. Measurement procedure.

1. Weigh the empty pitcher and record its empty weight (Step 1). This will be a constant that you always subtract from the weight of the pitcher of water.

2. Place the volumeter on a level-surfaced floor. To achieve comparable measurements, try to place the volumeter in the same location each time.

3. Prepare a comfortable seat beside the volumeter, for example, a stool or low chair. A closed toilet seat may also be convenient with the volumeter placed beside the toilet.

4. Place the pitcher under the volumeter spout. Under the pitcher, place any type of flat base, such as a plastic food storage container, to raise the pitcher up to the edge of the spout. This base is necessary so that no drops of water splash outside of the pitcher (Step 2).

5. Fill the volumeter with lukewarm water until it overflows into the pitcher. Wait for all air bubbles to settle. Top off the water level with a bit more water and wait for the overflow to completely stop dripping into the pitcher (Step 3).

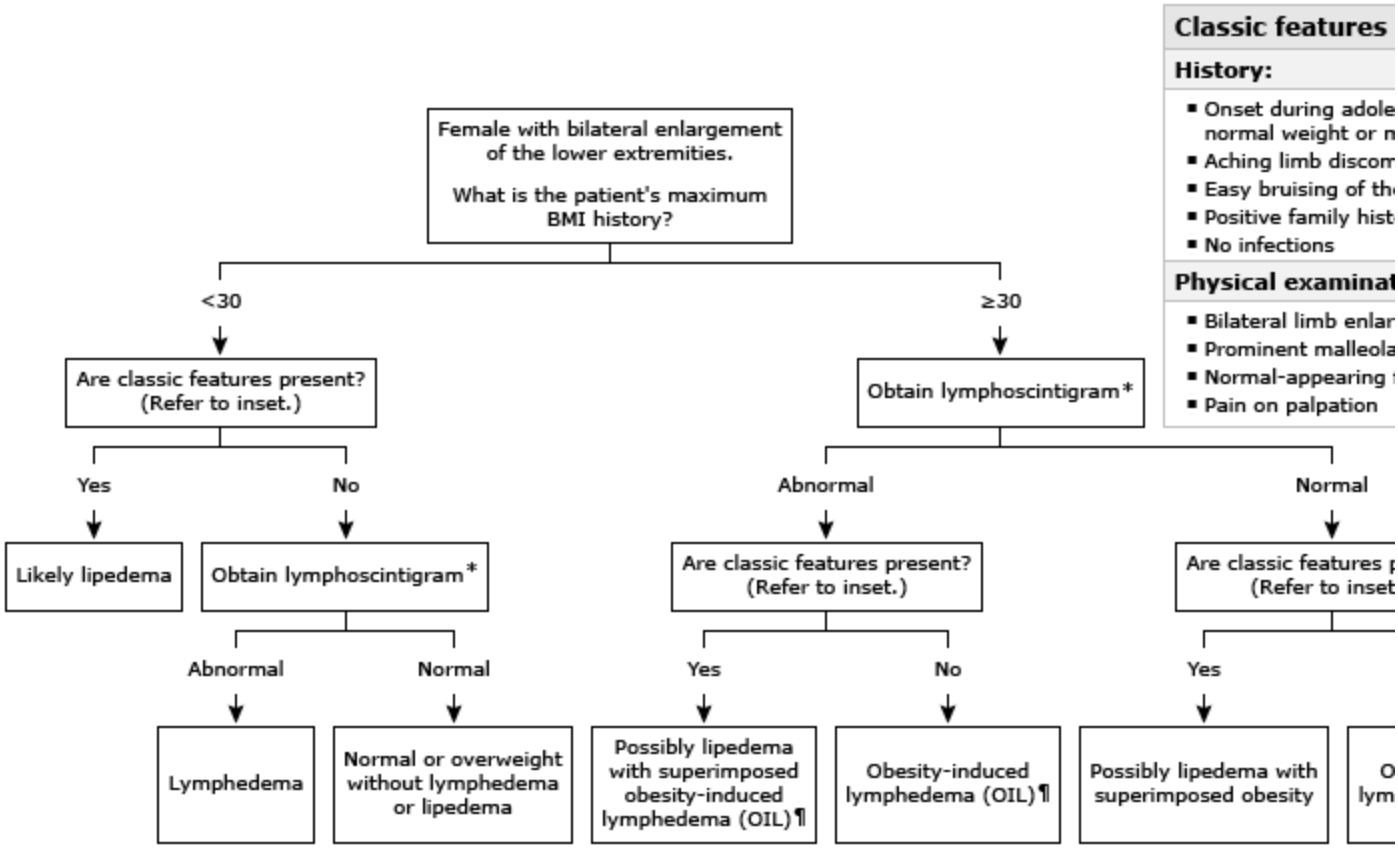
6. Empty the water out of the pitcher (Step 4). Dry the pitcher with a towel. Return the dry pitcher to its original spot under the spout of the volumeter.

7. You are now ready to measure your arm volume. Sit beside the volumeter. Slowly and gently lower your arm into the volumeter. Water will rush out through the spout into the pitcher. Continue lowering your arm until your middle finger touches the bottom of the volumeter, while keeping your fingers, wrist, and elbow in a fully extended and taut position (Step 5).

8. Hold this position until the water stops dripping into the pitcher. You can best see this by watching when the water in the pitcher becomes still.
9. Remove your arm and dry it with a towel.
10. Place the pitcher filled with the overflow water on the scale (Step 6).
11. Record the gram output showing on the scale. From this number, subtract the weight of the empty pitcher (Step 1). The difference equals the volume in grams of the water in the pitcher. This amount equals the volume in millilitres of your arm.
12. We recommend that you do at least two consecutive measurements, and preferably three (see Helpful Hints).
13. When you have finished measuring, the volumeter can be dragged or lifted by the spout and tipped into the bathtub or shower to empty.
III. Helpful hints
The most important procedure in measuring arm volume is Procedure 8: holding the arm immobile in the volumeter until the water stops dripping. This may take up to one minute. It is therefore important to be comfortable and relaxed when you take your arm measurement. Your seat should be comfortable. To avoid straining your back, try to bend from the waist and keep your back straight.
Measuring in the bathtub: since the floor of the bathtub is not a level surface, it may not be an ideal location for the volumeter. Also, sitting on the side of a bathtub (in a straddle or side-saddle position) is not usually comfortable.
We recommend that you take three measurements in a row and calculate the average, in case of an erratic measurement. By comparing three measurements, you can judge your skill at measurement. With practice, your measurements may vary by less than 10 mililiters, which is highly precise.
If you discover that the six-inch pipe has been cut too long and your middle finger does not touch bottom before the top of the volumeter hits your armpit, you can use a "landmark," such as a freckle on your upper arm, and stop immersion at that landmark. You can also add a "false bottom" to your volumeter by filling a plastic container with vase gems, marbles, or polished stones and placing the weighted container in the volumeter.
To lower costs of making the volumeter, patients can group together to have several made at one time.
We recommend that you not modify the design of the home use volumeter. It is the result of trial and error and numerous prototypes over two years. Even a minor design change may change the volume and shape of the water meniscus at the top of the cylinder of water and result in unreliable measurements.

Graphic 53493 Version 2.0

Diagnostic algorithm to differentiate lipedema from obesity



This algorithm is intended for use in conjunction with additional UpToDate content on lipedema.

OWL: obesity without lymphedema; OIL: obesity-induced lymphedema; BMI: body mass index.

* An abnormal test shows delayed inguinal uptake of tracer and/or dermal backflow.

¶ OIL can occur with a maximum BMI history >40.

Contributor Disclosures

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Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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