

THE DIAGNOSIS AND TREATMENT OF PERIPHERAL LYMPHEDEMA

Consensus Document of the International Society of Lymphology

This International Society of Lymphology (ISL) Consensus Document is the current revision of the 1995 Document for the evaluation and management of peripheral lymphedema (1). It is based upon modifications suggested and published following the 1997 XVI International Congress of Lymphology (ICL) in Madrid, Spain (2), discussed at the 1999 XVII ICL in Chennai, India (3), considered at the 2000 (ISL) Executive Committee meeting in Hinterzarten, Germany (4), and derived from integration of discussions and written comments obtained during and following the 2001 XVIII ICL in Genoa, Italy as modified at the 2003 ISL Executive Committee meeting in Cordoba, Argentina (5).

The document attempts to amalgamate the broad spectrum of protocols advocated worldwide for the diagnosis and treatment of peripheral lymphedema into a coordinated proclamation representing a "Consensus" of the international community. The document is not meant to override individual clinical considerations for problematic patients nor to stifle progress. It is also not meant to be a legal formulation from which variations define medical malpractice. The Society understands that in some clinics the method of treatment derives from national standards while in others access to medical equipment and supplies is limited and therefore the suggested treatments are impractical. We continue to struggle to keep the document concise while balancing the need for depth and details. With these considerations in mind, we believe that

this version of the Consensus represents the best judgment of the ISL membership on how to approach patients with peripheral lymphedema as of 2003. We anticipate that the document will and should be challenged, debated in the pages of Lymphology (e.g., as Letters to the Editor), and ideally become a continued focal point for robust discussion at local, national and international conferences in lymphology and related disciplines. We further anticipate as experience evolves and new ideas and technologies emerge that this "living document" will undergo periodic revision and refinement.

I. GENERAL CONSIDERATIONS

Lymphedema is an external (or internal) manifestation of lymphatic system insufficiency and deranged lymph transport. It may be an isolated phenomenon or associated with a multitude of other disabling local sequelae or even life-threatening systemic syndromes. In its purest form, the central disturbance is a *low output failure* of the lymphovascular system, that is, overall lymphatic transport is reduced. This derangement arises either from congenital lymphatic dysplasia (primary lymphedema) or anatomical obliteration, such as after radical operative dissection (e.g., axillary or retroperitoneal nodal sampling), irradiation, or from repeated lymphangitis with lymphangiosclerosis (secondary lymphedema) or as a consequence of functional deficiency (e.g., lymphangiospasm, paralysis, and valvular insufficiency) (primary or

secondary lymphedema). The common denominator, nonetheless, is that lymphatic transport has fallen below the capacity needed to handle the presented load of microvascular filtrate including plasma protein and cells that normally leak from the bloodstream into the interstitium. Swelling is produced by accumulation in the extracellular space of excess water, filtered plasma proteins, extravascular blood cells and parenchymal cell products. This process culminates in proliferation of parenchymal and stromal elements with excessive deposition of ground matrix substances. *High output failure* of the lymph circulation, on the other hand, occurs when a normal or increased transport capacity of intact lymphatics is overwhelmed by an excessive burden of blood capillary filtrate. Examples include hepatic cirrhosis (ascites), nephrotic syndrome (anasarca), and deep venous insufficiency of the leg (peripheral edema). Although the final pathway is the manifestation of tissue edema whenever lymph formation exceeds lymph absorption, the latter entities should properly be distinguished from lymphedema, which is characterized by decreased lymphatic transport. In some syndromes where high output lymphatic transport failure is longstanding, a gradual functional deterioration of the draining lymphatics may supervene and thereby reduce overall transport capacity. A reduced lymphatic circulatory capacity then develops in the face of increased blood capillary filtration. Examples include recurring infection, thermal burns, and repeated allergic reactions. These latter conditions are associated with "safety valve insufficiency" of the lymphatic system and can be considered a mixed form of edema/lymphedema and as such are particularly troublesome to treat.

Peripheral lymphedema associated with chylous and non-chylous reflux syndromes is an infrequent but complex condition that requires specific diagnostic measures and treatment methods.

