Diagnosis and Treatment of Primary Lymphedema

Consensus Document of the International Union of Phlebology (IUP)-2013

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Abstract

Primary lymphedema can be managed effectively as a form of chronic lymphedema by a sequenced and targeted treatment and management program based around a combination of Decongestive Lymphatic therapy (DLT) with compression therapy, when the latter is desired as an adjunct to DLT.

Treatment in the maintenance phase should include compression garments, self management, including self massage, meticulous personal hygiene and skin care, in addition to lymphtransport-promoting excercises and activities, and, if desired, pneumatic compression therapy applied in the home.

When conservative treatment fails, or gives sub optimal outcomes, the management of primary lymphedema can be improved, where appropriate, with the proper addition of surgical interventions, either reconstructive or ablative. These two surgical therapies can be more effective when fully integrated with manual lymphatic drainage (MLD)-based DLT postoperatively.

Compliance with a long-term commitment to MLD/DLT and particularly compression postoperatively is a critical factor in determining the success of any new treatment strategy involving either reconstructive or palliative surgery.

The future of management of primary lymphedema has never been brighter with the new prospect of gene-and perhaps stem celloriented management.

Key words: Primary lymphedema, Truncular lymphatic malformation, Decongestive Lymphatic Therapy, Reconstructive surgery, Ablative surgery, Compression therapy, Compliance, Gene-oriented management

I. Introduction

Background

The management of chronic swelling of the limbs and especially the trunk due to primary lymphedema remains a challenge for patients and clinicians worldwide. Progress over the past several decades has been significant, both in the diagnosis of and therapy for this disabling condition. The International Union of Phlebology invited an expert multidisciplinary panel to convene and arrive at a consensus on the management of patients with primary lymphedema in 2009. The current document represents the update.

The goal of the document is not to overrule previously published expert guidelines from other specialty societies or boards. The charge of the panel was to bring together and evaluate the very best and most commonly used available diagnostic tests and therapies for primary lymphedema, which can ultimately be recommended to clinicians treating patients with this condition worldwide.

Recommendations in the document are graded according to scientific evidence. The panel adopted the system used by Guyatt et al[1, 2], and the document has two grades of recommendations: Grade 1 (strong) recommendation, which is reserved for those tests or procedures for primary lymphedema, where the benefits clearly outweigh the associated risks and Grade 2 (weak) recommendation, which is reserved for those diagnostic tests or procedures, where the benefits do not significantly outweigh the associated risks. The quality of evidence can be high (A), medium (B), low or very low (C) (Table 1)

Table 1. Grading Recommendations According to Evidence[1]

Grade of Recommendation/Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk	RCTs with important limitations (inconsistent results,	Strong recommendation, can apply to most

	and burdens, or vice versa	methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

The document presents contemporary concepts encompassing a broad range of new and old diagnostic modalities and treatment options that are currently available in the management of primary lymphedema. We respect all of the currently available consensus documents, previously prepared by the many national and international societies, addressing all issues related to primary lymphedema. We strongly encourage the review

of these expert documents as additional references in addition to this consensus document.[3-6]

This document is not meant to overburden the individual, local or national medical communities with specific recommendations, as these may be impractical to some where there is limited availability and access to the recommended technology. On the other hand, we hope that those with experience, knowledge and expertise beyond that described in this document will continue to offer their input to this living consensus document.

The majority of the available data reviewed in the consensus belong to 2B or 2C, and at best, a small number belong to 1C or 2A. Only a few studies reviewed in this consensus have a strong recommendation based on low-quality or very low quality evidence where the benefits clearly outweigh the associated risks. Because of problems associated with the methodology and quality of supporting evidence obtained from observational studies or case series, these data will be limited to a strong recommendation but may change when higher quality evidence becomes available.[1-2]

With these considerations in mind, we support both manual lymphatic drainage (MLD) based decongestive lymphatic therapy (DLT) [7-10] as the mainstay of treatment and management of primary lymphedema, and the surgical aspect of primary lymphedema care [11-14]. This should improve the brevity and precision of the document, while balancing the need for in depth analysis, thereby permitting IUP members to exercise the best judgment in choosing a current approach to patients with primary lymphedema.

Although lymphedema is currently defined to be an externally (extrinsic) or internally (intrinsic) generated manifestation of lymphatic system insufficiency and deranged lymph transport[5], the future of the diagnosis and classification of primary lymphedema is likely to be determined by the pathophysiology or genetic basis of the underlying condition [15-18] which would make the present classification[19,20] such as congenital /praecox /tarda, unnecessary.[21]

It is our hope that this document will stimulate further inquiry and discussion regarding all aspects of primary lymphedema and that it will form a starting point for future discussions and ultimately become a “living document," where periodic updates and revisions are made incorporating new ideas, technologies and directions.

