Advances and Controversies in the Contemporary Management of Chronic Lymphedema

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Abstract

The lymphatic system is essential for normal body function, as its role is to recover fluid passed to the interstitial tissue from capillaries and to carry it back to the systemic circulation. Failure of the lymphatic system results in accumulation of the interstitial fluid; it can be caused by structural anomalies of the lymph vessels and the lymph conducting elements of the lymph nodes, or by the overload of the anatomically normal lymphatic network (dynamic insufficiency). Accumulation of protein-rich interstitial fluid leads to chronic inflammation, secondary changes in the subcutaneous tissue and skin, and progressive fibrosis causing sclerosis and irreversible tissue changes, also called elephantiasis. During the past few decades, our understanding of the etiology and pathogenesis of chronic lymphedema have significantly improved and so did evaluation and therapy. In this review, we will present first the magnitude of the problem and then focus on recent key advances and controversies in contemporary management.

Keywords: Complete decongestive therapy, compression, elephantiasis, excisional surgery, filariasis, intermittent pneumatic compression, liposuction, lymph node transplantation, lymphatic grafting, lymphedema, lymphovenous anastomosis, manual lymph drainage

Introduction

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The Magnitude of the Problem

Lymphedema is a common and frequently debilitating disease, millions of individuals in the world are affected. Its prevalence was underestimated as well as its morbidity. Chronic edema prevalence, assessed in one UK epidemiological study, was around 4/1000 persons and more than one-half of the cases were related to primary and secondary lymphedema.[1] Data concerning patients after breast cancer surgery showed that 41% of them would develop lymphedema defined by heaviness and swelling at 30-month follow-up.[2] The estimated prevalence of lymphatic filariasis is 68–120 million people and it is the second most frequent and most invalidating tropical disease after malaria.[3-6] Filariasis-related lymphedema alone is responsible for at least 5.9 million disability years.[6] Poor quality of life associated with chronic edema affects the professional status in 9%.[1] Moreover, treatment of lymphedema consumes a substantial healthcare budget. In one study, hospital charges for breast cancer patients with lymphedema were increased by >$ 23,000.[7]
Contemporary Management

Lymphedema can be significantly improved by existing therapeutic options. These are divided into medical and surgical treatment. Medical or conservative management includes decongestive physiotherapy, compression pumps or garments, and drug therapy. Surgical interventions can be reconstructive or excisional. Most lymphedema studies that assess outcomes are of low-to-very low-quality evidence, and satisfactory comparative studies are missing. Combination of several methods, therefore, may be a good option and therapeutic strategies should be adapted to each patient. At all times, the patient’s values and quality of life should be considered.

Medical management

Medical management of established lymphedema is always recommended regardless of the lymphedema etiology. Timing and the therapeutic strategy are the key factors. The effectiveness of the treatment is greatly improved, when the different interventions are applied in the early stages of the disease and with the right sequence. When available, the nonsurgical approach is dominated by the complete decongestive physiotherapy (CDP) used first to maximally decrease the volume of lymphedema in the acute phase of the treatment. Compression therapy is indicated to consolidate the volume reduction. Adjunctive treatments include the specific anti-filariasis treatment, aggressive antibiotherapy to control infections, as well as new genetic and pharmacological treatments.

Many patients will also need support by psychotherapy as this invalidating condition is associated with psychological and social life impairment.

The recent guidelines of the American venous forum on physical and medical therapy in lymphedema are presented in Table 1.[8]

The Consensus document of the International Society of Lymphology (ISL)[11] point out the prerequisites of the successful lymphedema management: availability of well-trained physicians, physiotherapists, specialized centers and cooperation with health insurers understanding the needs of patients.