In the treatment of "classical" lymph-

dema of the limbs (that is, peripheral lymphedema), improvement in swelling can usually be achieved by non-operative therapy. Because lymphedema is a chronic, generally incurable ailment, it requires, as do other chronic disorders, lifelong care and attention along with psychosocial support. The continued need for therapy does not mean a priori that treatment is unsatisfactory, although often it is less than ideal. For example, patients with diabetes mellitus continue to need drugs (insulin) or special diet (low calorie, low sugar) in order to maintain metabolic homeostasis. Similarly, patients with chronic venous insufficiency require lifelong external compression therapy to minimize edema, lipodermatosclerosis and skin ulceration. The compliance and commitment of the patient is also essential to an improved outcome. For example, in a patient with diabetes, poor compliance can result in weight loss, polyuria, and even coma and, long-term, also blindness, renal failure, and stroke. With chronic venous insufficiency, poor patient cooperation may be associated with progressive skin ulceration, hyperpigmentation, and other trophic changes in the lower leg. Similarly, failure to control lymphedema may lead to repeated infections (cellulitis/lymphangitis), progressive elephantine trophic changes in the skin, sometimes crippling invalidism and on rare occasions, the development of a highly lethal angiosarcoma (Stewart-Treves syndrome).

II. STAGING OF LYMPHEDEMA

Whereas most ISL members generally rely on a three stage scale for classification of a lymphedematous limb, an increasing number recognize Stage 0 which refers to a latent or sub-clinical condition where swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs (Stages I-III). Stage I represents an early accumulation of fluid relatively high in protein content (e.g., in comparison with "venous" edema) and

subsides with limb elevation. Pitting may occur. Stage II signifies that limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage II, the limb may or may not pit as tissue fibrosis supervenes. Stage III encompasses lymphostatic elephantiasis where pitting is absent and trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop. Within each Stage, severity based on volume difference can be assessed as minimal (<20% increase) in limb volume, moderate (20-40% increase), or severe (>40% increase).

These Stages only refer to the physical condition of the extremities. A more detailed and inclusive classification needs to be formulated in accordance with improved understanding of the pathogenetic mechanisms of lymphedema (e.g., nature and degree of lymphangiodyplasia, lymph flow perturbations and nodal dysfunction as defined by anatomic features and physiologic imaging and testing) and underlying genetic disturbances, which are gradually being elucidated.

Some healthcare workers examining disability utilize the World Health Organization's guidelines for the International Classification of Functioning, Disability, and Health (ICF). Quality of Life issues (social, emotional, physical disabilities, etc.) may also be addressed by individual clinicians and can favorably impact therapy and compliance (maintenance).

III. DIAGNOSIS

An accurate diagnosis of lymphedema is essential for appropriate therapy. In most patients, the diagnosis of lymphedema can be readily determined from the clinical history and physical examination. In other patients confounding conditions such as morbid obesity, venous insufficiency, occult trauma, and repeated infection may complicate the clinical picture. Moreover, in considering the basis of unilateral extremity lymphedema, especially in adults, an occult visceral tumor

obstructing or invading more proximal lymphatics needs to be considered. For these reasons, a thorough medical evaluation is indispensable before embarking on lymphedema treatment. Co-morbid conditions such as congestive heart failure, hypertension, and cerebrovascular disease including stroke may also influence the therapeutic approach undertaken.

A. Imaging

If the diagnosis of lymphedema is unclear or in need of better definition for prognostic considerations, consultation with a clinical lymphologist or referral to a lymphologic center if accessible is recommended. The diagnostic tool of isotope lymphography (also termed lymphoscintigraphy or lymphangioscintigraphy) has proved extremely useful for depicting the specific lymphatic abnormality. Where specialists in nuclear medicine are available, lymphangioscintigraphy (LAS) has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. Although LAS has not been standardized (various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection site, epi- or subfascial injection, one or more injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques), the images, which can be easily repeated, offer remarkable insight into lymphatic (dys)function.

LAS provides both images of lymphatics and lymph nodes as well as semi-quantitative data on radiotracer (lymph) transport, and it does not require dermal injections of blue-dye (as used for example in axillary or groin sentinel node visualization i.e., lymphadenoscintigraphy). Dye injection is occasionally complicated by an allergic skin reaction or serious anaphylaxis. Moreover, clinical interpretation of lymphatic function after vital dye injection alone ("the blue test") is often misleading. Direct oil contrast

lymphography, which is cumbersome and occasionally associated with minor and major complications, is usually reserved for complex conditions such as chylous reflux syndrome and thoracic duct injury. Non-invasive duplex-Doppler studies and occasionally phlebography are useful for examining the deep venous system and supplement or complement the evaluation of extremity edema. Other diagnostic and investigational tools used to elucidate lymphangiodysplasia/lymphedema syndromes include magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography (US), indirect (water soluble) lymphography (IL) and fluorescent microlymphangiography (FM). DEXA, or bi-photon absorptiometry, may help classify and diagnose a lymphedematous limb but its greatest potential use may be to assess the chemical components of limb swelling (% fat, water, lean mass) before and after treatment. IL and FM are best suited to depict initial and terminal lymphatics and accordingly have limited clinical usefulness. US has found its most practical value in depicting the dance of the living adult worms in scrotal lymphatic filariasis.

