



# Overview of Management in Lower Limb Edema

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Satyendra K. Tiwary and Vivek Kumar Katiyar

## 18.1 Introduction

Lower limb swelling is one of the most common manifestation in clinical practice in many local and systemic diseases. Usually, the condition may be due to trivial cause most of the time but sometimes delayed clinical consultation and irreversibility of the changes due to disease may lead to difficulty in management. A good clinical history with proper clinical examination is essential to confirm the diagnosis and plan further management of the disease.

## 18.2 Clinical Examination

Clinical examination should be carried out in both the limbs irrespective of their involvement. Examination starts with the inspection mainly to check for any color changes, asymmetry, scars, ulcers, etc. (Fig. 18.1).

Chronic diseases usually present with thickened and discolored skin. Skin changes are also evident in varicose veins. In erysipelas, local edema is often present in addition to skin redness and tenderness. Elevated temperature is present in acute conditions like cellulitis. Pitting edema may be caused by deep vein thrombosis, venous insufficiency, and early stages of lymphedema as well as systemic causes like CHF, edema due to renal etiologies, etc. Non-pitting edema can be seen in cases of filariasis and hypothyroidism. Tenderness of affected area points toward more local causes.

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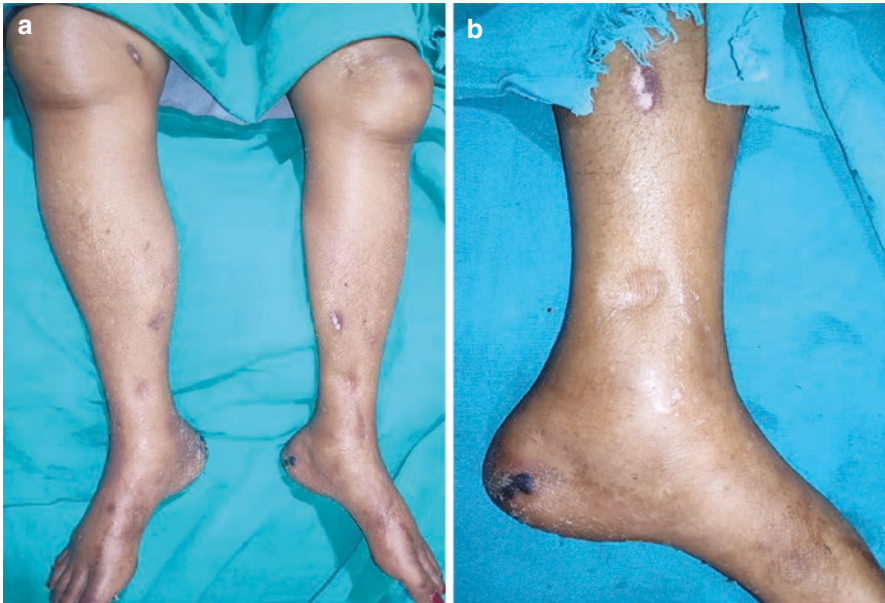
S. K. Tiwary (✉) · V. K. Katiyar

Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

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**Fig. 18.1** (a), (b) Post-traumatic lower limb Edema

Clinical examination of both limbs is essential. The Leg-O-Meter (François Zuccarelli, MD, Hospital St-Michel, Service de Chirurgie Vasculaire, Département de Phlébologie et d'Angéiologie, Paris, France) designed to measure the circumference of the ankle or calf [1]. It is simple to apply for assessing the limb swelling related to venous disease but not related to lymphedema.

Water displacement volumetry is more accurate to assess the limb volume than the circumferential measurements with a tape [2]. The tissue tonicity can also be used to assess the disease but it is more useful in assessing the response of treatment [3]. Bioelectrical impedance is one of the efficient methods to evaluate the swelling but has not yet been evaluated for leg edema [4]. Cesarone [5] developed the edema measuring device.

A plastic plate with protrusions or holes is applied over the swollen limb which applies the pressure and measures the edema. It can differentiate between primary and secondary edema and can be used as a screening tool.

## 18.3 Radiologic Investigation

### 18.3.1 Lymphangiogram

This technique was mainly used for visualizing the anatomy of lymphatics. It is an invasive technique. In this technique, direct cannulation of lymphatic through a small incision in skin is carried out. It is painful and time consuming and leads to

infection, local inflammation, and fibrosis. This also increases the risk of hypersensitivity reaction and emboli [6].

So, this technique is not used largely. It is only useful in operative interventions like bypass procedure [7].

### 18.3.2 Lymphoscintigram

Lymphoscintigram is the gold standard technique, and was introduced in 1953. In this technique, radiolabeled protein is used to assess the lymphatic function, lymph movement, lymph drainage, and response to treatment [8].

The radioisotope, usually technetium Tc 99 m-labeled colloid including antimony sulfur and albumin [9] are used. The heptaminol adenosine phosphate is used to increase the lymph flow and measurement [10].