Complete decongestive physiotherapy

CDP is a pillar of the lymphedema treatment with its efficiency supported by several studies.[12-14] After the acute phase of treatment, when a significant decrease in volume is achieved, lifelong compression therapy can be used alone. In the long run, treatment should always be associated with self-care management.[13]

The CDP effects include improvement of lymphatic function and reduction of tissue fibrosis. Two elements are composing CDP: manual lymph drainage (MLD) and compression therapy.[8,15]

CDP protocol depends on the stage of lymphedema.[9] It starts with phase I of decongestion: 1–3 MLD sessions

| Table 1: Guidelines 6.3.0. of the American Venous Forum on Lymphedema: Physical and medical therapy[8] |
|-------------------------------------------------|----------|-----------------|-----------------|
| Number of guideline | Guideline                                                                                     | Grade of recommendation | Grade of evidence |
|---------------------|------------------------------------------------------------------------------------------------|--------------------------|-------------------|
|                      | To reduce lymphedema we recommend multimodal CDT that includes manual lymphatic drainage; multilayer short-stretch bandaging; remedial exercise; skin care; and instruction in long-term management | 1                        | B                 |
| 6.3.1               | To reduce lymphedema we recommend short-stretch bandages that remain in place >22 h/day | 1                        | B                 |
| 6.3.2               | To reduce lymphedema we recommend treatment daily, a minimum of 5 days/week and continue until normal anatomy or a volumetric plateau is established | 1                        | B                 |
| 6.3.3               | To reduce lymphedema we suggest compression pumps in some patients | 2                        | B                 |
| 6.3.4               | For maintenance of lymphedema we recommend an appropriately fit compression garment | 1                        | A                 |
| 6.3.5               | For maintenance of lymphedema in patients with advanced (Stage II and III) disease we recommend using short-stretch bandages during the night. Alternative compression devices may substitute for short-stretch bandages | 1                        | B                 |
| 6.3.6               | For remedial exercises we recommend wearing compression garment or bandages | 1                        | C                 |
| 6.3.7               | For cellulitis or lymphangitis we recommend antibiotics with superior coverage of Gram-positive cocci, particularly Streptococcus. Examples include cephalaxin, penicillin, clindamycin, erythromycin | 1                        | A                 |
| 6.3.8               | For prophylaxis of cellulitis in patients with >3 episodes of infection we recommend antibiotics with superior coverage of Gram-positive cocci, particularly Streptococcus, at full strength for 1 week/month, examples include cephalaxin, penicillin, clindamycin, erythromycin | 1                        | A                 |
| 6.3.9               | For patients with lymphedema we recommend risk factor modifications to decrease obesity, treat chronic venous insufficiency and to promote skin care and exercise | 1                        | C                 |

CDT: Complex decongestive therapy
per day, compression and exercises for 14–35 days. In the lymphedema stage II to III, the phase of optimization continues this regiment for several years. Then, in the further phase of preservation (Phase II), MLD can be spaced to 1–2 times/week. Compression and exercises are indicated as lifelong [Table 2].[9]

The successful outcome of the therapy requires the commitment of both the patient and the medical team. Comprehensive assessment of lymphedema and other medical issues should precede the treatment. The contraindications to CDP include acute erysipelas, acute thrombophlebitis, deep vein thrombosis, decompensated heart failure, and advanced Stage IV peripheral artery occlusive disease.[9]

**Manual lymph drainage**

MLD is an important component of CDP, especially for lymphedema that includes parts of the body other than to extremities.[16] Treatment is conducted in 30–60 min sessions, weekly or monthly, depending on the stage and severity of lymphedema,[9,17] as well as on the patient’s health care structure.

Well-trained lymphedema therapist can activate the lymph movement from the region containing lymph accumulation, redirecting the lymph through lymphatic collaterals toward the normally functioning lymphatic pathway. MLD session starts with the techniques decongesting the proximal zones and continues with gentle, rhythmic hand’s movements stretching the swollen skin to stimulate the superficial lymphatic network without increase of the blood flow. Among the renown techniques are the Leduc et al.,[18] Földi.[15] and Casley-Smith methods, each of them appears to be equally efficient. However, high-quality evidence supporting the efficacy of MLD is still missing.[19]

Simple lymphatic drainage, simplified version of the MLD, may be beneficial in the maintenance of achieved improvement. MLD treatment can be helped by the lymphofluoroscopy mapping.[19]

**Compression therapy**

Compression therapy is the key treatment in all therapeutic strategies.[20] Its efficacy is well established through randomized controlled trials.[14,21] Inelastic bandages or hosiery stimulate lymphatic drainage during the muscular activity and oppose the extension of lymphedema.