B. Genetics

Genetic testing is almost becoming practical to define a limited number of specific hereditary syndromes with discrete gene mutations such as lymphedema-distichiasis (*FOXC2*) and some forms of Milroy disease (*VEGFR-3*). The future holds promise that such testing combined with careful phenotypic descriptions will become routine to classify familial lymphangiodysplastic syndromes and other congenital/genetic-dysmorphic disorders characterized by lymphedema, lymphangiectasia, and lymphangiomatosis.

C. Biopsy

Caution should be exercised before removing enlarged regional lymph nodes in the setting of longstanding peripheral

lymphedema as the histologic information is seldom helpful, and such excision may aggravate distal swelling. Fine needle aspiration with cytological examination by a skilled pathologist is a useful alternative if malignancy is suspected. Use of sentinel node biopsy in the groin or axilla in staging malignancy such as breast and melanoma, if validated for determining metastasis, may lessen the incidence of peripheral lymphedema by discouraging removal of normal lymph nodes.

IV. TREATMENT

Therapy of peripheral lymphedema is divided into conservative (non-operative) and operative methods. Applicable to both methods is an understanding that meticulous skin hygiene and care (cleansing, low pH lotions, emollients) is of utmost importance to the success of virtually all treatment approaches. Basic range of motion exercises of the extremities, especially combined with external limb compression, and limb elevation is also helpful to virtually all patients undergoing treatment.

A. Non-operative Treatment

1. Physical therapy

a. Combined physical therapy (CPT) (also known as Complete or Complex Decongestive Therapy (CDT) or Complex Decongestive Physiotherapy (CDP) among others) is backed by longstanding experience and generally involves a two-stage treatment program that can be applied to both children and adults. The first phase consists of skin care, light manual massage (manual lymph drainage), range of motion exercise and compression typically applied with multi-layered bandage-wrapping. Phase 2 (initiated promptly after Phase 1) aims to conserve and optimize the results obtained in Phase 1. It consists of compression by a low-stretch elastic stocking or sleeve, skin care, continued "remedial" exercise, and repeated light massage as needed.

Prerequisites of successful combined physiotherapy are the availability of physicians (i.e., clinical lymphologists), nurses, and therapists highly trained and educated in this method, acceptance of health insurers to underwrite the cost of treatment, and a biomaterials industry willing to provide high quality products. Compressive bandages, when applied incorrectly, can be harmful and/or useless. Accordingly, such multilayer wrapping should be carried out only by professionally trained personnel. Newer manufactured devices to assist in compression (i.e. pull on, velcro-assisted, quilted, etc.) may relieve some patients of the bandaging burden and perhaps facilitate compliance with the full treatment program. Some clinics find that patient self-care and risk reduction strategies help maintain edema reduction.

CPT may also be of use for palliation as, for example, to control secondary lymphedema from tumor-blocked lymphatics. Treatment is typically performed in conjunction with chemo- or radiotherapy directed specifically at producing tumor regression. Theoretically, massage and mechanical compression could promote metastasis in this setting by mobilizing dormant tumor cells, although only diffuse carcinomatous infiltrates which have already spread to lymph collectors as tumor thrombi might be mobilized by such treatment. Because the long-term prognosis for such an advanced patient is already dismal, any reduction in morbid swelling is nonetheless decidedly palliative.

A prescription for low stretch elastic garments (custom made with specific measurement if needed) to maintain lymphedema reduction after CPT is essential for long-term care. Preferably, a physician should prescribe the compression garment to avoid inappropriate usage in a patient with medical contraindications such as arterial disease, painful postphlebotic syndrome or occult visceral neoplasia. Generally the highest compression level tolerated (~20-60 mm Hg) by the patient is likely to be the most beneficial.