The sensitivity and specificity of the lymphoscintigram are 73% to 97% and 100% [11], respectively. Contrast lymphangiogram can also be used to elucidate the lymphatic anatomy.

After the isotope injection, the lymphatics may or may not be visualized within the first hour. Some patients may show normal lymphatics or missed diagnosis. Only delayed film (2–24-hour post-isotope injection) shows the real eccentricities [12].

Condensed image processing using a modified Kleinhaus score and time-activity curves [13] are used to enhance the detection of abnormalities of the lymphatic system.

Lymphoscintigram can differentiate between lymphedema and edema of venous origin [14].

In case of varicose veins and deep vein incompetence [7], lymphoscintigraphy reveals significantly reduced lymph drainage. This is suggestive of association between chronic venous insufficiencies with lymphatic insufficiency.

Both epifascial and subfascial lymphatics are abnormal in lymphedema, while in post-thrombotic disease, there is a decrease in the subfascial lymphatic flow whereas the epifascial flow remains normal [15], it can differentiate between post-thrombotic disease and lymphedema [15].

In lipedema patients, lymphoscintigraphy will confirm that peripheral lymphatics remain normal. Asymmetry may be appearing in bilateral lipedema disease suggestive of the dynamic nature of the lymphoscintigram. Lymphoscintigraphy also depicts the impairment of lymphatic drainage or lymphatic disruption after arterial reconstruction.

### 18.3.3 Indocyanine Green Lymphography

In this technique, fluorescence lymphography using contrast ICG leads to the diagnosis of lymphedema [16]. Indocyanine Green Lymphography (ICG-LG) clearly visualizes superficial lymph flow without radiation exposure, and recently has found its way to the evaluation of lymphedema.

### 18.3.4 Ultrasound

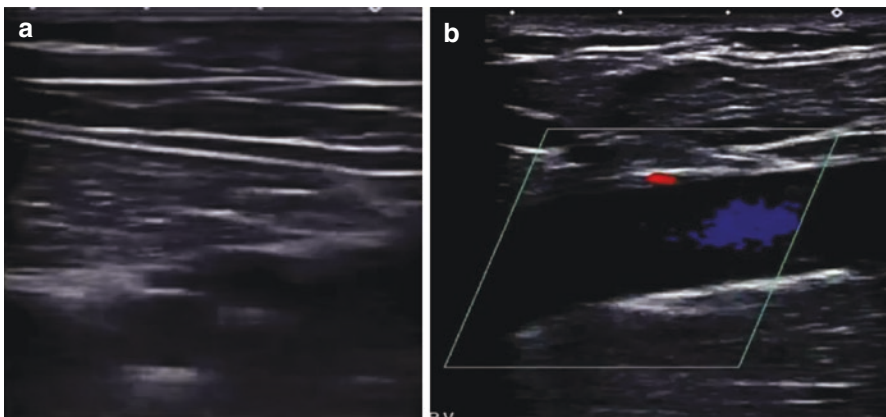
Volume changes in dermis, subcutaneous layer, and an increase/decrease in the muscle mass along with structural changes like hyperechogenic dermis and hypoechogenic subcutaneous layer may appear in limb swelling on ultrasound. It does not give information about the anatomy of lymphatics [17].

### 18.3.5 Duplex Ultrasound

Duplex USG uses two modalities—Doppler and B-mode to assess the speed of blood flow and visualize the structure of leg vessels. Duplex ultrasonography is a noninvasive, cheap, and reliable investigation to establish a diagnosis of DVT. A combination of a duplex scan and lymphoscintigram might be able to diagnose the cause of limb edema in majority of the patients (Fig. 18.2a and b). However, some authors refute the correlation between chronic limb edema and increased venous reflux [18]. Intraluminal blood clot appears hypoechoic or anechoic in acute cases whereas in chronic DVT, it appears hyperechoic with peripheral revascularization on color Doppler imaging.

### 18.3.6 Computed Tomography

Computed tomography scan can be used to confirm the diagnosis and to assess the effect of treatment. The CT scan imaging show skin and subcutaneous compartment thickening increased fat density, thickened perimuscular aponeurosis [19] and honeycomb appearance. Honeycomb appearance is not seen in venous disease but subcutaneous compartment and skin thickening may appear. In lipedema, there is



**Fig. 18.2** (a) Color Doppler showing increased subcutaneous tissue thickness in edema. (b) Color Doppler showing blood flow in lower limb

thickened subcutaneous compartment, normal skin thickness with normal subfascial compartment.

In DVT thickened subcutaneous layer, with signs of lymphedema, enlarged muscle area and enlarged superficial veins may be seen. CT scan is unreliable in DVT.

### 18.3.7 Magnetic Resonance Imaging

To differentiate among lymphedema, lipedema, and phlebedema [20] Magnetic Resonance Imaging (MRI) can be used [21].