The reduction in edema is achieved through several mechanisms:

- Antibiotic activity
- Increased pressure of the tissues limiting the microvascular filtration; hence, reduced lymphatic load
- Stimulation of the lymphatic pump and drainage
- Displacement of the fluids to the noncompressed zones.[22]

Inelastic bandages together with protecting soft padding are used for the irregularly swollen limbs.[17] This can improve the application of compression to the deformed extremity and enhance the reduction of lymphedema.[14]

Hosiery has a graduated strength and exists in different forms of stockings and sleeves. Its major advantage is self-application by the patient, who must be well trained. Compression garments with the pressure range 30–40 mmHg are prescribed in the maintenance phase. They can be overlapped, which increases the pressure and the stiffness of the material.[22] This method is helpful especially in the case of elderly, obese patient, those with advanced arthritis or those supporting the higher pressure with difficulty.

Velcro garment is easier to apply and adjustable to the decreasing limb volume.[21] A randomized controlled trial demonstrated the superiority of Velcro device over the standard compression bandages.[21]

A lot of patients can be helped using intermittent pneumatic compression (IPC).[23] This method is certainly indicated in patients with limited mobility and in case of lymphovenous origin of swelling. It can be used in addition to other methods.

| Stage | Phase I: Decongestion | Phase II: Optimization | Phase III: Preservation |
|-------|-----------------------|------------------------|------------------------|
| No swelling, pathological lymphoscintigram | Prevention of lymphedema | MLD series | MLD series or 1x/week |
| Stage I | Edema of soft consistency | 14–21 days | 2-5 years | MLD series or 1x/week |
| | Compression | MLD 1x/day | MLD 1-2x/week | Long-term compression |
| | Exercise | | Compression | Exercise |
| | | | Exercise | Repetition of Phase I |
| Stage II | Edema with secondary tissue alterations | 24–28 days | 5-10 years | MLD series or 1-2x/week |
| | Compression | MLD 2x/day | MLD 2-3x/week | Long-term compression |
| | Exercise | | Compression | Exercise |
| | | | Exercise | Repetition of Phase I |
| Stage III | Elephantiasis | 28-35 days | 5-10 years | MLD series or 1-2x/week |
| | Compression | MLD 2-3x/day | MLD 2-3x/week | Long-term compression |
| | Exercise | | Compression | Exercise |
| | | | Exercise | Repetition of Phase I |
of compression therapy. Clinical and health economic benefits of pneumatic compression were demonstrated in the retrospective analysis of an insurance database of 718 lymphedema patients.\[^{24}\] Controlled studies have shown that a sequential high-pressure IPC is more effective than conventional single chamber devices in the acute phase of lymphedema treatment.\[^{25}\]

Optimal pressure of compression varies following the age of the patient, stages, and location of lymphedema.\[^{9}\] For example, in the elderly over 70 years, 20–30 mmHg and lesser application time is recommended. Furthermore, the earlier the stage, the smaller pressure is required. A very high pressure (>70 mmHg) is counterproductive.\[^{22}\] The isolated lymphedema lymphedema treatment recommend the highest tolerated by patient pressure as the most beneficial.\[^{11}\]