Failure of CPT is confirmed only when intensive non-operative treatment in a clinic specializing in management of peripheral lymphedema and directed by an experienced clinical lymphologist has been unsuccessful.

b. Intermittent pneumatic compression. Pneumomassage is usually a two-phase program. After external compression therapy is applied, preferably by a sequential gradient "pump," form-fitting low-stretch elastic stockings or sleeves are used to maintain edema reduction. Displacement of edema more proximally in the limb and genitalia and the development of a fibrosclerotic ring at the root of the extremity with exacerbated obstruction of lymph flow needs to be assiduously avoided by careful observation.

c. Massage alone. Performed as an isolated technique, classical massage or effleurage usually has limited benefit. Moreover, if performed overly vigorously, massage may damage lymphatic vessels.

d. Wringing out. "Tuyautage" or wringing out performed with bandages or rubber tubes is probably injurious to lymph vessels and should seldom if ever be performed.

e. Thermal therapy. Although a combination of heat, skin care, and external compression has been advocated by some practitioners in Europe and Asia, the role and value of thermotherapy in the management of lymphedema remain unclear.

f. Elevation. Simple elevation of a lymphedematous limb often reduces swelling particularly in the early stage of lymphedema. If swelling is reduced by antigravimetric means, the effect should be maintained by wearing of a low-stretch, elastic stocking/sleeve.

2. Drug therapy

a. Diuretics. Diuretic agents are occasionally useful during the initial treatment phase of CPT. Long-term administration of diuretics, however, is

discouraged for it is of marginal benefit in treatment of peripheral lymphedema and potentially may induce fluid and electrolyte imbalance. Diuretic drugs maybe helpful to treat effusions in body cavities (e.g., ascites, hydrothorax) and with protein-losing enteropathy. Patients with peripheral lymphedema from malignant lymphatic blockage may also derive benefit from a short course of diuretic drug treatment.

b. **Benzopyrones.** Oral benzopyrones, which are thought to hydrolyze tissue proteins and facilitate their absorption while stimulating lymphatic collectors, are neither an alternative nor substitute for CPT. The exact role for benzopyrones (and related rutin and bioflavonoid compounds) as an adjunct in primary and secondary lymphedema treatment including filariasis is still not definitively determined including appropriate formulations and dose regimens. Coumarin, one such benzopyrone, in higher doses has been linked to liver toxicity.

c. **Antimicrobials.** Antibiotics should be administered for bona fide superimposed acute inflammation (cellulitis/lymphangitis or erysipelas). Typically, these episodes are characterized by erythema, pain, high fever and, less commonly, even septic shock. Mild skin erythema without systemic signs and symptoms does not necessarily signify bacterial infection. If repeated limb “sepsis” recurs despite optimal CPT, the administration of a prophylactic antibiotic (usually broad spectrum) is recommended. Fungal infection, a common complication of extremity lymphedema, can be treated with antimycotic drugs (e.g., flucanazole, terbinafine). In most instances, washing the skin using a mild disinfectant followed by antibiotic-antifungal cream is helpful.

d. **Filariasis.** To eliminate microfilariae from the bloodstream in patients with lymphatic filariasis, the drugs diethyl-carbamazine, Albendazole, or Ivermectin are recommended. Killing of the adult nematodes by these drugs (macrofilaricidal effect) is variable and may be associated with an

inflammatory-immune response by the host with aggravation of lymphatic blockage. Short and long-term efficacy of antibiotics (e.g., penicillin or doxycyclin) separate from skin hygiene in patients with lymphatic filariasis to prevent elephantine trophic changes remains to be determined.

e. **Mesotherapy.** The injection of hyaluronidase or similar agents to loosen the extracellular matrix is of unclear benefit.

f. **Immunological therapy.** Efficacy of boosting immunity by intraarterial injection of autologous lymphocytes is unclear.

g. **Diet.** No special diet has proved to be of therapeutic value for uncomplicated peripheral lymphedema. In an obese patient, however, reducing caloric intake combined with a supervised exercise program is of distinct value in decreasing limb bulk. Restricted fluid intake is not of demonstrated benefit. In chylous reflux syndromes (e.g., intestinal lymphangiectasia), a diet low in long-chain triglycerides (absorbed via intestinal lacteals) and high in short and medium chain triglycerides (absorbed via the portal vein) is of benefit especially in children.

3. Psychosocial rehabilitation.

Psychosocial support with a quality of life assessment-improvement program is an integral component of any lymphedema treatment.

B. Operative Treatment

Operations designed to alleviate peripheral lymphedema by enhancing lymph return have not as yet been accepted worldwide and often require combined physiotherapy after the procedure to maintain edema reduction. In selected patients, these procedures may act as an adjunct to CPT or be undertaken when CPT has clearly been unsuccessful. In some specialized centers, operative treatment within specific guidelines may be a preferred approach.