Lymphedema appears as increased subcutaneous tissue volume, circumferential edema, honeycomb appearance between the muscle and subcutis with marked thickening of the dermis [20]. MRI cannot differentiate the primary and secondary lymphedema. MRI can also prove useful to assess the result of reconstructive surgery.

In case of DVT, MRI shows the edema of leg muscles mainly in posterior compartments and soft tissue swelling consists only of fat with normal lymphatics in lipedema.

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## 18.4 Management of Pedal Edema

Management of limb edema depends upon its etiology.

**A. Venous Insufficiency** Mild cases of venous insufficiency can be improved by limb elevation only. In chronic cases, compression stocking is useful. Compression stocking should not be used in peripheral vascular disease as it may aggravate the symptoms. Pneumatic compression stocking may be used in patients where stockings are contraindicated. Topical steroids and emollients can be used for skincare and prevention of ulceration, dryness, etc. Diuretics can cause metabolic derangement so should be avoided.

**B. Congestive Heart Failure and Chronic Liver Disease** In case of CHF in mild cases, limb elevation fluid restriction and salt restriction can improve the mild stage of limb edema. Diuretics can be used in non-responding cases. If liver failure is present, chronic hypoalbuminemia can be corrected by albumin infusion. It can provide temporary relief from the symptoms.

**C. Chronic Renal Failure** In case of renal failure fluid, salt restriction is the primary line of management.

Diuretics can be used in refractory cases. Hyperkalemia can be caused by aldosterone antagonist and so, should be avoided.

**D. Obstructive Sleep Apnea** Due to pulmonary hypertension limb edema may occur it can be controlled by weight reduction and positive pressure ventilation.

**E. Deep Vein Thrombosis** Chronic bedridden patients are prone to DVT. For prevention of DVT pneumatic compression, bandages, and stockings can be used. Anticoagulant therapy should be started prophylactically as well as therapeutically.

**F. Lymphedema** Mild lymphedema can be managed by limb exercise, limb massage, limb elevation, compression bandages, stockings, etc., in chronic and symptomatic cases, surgical procedures can be performed.

**G. Lipedema** Weight loss can improve the symptoms. It has no definitive treatment.

**H. Idiopathic Edema** It can be improved by treatment with aldosterone antagonists like spironolactone.

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## 18.5 Treatment

### 18.5.1 Lifestyle Modification

Lifestyle modifications are essential for prevention as well as treatment of lower limb edema.

**Exercise/movement:** The contraction and relaxation of muscle may lead to decrease the edema by pumping the excess fluid back toward the heart.

**Massage:** On stroking the affected area pressure may change and help the drainage of excessive fluid toward the heart. Precaution should be taken as massage should not be vigorous as it can be painful.

**Elevation:** Elevation of limb above the level of the heart may lead to resolution of swelling/edema of the limb due to gravity.

**Protection and skincare:** The swollen area is susceptible to infection and injury. Always protect the affected area from injury and keep it dry and clean.

**Reduce salt intake:** Excessive salt intake may lead to retention of fluid and worsen edema.

Heat therapy produces some benefits to limb swelling but the mechanism is not fully known. It can be done using hot water, microwave, or electromagnetic radiation. It produces dilatation of blood capillaries, increases venous return and decreases dermal inflammation.

Balneotherapy is the use of thermal or mineral water (1 gm/L conc.) for treatment of disease. It acts through mechanical, chemical, and physical mechanisms to treat and reduce pain and edema. It improves circulation and muscle relaxation. It also improves the immune system.

Chronic lymphedema can persist lifelong. So, results can improve by fully understanding and committing to all therapeutic measured and psychological support. Weight reduction also has a positive impact on limb swelling.

Aggressive antibiotic therapy helps when needed like in the case of cellulitis. The infection can cause lymphatic deterioration. For filariasis, prevention and treatment are important because it affects a large population in a country like India.

In areas where compression therapy is not feasible, Kinesio taping can be used which improves lymphatic drainage by skin traction during movements.

## 18.5.2 Physical Modalities and Compression

The first-line treatment for lymphedema is complex physical therapy.

**Compression Stockings** The compression stockings are used in the management of long-term chronic edema. It can be used as a prophylaxis in a high-risk patient who is prone to develop limb edema. The stocking is based on the patient's general condition, mobility, and limb size. The stocking is applied from foot with padding of all bony prominences excluding the toes. The stocking should be worn from the morning before leaving the bed till the time to go to bed.

**Graduated Compression Bandages** It is used in chronic forms of severe edema. The bandage is made of various materials applied in overlapping layers. The effect depends upon pressure exerted, number of layers, components used in bandage, and elastic properties.

According to pressure exerted near the ankle joint, stocking is classified as class I–class IV. The type of stockings depends upon the length and circumference of the leg and the pressure required (Table 18.1).