### Other methods

- **Since lymphedema is a lifelong chronic condition, it is important for the patients to learn all measures related to lifestyle to help management of their disease**
  - Psychological support for the patients is crucial from several points of view. Lymphedema is a debilitating chronic disease, in which the best results of treatment can be expected only for individuals having full understanding and commitment to all therapeutic measures, each of those having the impact on the global treatment effect. Severe lymphedema will require a professional reorientation in ~10% of patients.\[^{26}\] Hence, these patients need robust psychosocial support. Quality-of-life assessment and improvement program should be part of all protocols for lymphedema treatment
- **Weight reduction is one effective way for improvement of lymphedema, as higher body mass index correlates with its severity.**\[^{27,28}\] Different diets could be beneficial, such as those rich in omega-3 fatty acids, considered as anti-inflammatory; or a medium-chain triglycerides diet, that reduces the lymphatic load in chylous reflux syndromes.\[^{11}\] Specific vitamin supplements might be indicated with low-fat diets
- **Protection of the skin against mycotic and bacterial infections, trauma and insects’ bites aim to prevent episodes of erysipelas/cellulitis. Skincare with strict rules of personal hygiene, rehydration, antifungal, and softening treatments reduce hyperkeratosis and skin alterations. This not only reinforces cutaneous barrier against microbial infections but also facilitates the limbs’ movements.**\[^{17}\] Antihistamine drugs can help itching and congestive dermatitis reduction\[^{19}\]
- **Recent recommendations advertise an aggressive antibiotic therapy when necessary.**\[^{8,29}\] Antibiotic of choice for cellulitis is oral amoxicillin 500 mg every 8 h, efficient in Streptococcus and Staphylococcus infections. If evidence of \textit{Staphylococcus aureus}, fluoxacin 500 mg every 6 h is recommended. In case of allergy to penicillin Erythromycin 500 mg every 6 h can be administrated. In the presence of more than two cellulitis episodes per year, low daily dose of penicillin V or other broad-spectrum antibiotic is successfully used to prevent the infection recurrences and further deterioration of the lymphatic network.\[^{11,29,30}\] According to the lymphedema Support Network, patients with a history of attack of cellulitis should have a 2-week supply of antibiotic (amoxicillin or erythromycin), especially when they are traveling\[^{29}\]
  - **Limb elevation at rest, respiratory therapy, and physical exercises might help to maintain the edema reduction by acting on the venous system pressures and by improving lymphatic circulation. Although there is no scientific evidence to confirm the role of fitness in lymphedema patients, exercise certainly promote intradermal lymph movement.**\[^{31}\] The beneficial effect of Tai Chi and Qi Gong exercises was shown in Moseley \textit{et al.} study.\[^{32}\] The specific programs exist for upper and lower extremity lymphedema. They include gentle, rhythmic exercises associated with self-massage\[^{33}\]
  - **Balneotherapy has its supporters in Europe and Asia. Combination of aquatic therapy, skin care, heat, and exercises is successfully applied in many patients.**\[^{11}\] Aquatic treatment seems to be especially indicated due to the water pressure and beneficial effect on the skin
  - **Other methods, such as hyperbaric oxygen and low-level laser therapy were suggested in the patients with breast cancer lymphedema, despite recent negative results in the randomized trial.**\[^{11,34-38}\] Ultrasounds and shockwaves are supposed to break up fibrotic tissue\[^{11}\] in selected patients
  - **Kinesio Taping is suggested especially in the areas where the compression therapy is difficult to apply. This method could improve lymphatic drainage by traction exerted on the skin during the movements\[^{19}\]**
  - **Some pharmacological agents were used as adjunctive therapy of lymphedema. Among them micronized purified flavonoid Fraction (Dalfon 500 mg,\[^{40}\] Cyclo 3 fort,\[^{41}\] and benzopyrones,\[^{42,43}\] Although a small randomized trial demonstrated their efficacy, these treatments are still controversial. New compounds are emerging based on the understanding of inflammatory nature of lymphedema\[^{44}\]**
  - **Prevention and treatment of filariasis are of importance, as lymphatic filariasis affects at least 68 million individuals in 73 countries.**\[^{6}\] In India, preventive chemotherapy combines two drugs administered annually to at-risk population: albendazole (400 mg) with ivermectin (150–200 mcg/kg) or diethylcarbamazine citrate (6 mg/kg). This treatment has the effect on the presence of microfilariae in the blood, hence the limitation of microfilariae spread to mosquitoes.\[^{6}\]"
Surgical treatment is indicated in case of nonresponse to the medical therapy conducted for at least 6 months, or in case of difficult to manage recurrences of cellulitis/lymphangitis. The recommendations of the American venous forum on the principles of the surgical treatment of chronic lymphedema are summarized in Table 3.\[45\]