1. Resection

The simplest operation is “debulking”, that is, removal of excess skin and subcutaneous tissue of the lymphedematous limb. The major disadvantage is that superficial skin lymphatic collaterals are removed or further obliterated. After aggressive CPT, redundant skin folds may require excision. Debulking is probably useful in treatment of advanced fibrosclerotic lymphedema (elephantiasis). Caution should be exercised in removing enlarged lymph nodes or soft-tissue masses (e.g., lymphangiomas) in the affected extremity as lymphedema may worsen thereafter.

Omental transposition, enteromesenteric bridge operations, and the implantation of tubes or threads to promote perilymphatic spaces (substitute lymphatics) have not shown long-term value. Chylous and other reflux syndromes are special disorders which may benefit from CT-guided sclerosis, operative ligation of visceral dysplastic lymphatics, and/or lymphatic to venous diversion.

Liposuction has been reported to alleviate non-pitting, non-fibrotic upper extremity lymphedema due to excess fat deposition (which has not responded to non-operative therapy) as, for example, after treatment of breast cancer. At this time, results are encouraging but long-term management requires strict patient compliance with dedicated wearing of a low-stretch elastic compression sleeve. This operation should be performed by an experienced team of surgeon, nurses and physiotherapists to obtain optimal outcomes.

2. Microsurgical procedures

This operative approach is designed to augment the rate of return of lymph to the blood circulation. The surgeon should be well-schooled in both microsurgery and lymphology.

a. Reconstructive methods. These

sophisticated techniques involve the use of a lymphatic collector or an interposition vein segment to restore lymphatic continuity. Autologous lymph vessel transplantation generally has been restricted to unilateral peripheral lymphedema due to the need for one healthy leg to harvest the graft.

b. Derivative methods. Although lympho-venous and lympho-nodal venous shunt are promising, these procedures still require confirmation of long-term patency and demonstration of improved lymphatic transport (i.e., objective physiologic measurements of long-term efficacy). Experience with these procedures over the last 20 years suggests that improved and more lasting benefit is forthcoming if performed early in the course of lymphedema.

3. Treatment Assessment

In each patient undergoing therapy, an assessment of limb volume should be made before, during and after treatment. This volume can be measured by water displacement, derived from circumferential measurements using the truncated cone formula, by perometer, or by other means. It is desirable, however, that treatment outcomes be reported in a standardized manner in order to compare and contrast the effectiveness of various treatment protocols. Additional assessments by imaging modalities such as lymphangioscintigraphy to document functional changes in lymphatic drainage and DEXA or magnetic resonance imaging to determine volume and tissue compositional changes would add scientific rigor to analysis of the different treatment approaches. Tissue alterations and fluid changes may also be examined by tonometry and bio-electrical impedance. Psychosocial indices and visual analog scales of patient perceptions are also useful.

V. RESEARCH AGENDA

While recognizing and encouraging individual investigators to pursue many different avenues of investigation, some general directions can be formulated. Ongoing epidemiologic studies on the incidence and prevalence of lymphedema regionally and worldwide will benefit from the further development and establishment of standardized, secure, intercommunicating database-registries. Assessment of lymphedema risk and steps for lymphedema prevention in different groups of at risk patients need to be determined. Studies might include research on minimizing or preventing secondary lymphedema through altered operative/sampling techniques (e.g., sentinel node biopsy or precise anatomical knowledge of derivative pathways), vector control and prophylactic drugs for filariasis, identification of patients with heritable genetic defects for lymphangiodysplasia (lymphedema), and use of massage or compression where lymphatic drainage is subclinically impaired as documented by imaging techniques (e.g., LAS). Research in molecular lymphology including lymphatic system genomics and proteomics should be encouraged. With the cellular and molecular basis of lymphedema-associated syndromes better defined, an array of specific biologically-based treatments including modulators of lymphatic growth and function should become available. Improved imaging techniques and physiological testing need to be devised to allow more precise non-invasive methods to measure lymph flow dynamics and lymphangion activity. As knowledge accrues, the current crude classification of lymphedema should be revisited and modified to include a more encompassing clinical description based on genetic, anatomic, and functional disability. Accordingly, treatment, whether by designer drugs, gene or stem cell

therapy, tissue engineering, physical methods or new operative approaches, should be directed at preventing, reversing or ameliorating the specific lymphatic defect and restoring function and quality of life.

VI. CONCLUSION

Lymphedema may be simple or complex but should not be neglected. Accurate diagnosis and effective therapy is now available, and lymphology itself is now recognized as an important speciality in which clinicians are carefully trained in the intricacies of the lymphatic system, lymph circulation and its related disorders. The emerging era of molecular lymphology should result in improved understanding, evaluation and treatment in clinical lymphology.

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