**Table 18.1** Selection criteria for compression bandages [22]

Stage	Pressure	Lower limb disease/condition
Class I	15–23 mmHg	<ul style="list-style-type: none"> <li>• Mild venous insufficiency or in cases where higher pressure cannot be used due to other existing conditions</li> <li>• Prevention of venous thrombosis</li> <li>• Prevention of varicose veins, e.g., during pregnancy</li> </ul>
Class II	24–34 mmHg	<ul style="list-style-type: none"> <li>• Venous insufficiency</li> <li>• Varicose eczema and venous leg ulcers</li> <li>• Mild lymphatic edema and edema post-cancer surgery</li> <li>• Follow-up care after varicose vein surgery and erysipelas</li> <li>• Treatment and prevention of deep vein thrombosis and superficial venous thrombophlebitis</li> </ul>
Class III	35–49 mmHg	<ul style="list-style-type: none"> <li>• Severe edema not managed with lower pressure</li> </ul>
Class IV	50+ mmHg	<ul style="list-style-type: none"> <li>• Very severe lymphatic edema or severe venous insufficiency</li> </ul>

**Pneumatic Compression Pump** Pneumatic compression devices are made up of air pump and inflatable garment to create compression for legs or other body parts [23]. The functional aim of the device is to squeeze fluid from the underlying tissue and veins, and displace it proximally. When the inflatable sleeves deflate, the veins fill up with blood. The intermittent compressions device will ensure the movement of fluid and venous blood.

**Complex Physical Therapy or Complete Decongestive Therapy** CPD is the one of the effective approaches for lymphedema treatment. It improves the lymphatic function and reduction of fluid accumulation. Lifelong compression therapy can be used. It has two components, manual lymph drainage (MLD) and compression therapy [24].

The therapy depends upon phases of edema. In phase I of decongestion 1–3 MLD per decompression and exercises for 2–5 weeks.

### 18.5.3 Manual Lymphatic Drainage

There are two methods to achieve interstitial fluid movement to manage subcutaneous edema of the leg and foot [25]. One way is by encouraging fluid movement in the extra vascular space and second by stimulating fluid movement from the extra vascular space into the venous system. The edematous fluid is redirected through collaterals toward normally functioning pathway or by increasing the activity of the normal lymphatics [26]. The procedure is performed proximally to distally in a lying down position for up to 30–60 minutes daily, weekly or monthly, depending on the stage and severity [20, 27].

The treatment can be accentuated by the lymph fluoroscopy mapping [28].

The techniques are Leduc et al. Földi [29] and Casley-Smith methods, both being equally efficient. Even still, there have been no exclusive evidences for MLD and its efficacy for edema.

**Compression Therapy** Compression stockings improve symptoms by providing graduated compression therapy to control leg swelling and discomfort [30].

It is a simple and effective measure to increase the blood flow activity in the lower limbs and strengthening the vein support. It applies gentle pressure to the ankles and legs which promotes venous return and impedes stasis. It stretches out vein walls and improves the limb circulation, which helps in eliminate the swelling.

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## 18.6 Medical Management

### 18.6.1 Benzopyrones

Benzopyrones are effective for treatment of lymphedema. The drug acts by reducing the edema fluid, increasing the softness of tissue and decreasing the elevated



temperature [31]. It also increases the number of macrophages and enhances the proteolysis which helps in removal of protein and edema with reduction of the inflammation and infection [32]. It also improves the symptoms like hardness, heaviness and swelling. The adverse effects of this drug are nausea, vomiting, and diarrhea which are relatively uncommon and resolve spontaneously. The drug can be used with physical measures [33].

This drug is banned for use in the United Kingdom, Australia and France due to reports of hepatotoxicity [33].

**Micronized Purified Flavonoid Fraction(MPFF)** It is said to decrease the limb swelling by aiding the chronic venous insufficiency by decreasing the venous stasis and also improves the post-surgery edema [34]. The mechanism of action of Micronized Purified Flavonoid Fraction is to reduce the capillary permeability and inflammation of the tissue. This drug is under trial for lower limb lymphedema.

**Immunotherapy** Role of immunotherapy is not well understood. Activated antilymphatic lymph infused into arteries by injection activates macrophages in the interstitial tissue, which decomposes the excess protein. The activated macrophages and CD4T cells play a role in proliferation of lymphatic endothelial cells and aberrant lymphangiogenesis. The role of activated lymph still remains unclear.

**Gene Therapy** Gene abnormality is reported in primary lymphedema. Hepatocyte growth factor (HGF) neovascularization related to lymph vessels neogenesis is suggested. It is reported that peripheral vascular growth in limbs with severe ischemia is related to HGF in rat breast cancer model [35, 36].

**9-Cis Retinoic Acid** Retinoic acids (RAs) regulating genes have an essential role in cell proliferation, differentiation, apoptosis, and metabolism. They induce lymphangiogenesis through fibroblast growth factor (FGF) receptor-dependent pathway. Some studies have found that 9-*cis* retinoic acid aids lymphangiogenesis and improves lymphedema [37]. Further experiments are required to establish a strong consequence.