**Reconstructive surgery**

The reconstructive surgery requires suitable anatomy of the lymphatic system. The preoperative evaluation includes lymphoscintigraphy, magnetic resonance examination, or near-infrared fluorescence lymphatic imaging using indocyanine green.\[48\]

The best results are obtained in the early stages of the disease with preserved lymphatic contractility, and in the cases of secondary pelvic or axillary obstruction.\[45\] These interventions are extremely difficult and necessitate experienced microsurgical centers.

Lymphatic reconstructions can be divided into three main types as follows: lymphovenous anastomosis (LVA), lymphatic grafting, and lymph node transplantation.

- LVA drain lymph from lymph vessel or node into the vein distal to the obstructed segment; several techniques are used, most of them being end-to-end or end-to-side variants.\[31\] A systematic meta-analysis of 22 studies in patients having LVA procedures for peripheral lymphedema reveals consistent improvement and safety.\[52\] The authors concluded that “lymph node transplantation may provide better outcomes compared with lymphovenous shunt.”\[53\] Some concerns were raised for LVA because of poorly documented late patency. Nodovenal shunt (end-to-end or end-to-side anastomosis)\[32\] was proposed in lymphatic filariasis treatment, especially in a case of genital lymphedema.\[6\] A large number of patients were operated by Campisi\[54,55\] who developed a specific protocol of fibro-lipo-aspiration with lymph vessel sparing procedure to treat advanced lymphedema after multiple LVA\[53\]

- Lymphatic grafting was developed by Baumeister.\[56\] Principal indications in some rare cases.

- Vascularized lymph node transplantation (VLNT) was described by Becker.\[59-61\] The authors applied this technique in postmastectomy lymphedema. The lymph nodes from the femoral region were transplanted microsurgically to the axillary region. Almost all patients showed amelioration after procedure and cure was observed in 41.6% of cases. Saaristo et al.\[62\] followed VLNT as an optimal option during simultaneous breast and lymphatic reconstruction in patients with lymphedema after mastectomy. Other group reported favorable outcomes after VLNT.\[63,64\] Recent literature review\[65\] stated clear benefits. However, this should be confirmed in comparative studies with uniform patient selection and monitoring. Another VLNT indication reported was hypoplastic congenital lymphedema.\[66\]

Altogether, despite controversy related to the results’ reproducibility, reconstructive microsurgery can provide good effects with reports of up to 87% subjective and 83% objective improvement in the centers of excellence.\[55\] Timing of the intervention is a crucial factor as well as patient compliance with the life-long medical therapy.\[20\]

**Excisional surgery**

Excisional or debulking surgery may be needed to eliminate the skin excess after successful conservative lymphedema treatment. Excisional procedure may also be part of the therapeutic strategy in patients with important lymphedema limiting the movements and with poor efficiency of medical therapy. Direct excision of lymphedema tissue keeps its indications in some rare cases.\[57\] The inconvenience of these procedures is the removal of skin lymphatic network. Important scarring, difficult wound healing, and secondary infections are major complications.\[11\]

**Liposuction**

A place is reserved to liposuction, helpful in lymphedema secondary to the adipose tissue deposit and in some selective

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**Table 3: Guidelines 6.4.0. of the American Venous Forum on the principles of the surgical treatment of chronic lymphedema\[48\]**

| Number of guideline | Guideline                                                                 | Grade of recommendation | Grade of evidence |
|---------------------|---------------------------------------------------------------------------|-------------------------|-------------------|
| 6.4.1               | All interventions for chronic lymphedema should be preceded by at least 6 months of nonoperative compression treatment | 1                       | C                 |
| 6.4.2               | We suggest excisional operations or liposuction only to patients with late-stage nonpitting lymphedema who fail conservative measures | 2                       | C                 |
| 6.4.3               | We suggest microsurgical lymphatic reconstruction in centers of excellence for selected patients with secondary lymphedema if performed early in the course of the disease | 2                       | C                 |
cases of nonpitting nonfibrotic primary or secondary lymphedema. Patients with fibrotic lymphedema might benefit from power-assisted liposuction breaking down fibrotic tissue.