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## 18.7 Surgical Treatment

The recommendations of the American Venous Forum on the principles of the surgical treatment of chronic lymphedema are summarized in Table 18.2 [38].

The surgical treatment is only considered after failure of all the nonsurgical measures in chronic and symptomatic cases for more than 6 months of therapy. Surgical interventions in lymphatic are very difficult and require a trained surgical team. The goal is reconstruction and restoration of the functional continuity with reduction of edema volume by excision surgery causing the handicapping.

**Table 18.2** Guidelines of the American Venous Forum on the principles of the surgical treatment of chronic lymphedema [38]

Guideline	Grade of recommendation		Grade of evidence
	1. Strong	2. Weak	A - High quality B - Moderate quality C - Low or very low quality
All interventions for chronic lymphedema should be preceded by at least 6 months of non-operative treatment	1		C
Excisional operations or liposuction only to patients with late-stage non-pitting lymphedema who fail conservative measurement	2		C
Microsurgical lymphatic reconstruction in Centre of excellence for selected patients with secondary lymphedema if performed early in the course of disease	2		C

Preoperative evaluation and postoperative outcome cannot be overemphasized. Optimizing the limb before surgery is necessary. To prevent the chances of recurrence, it is important for the patient to wear a compression stocking.

Surgical management can be divided into the following types [39]:

1. Bypass procedures and lymphovascular anastomoses
2. Debulking or excisional surgery
3. Prophylactic surgery

## 18.8 Surgical Bypass Procedures

It is useful in selective cases of chronic limb edema after failure of medical therapy where the venous system is competent and intact lymphatic structures, such as regional lymphatics and lymph nodes, are present.

**Lymphovenous anastomosis** for the treatment of chronic lymphedema was first attempted by Nielubowicz and Olszewski. It is the anastomoses of lymph vessel or lymph node to the vein distal to the obstructing segment [40, 41].

End-to-end or end-to-side lymphatic-venous anastomosis can be performed [42]. It can have complications such as venous thrombosis at the anastomotic site blockage of lymphatics [42].

End-to-end technique avoids venous reflux into the lymphatics and thus decreases the risk of venous thrombosis. The risk of anastomotic stricture formation can be avoided by using a secondary tributary of the main vein as the site of anastomoses. The lymphatic capsule-venous anastomosis can be performed in pediatric patients.

Ipsen concluded that lymphovenous bypass decreased limb circumference by 0.8 to 4.1 cm in secondary lymphedema but no change was noted in primary lymphedema cases.

**Lymphatic autotransplantation:** Lymphatic grafting introduced by Baumeister is used for secondary lymphedema [43]. In this procedure, the normal, functionally unaffected vessels are used to bypass the obstruction area. It can be performed successfully even with coexisting venous disease.

**Autologous Interposition Vein Grafting** can also be used in coexisting venous disease. The procedure involves lymphatic-venous-lymphatic anastomoses directly. The contraindications of the surgery are severe hypoplasia, aplasia of lymphatics or lymph nodes, and extensive damage to the superficial as well as deep lymphatics. The patient who is contraindicative for bypass procedure can be considered for debulking procedure.

**Adipo lymphaticovenous transfer** was performed by Tanaka with the use of long saphenous vein along with its lymphatics. Free autografts of the greater omentum have also been used. It has satisfactory results in short series. Necrosis is the main complication in this procedure.

**Vascularized lymph node transplantation** was described by Backer [44, 45].

Lymph nodes from the inguinal region were transplanted microsurgically to the axillary region in mastectomy lymphedema patients. It can be done in selected patients and necessitates monitoring. The procedure can also be used in congenital prophylactic lymphedema [46]. The results are not well established. The skill of the surgeon and timing of intervention is a crucial factor along with lifelong medical therapy [47].

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## 18.9 Debulking Procedures

This procedure is not truly debulking. In this procedure, the **subcutaneous drainage of lymphedema** fluid is achieved by using multi-perforated silicon tubes, which are linked to a chamber by a one-way valve. The chamber is connected to the venous drainage system via the long saphenous vein in the same manner as a peritoneo-venous shunt. In this procedure, up to 70% reduction in size has been reported. However, it has a limited role in long-term patency due to high protein content of edema fluid blocking the system.

**Charles procedure** is a well-known procedure in which en bloc removal of the skin, subcutaneous tissue, and deep fascia is done. The radical excision of subcutaneous tissue is followed by primary or staged skin grafting. In primary skin grafting, either skin from the excised tissue or from a non-affected area is used. Staged skin grafting also reports good results. There was no difference in results in primary or secondary edema. Skin and subcutaneous excision combination with liposuction improve symptoms but can develop into foot edema. In Charles' procedure, only the affected part of the limb is treated and the cosmetic outcome is poor.

Servelle described a technique of two-stage reduction where the first stage involves the medial aspect and the second stage involves the lateral aspect of the limb. This procedure is *total superficial lymphangiectomy* and is a modification of the Homan procedure.

The complications of debulking procedure include infection, necrosis, scarring, difficult wound healing of the skin graft, and poor cosmetic and functional results [48].

### **18.9.1 Liposuction**

It is useful in lymphedema secondary to adipose tissue deposits and in selective cases with non-fibrotic primary or secondary lymphedema which causes up to a 23% reduction in volume. Cellulitis is the main complication.

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### **18.10 Prophylactic Surgery**

Patients who require extensive lymph node dissection in pelvic region are prone to developing edema. In these patients, **prophylactic lymphatic tissue transplant** via omentoplasty may prove useful. The concept of omentoplasty was evaluated by Logmans and coworkers [49] and the concept of prophylactic lymphovenous anastomoses after ilioinguinal dissection was given by Orefice and coworkers [49]. Prophylactic bypass has reduced the frequency of edema and hospital stay.

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### **18.11 Conclusion**

In approaching lower limb edema, a variety of etiologies must be considered (Figure 18.3). History and physical examination are required for differentiation of causes and subsequent selection of cost-effective and appropriate diagnostic testing and management. Treatment mainly emphasizes on treating the etiology and systemic disease along with symptomatic treatment for the edema. Lifestyle modification physical exercise and compression bandaging can improve the condition. Medical treatment is not effective in every case and cannot cure completely. Surgical management is required in selective cases and has a limited outcome. Surgery cannot resolve the disease completely.

Some newer modalities have also evolved for the treatment of lower limb swelling but require further research to provide better outcomes. However, till now lifestyle modifications and physical modalities are the mainstay of treatment for lower limb swelling.