**TREATMENT GOAL AND OUTCOMES ASSESSMENT**

Therapeutic goal should be defined for each patient. Some protocols are time-consuming and expensive. Their set-up in the perspective of professionally active individuals can be difficult or impossible. Less aggressive treatment schedule might be more realistic and might preserve the quality of life. In general, management of lymphedema should fit into the life-long, feasible, and affordable plan.

The International Union of phlebology consensus document defined the goal of the therapy as follow:
- “Better social adaptation and socially useful life
- Better functional adaptation with physically normal activity, and
- Better psychological adaptation despite a psychologically unacceptable physical deformity.”

The main recommended treatment outcome is lymphedema volume measurement. Limb volume can be evaluated by:
- Circumferential measurement and truncated cone formula
- Water volumetry
- Perometry and other methods.

Volume assessment should be done on both affected and healthy limbs, before, during, and after treatment.

Tissue alterations’ examinations include ultrasound, magnetic resonance imaging, tonometry, and others. They can monitor the lymphatic flow and tissue’s structural changes.

Patient-defined outcomes, such as health-related quality of life evaluation, or self-assessment of treatment efficacy through visual analog scale/scoring system, are frequently part of the follow-up.

Best practice for the management of lymphoedema, international consensus, differentiated successful outcome of initial management from outcome of transition, and long-term management [Table 4].

**PERSPECTIVE FOR THE FUTURE**

Better prevention of secondary lymphedema following oncologic treatment is needed in view of the high prevalence of lymphatic complications. Prophylactic microsurgery with lymphatic reconstruction can be an option, when it is safe and with minimal risk of donor site lymphedema.

Tissue-engineered lymphatic grafts might provide some solution for lymphedema treatments. Nanocomposite polymers are promising candidates for the construction of endothelialized conduits with intraluminal valves which could be used in the future as lymphatic grafts.

| Successful outcome of initial management |
| Reduction in size/volume |
| Improved skin condition, subcutaneous tissue consistency, limb shape and function, symptom control |
| Enhanced patient/family/career involvement and self-management skills |

Successful outcome of transition management
- Maintenance or reduction of swelling size/volume
- No deterioration in tissue density, in limb shape
- Improvement in patient/career involvement and self-management skills

Successful outcome of long-term management
- No increase in swelling
- No deterioration in skin tissue density and condition
- No deterioration in shape
- Symptom control, improvement in patient/career involvement, and self-management skills

Angiogenic factors promoting lymphatic growth are objects of experimental studies. For example, the vascular endothelial growth factor receptor-3-specific mutant form was shown to induce lymphangiogenesis in a mouse model of lymphedema. The carcinogenic potential of these substances requires a lot of precaution in the future.

New pharmacological agents, such as 9-cis retinoic acid, were found to stimulate lymphangiogenesis and to promote lymphatic regeneration in animal studies. Identification of specific mutations associated with lymphatic malformations may guide the treatment strategy in patients with primary lymphedema or those with the predisposition to lymphedema after surgery. The targeted sequencing approach as the genetic diagnostic technique could help to personalize therapy and to improve early prenatal and postnatal diagnosis of lymphatic disease. Earlier diagnosis means earlier treatment and potentially better results.

**CONCLUSIONS**

Lymphedema patients deserve comprehensive management and utmost attention from the medical community. This condition touches a large population of individuals and generates considerable financial burden for the healthcare system. Although nonperfect and in majority of cases noncurative, the therapeutic options are available and they are efficient. Future research efforts should bring better solutions and will improve patients’ evaluation and management.

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There are no conflicts of interest.

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