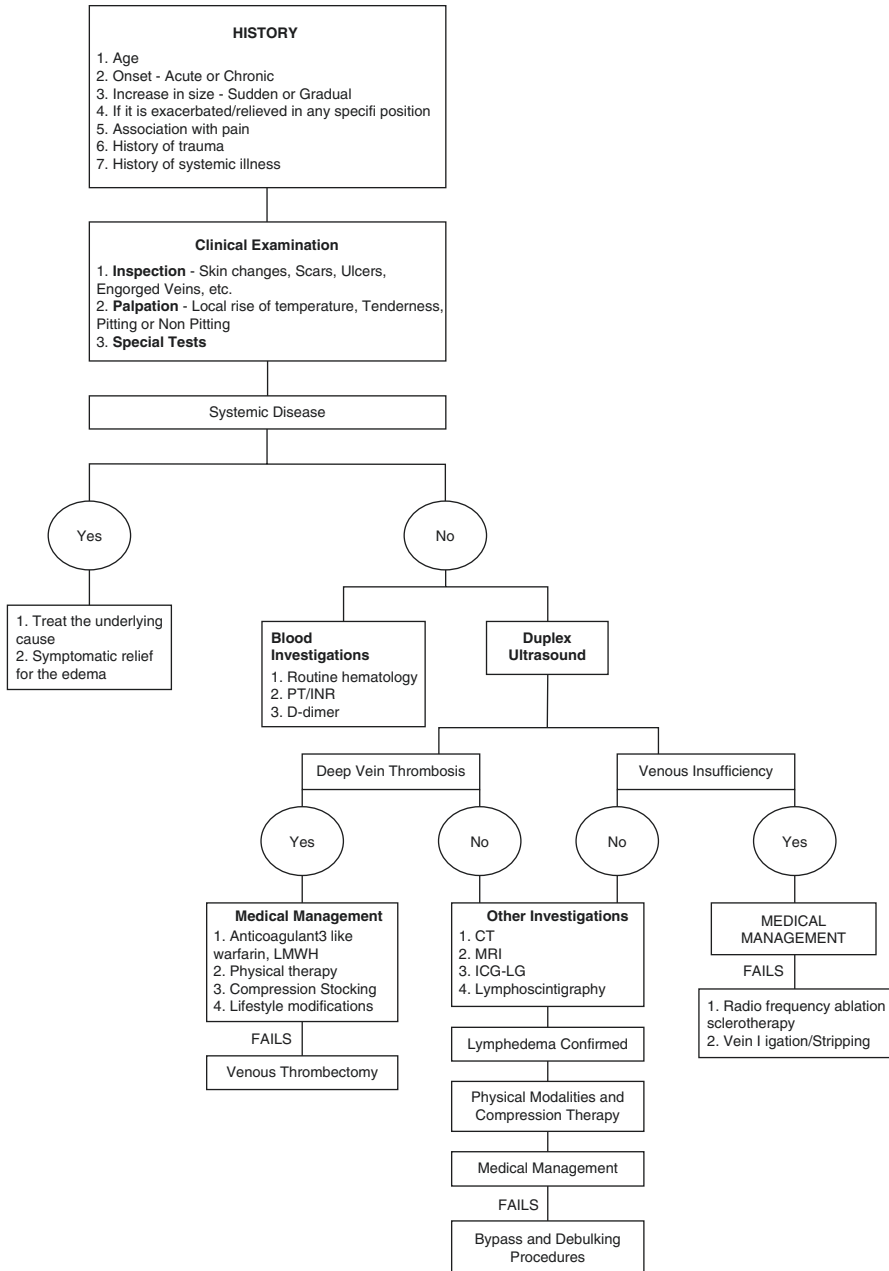


Fig. 18.3 Algorithm for evaluation and management of limb edema

## References

1. Berard A, Zuccarelli F. Test-retest reliability study of a new improved leg-O-meter, the leg-O meter II, in patients suffering from venous insufficiency of the lower limbs. *Angiology*. 2000;51:711–7.
2. Casley-Smith JR. Measuring and representing peripheral oedema and its alterations. *Lymphology*. 1994;27:56–70.
3. Liu NF, Olszewski W. Use of tonometry to assess lower extremity lymphedema. *Lymphology*. 1992;25:155–8.
4. Ward LC. Regarding Edema and leg volume: methods of assessment. *Angiology*. 2000;51:615–6.
5. Cesarone MR, Belcaro G, Nicolaidis AN, et al. The edema tester in the evaluation of swollen limbs in venous and lymphatic disease. *Panminerva Med*. 1999;41:10–4.
6. Weissleder H, Weissleder R. Interstitial lymphangiography: initial clinical experience with a dimeric nonionic contrast agent. *Radiology*. 1989;170:371–4.
7. Burnand KG, McGuinness CL, Lagattolla NR, Browse NL, El Aradi A, Nunan T. Value of isotope lymphography in the diagnosis of lymphoedema of the leg. *Br J Surg*. 2002;89:74–8.
8. Williams WH, Witte CL, Witte MH, McNeill GC. Radionuclide lymphangioscintigraphy in the evaluation of peripheral lymphedema. *Clin Nucl Med*. 2000;25:451–64.
9. Wheatley DC, Wastie ML, Whitaker SC, Perkins AC, Hopkinson BR. Lymphoscintigraphy and colour Doppler sonography in the assessment of leg oedema of unknown cause. *Br J Radial*. 1996;69:1117–24.
10. Thibaut G, Durand A, Follignon P, Bertrand A. Measurement of lymphatic flow variation by non-invasive method cases of lymphedema. *Angiology*. 1992;43:567–71.
11. Ter SE, Alavi A, Kim CK, Merli G. Lymphoscintigraphy: reliable test for the diagnosis of lymphedema. *Clin Nucl Med*. 1993;18:646–54.
12. Larcos G, Foster DR. Interpretation of lymphoscintigrams in suspected lymphoedema: contribution of delayed images. *Nucl Med Commun*. 1995;16:683–6.
13. Rijke AM, Croft BY, Johnson RA, de Jongste AB, Camps JA. Lymphoscintigraphy and lymphedema of the lower extremities. *J Nucl Med*. 1990;31:990–8.
14. Proby CM, Gane JN, Joseph AE, Mortimer PS. Investigation of the swollen limb with isotope lymphography. *Br J Dermatol*. 1990;123:29–37.
15. Brautigam P, Vanscheidt W, Foldi E, Krause T, Moser E. The importance of the subfascial lymphatics in the diagnosis of lower limb edema: investigations with semiquantitative lymphoscintigraphy. *Angiology*. 1993;44:464–70.
16. Mihara M, Hara H, Araki J, Kikuchi K, Narushima M, Yamamoto T, Iida T, Yoshimatsu H, Murai N, Mitsui K, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One*. 2012;7:e38182. <https://doi.org/10.1371/journal.pone.0038182>.
17. Doldi SB, Lattuada E, Zappa MA, Pieri G, Favara A, Micheletto G. Ultrasonography of extremity lymphedema. *Lymphology*. 1992;25:129–33.
18. Valentin LI, Valentin WH. Comparative study of different venous reflux duplex quantitation parameters. *Angiology*. 1999;50:721–8.
19. Marotel M, Cluzan R, Ghabboun S, Pascot M, Alliot F, Lasry JL. Transaxial computer tomography of lower extremity lymphedema. *Lymphology*. 1998;31:180–5.
20. Gordon K, Mortimer PS. Decongestive lymphatic therapy. In: Lee BB, Rockson SG, Bergan J, editors. *Lymphedema. A concise compendium of theory and practice*. 2nd ed. Cham, Switzerland: Springer International Publishing AG; 2018. p. 413–29.
21. Werner GT, Scheck R, Kaiserling E. Magnetic resonance imaging of peripheral lymphedema. *Lymphology*. 1998;31:34–6.
22. Stockport JC, Groarke L, Ellison DA, McCollum C. Single-layer and multilayer bandaging in the treatment of venous leg ulcers. *J Wound Care*. 1997;66(10):485–8.

23. International Society of Lymphology The diagnosis and treatment of peripheral lymphedema. Consensus document of the international society of lymphology. *Lymphology*. 2013;46:1–11.
24. Dean SM. Lymphedema: physical and medical therapy. In: Gloviczki P, editor. *Handbook of venous and lymphatic disorders*. Guidelines of the American venous forum. 4th ed. Boca Raton: CRC Press; 2017. p. 725–35.
25. Watanabe Y, Koshiyama M, Yanagisawa N. Treatment of leg and foot edema in women. *Women's Health Open J*. 2017;68–73. <https://doi.org/10.17140/WHOJ-3-124>.
26. Best Practice for the Management of Lymphoedema International Consensus. [(accessed on 17 July 2019)].
27. Foldi E, Foldi M, Rockson S. Complete decongestive physiotherapy. In: Lee BB, Rockson SG, Bergan J, editors. *Lymphedema. A concise compendium of theory and practice*. 2nd ed. Cham, Switzerland: Springer International Publishing AG; 2018. p. 403–11.
28. Johansson K, Karlsson K, Nikolaidis P. Evidence-based or traditional treatment of cancer-related lymphedema. *Lymphology*. 2015;48:24–7.
29. Földi E. The treatment of lymphedema. *Cancer*. 1998;83(12 Suppl):2833–4.
30. Badger CM, Peacock JL, Mortimer PS. A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer*. 2000;88:2832–7.
31. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha] pyrone. *N Engl J Med*. 1993;329:1158–63.
32. Casley-Smith JR, Casley-Smith JR. Modern treatment of lymphoedema, II: the benzopyrones. *Australas J Dermatol*. 1992;33:69–74.
33. Badger CMA, Preston N, Seers K, Mortimer P. Benzopyrones for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev*. 2004;2:CD003140.
34. Olszewski W. Clinical efficacy of micronized purified flavonoid fraction (MPFF) in edema. *Angiology*. 2000;5125–9.
35. Shigematsu H, Yasuda K, Iwai T, et al. Randomized, double-blind, placebo-controlled clinical trial of hepatocyte growth factor plasmid for critical limb ischemia. *Gene Ther*. 2010;17:1152–61.
36. Shigematsu H, Yasuda K, Sasajima T, et al. Transfection of human HGF plasmid DNA improves limb salvage in Buerger's disease patients with critical limb ischemia. *Int Angiol*. 2011;30:140–9.
37. Choi I, Lee S, Kyoung Chung H, et al. 9-cis retinoic acid promotes lymphangiogenesis and enhances lymphatic vessel regeneration: therapeutic implications of 9-cis retinoic acid for secondary lymphedema. *Circulation*. 2012;125:872–82.
38. Al-Ajam Y, Mohan AT, Saint-Cyr M. Principles of the surgical treatment of chronic lymphedema. In: Gloviczki P, editor. *Handbook of Venous and Lymphatic Disorders*. 4th ed. Guidelines of the American Venous Forum. Boca Raton: CRC Press; 2017. p. 737–746.
39. Tiwari A, Hamilton G, Myint F. Management of lower limb lymphoedema. Beard J Murray Seds. *Pathways in vascular surgery* Shrewsbury. England TFM Publishing. 2002:71–6.
40. Boccardo F, Fulcheri E, Villa G, Molinari L, Campisi C, Dessalvi S, et al. Lymphatic microsurgery to treat lymphedema: Techniques and indications for better results. *Ann Plast Surg* 2013;71:191–5.
41. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. *Breast Cancer Res Treat*. 2009;113:199–206.
42. Campisi C, Boccardo F, Tacchella M. Reconstructive microsurgery of lymph vessels: the personal method of lymphatic-venous-lymphatic (LVL) interpositioned grafted shunt. *Microsurgery*. 1995;16:161–6.
43. Baumeister RG. Lymphedema: surgical treatment. In: Cronenwett JL, Johnston KW, editors. *Rutherford's vascular surgery*. 8th ed. Philadelphia: Sauder's; 2014. p. 1028–42.
44. Becker C. Autologous lymph node transfers. *J Reconstr Microsurg*. 2016;32:28–33.

45. Batista BN, Germain M, Faria JC, Becker C. Lymph node flap transfer for patients with secondary lower limb lymphedema. *Microsurgery*. 2017;37:29–33.
46. Becker C, Arrive L, Saaristo A, Germain M, Fanzio P, Batista BN, et al. Surgical treatment of congenital lymphedema. *Clin Plast Surg*. 2012;39:377–84.
47. Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C, et al. Diagnosis and treatment of primary lymphedema. Consensus document of the international union of phlebology (IUP)-2013. *Int Angiol*. 2013;32:541–74.
48. International Society of Lymphology The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. *Lymphology* 2016; 49:170–184.
49. Logmans A, Kruyt RH, de Bruin HG, Cox PH, Pillay M, Trimbos JB. Lymphedema and lymphocysts following lymphadenectomy may be prevented by omentoplasty: a pilot study. *Gynecol Oncol*. 1999;75:323–7.