Pathophysiology- Alteration of lymphatic vessels

The lymphatic circulation is essential for the drainage of interstitial fluid. Lymph vessels are not only crucial to the recirculation of lymphocytes and proteins, and transport

of microorganisms by the lymph, but also to the transport of interstitial fluid to main blood circulation. [22]

The average human body weighing 65 kg contains 3 L of blood plasma and 12 L of interstitial fluid. Up to 8–12 L of afferent lymph are produced each day, of which 4–8 L of ultrafiltrate are reabsorbed into the bloodstream in the lymph nodes. Lymphatic vessels transport daily 4 L of efferent lymph into the bloodstream via the neck veins.

The concentration of proteins in plasma, interstitial fluid, afferent lymph, and efferent lymph is 70 g/L, 20–30 g/L, 20–30 g/L, and 60 g/L, respectively. The fluid turnover (including the volume of fluid reabsorbed in lymph nodes) reaches up to two-thirds of the total volume of interstitial fluid every 24 hours. [23]

The skin on the lower extremities contains a denser and more extensive network of lymphatic capillaries than the skin of the upper extremities. [24]
Due to orthostatic pressure, lower extremities have higher filtration pressure and influx of fluids, and it is thought that the capacity for lymph transport in the lower extremities is greater, in order to compensate for the higher influx of interstitial fluid caused by the effects of orthostatism and gravity.

Spontaneous contractility of lymphatic vessels is utilized in lymph transport. Regular contractions of lymph vessels, at a frequency of 2-4 per minute, have been observed in vitro. Spontaneous contractions of prenodal lymphatic vessels have been observed in human legs, and these contractions were shown to drive the lymph. [25] Internal extensions of lymphatic endothelial cells act as valves and guarantee a one-way lymph flow. [26, 27]
In steady state, the extravasation of fluids and proteins from blood vessels is balanced by lymphatic drainage and return into the bloodstream.

If microvascular filtration in blood capillaries and venules, as in the case of advanced chronic venous disease (CVD), exceeds the lymphatic drainage for sufficiently long periods, an edema occurs in afflicted areas by accumulation of tissue fluid in the interstitium.

In addition, lymphatic dysfunction and structural damages to lymphatic network are associated with varicose veins, and the subsequent lymph stasis and reduced lymph transportation lead to inflammation. [26] This is associated with lipid accumulation in the media of the diseased veins. Such accumulation of inflammatory lipids in the vein wall might further damage adventitial lymphatic vessels. [26]

II. Definition – General Consideration

Chronic lymphedema is a progressive and a relatively painless swelling of any peripheral tissue – limbs, head and neck, breast, trunk or genitals that is the result of a less-than-optimal transport capacity of the lymphatic system. Chronic lymphedema can be primary or secondary. In patients with **secondary lymphedema** a specific external cause (filariasis, previous surgery, radiation, malignancy, infection or inflammation, trauma, etc.) that is believed to impact on a presumed previously normally functioning lymphatic system is identified [27-31]. In patients with **primary lymphedema** the cause of decreased lymphatic transport can be an intrinsic "defect" [32-35] or a malfunction of the lymph conducting elements [36-39], which we believe is due to a genetically determined abnormality of lymphatic anatomy or function.

The preponderance of primary chronic lymphedema represents the clinical expression of heritable abnormal structural development, and defined as a truncular lymphatic malformation (LM) [32, 40]. In these circumstances, a malformation is clinically manifest as a macroscopic structural abnormality, but some primary lymphoedemas have very little structural derangement but represent a functional defect that is molecular in orgin. Therefore, a malformation may not necessarily have attributes that can be imaged but may ultimately require detection or definition in molecular or other functional terms.

LMs are a common type of congenital vascular malformation (CVM). [41-44] They occur as independent (predominant) malformations or can be combined with other CVMs such as venous malformations (VM) [45-47], arterio-venous malformations (AVM)[48-50], and/or capillary malformations (CM)[51, 52]. Combined malformations are classified as hemolymphatic malformations (HLM) [53-55] according to the Hamburg Classification. [56-58]

Primary lymphedema is believed to represent mainly a clinical condition due to truncular malformations of the lymphatic system with lymphatic truncular hypoplasia (89%), aplasia, numerical hyperplasia, or dilation (lymphangiectasia-10%) with valvular incompetence. Selective lymph node dysplasia rarely predisposes an individual to primary lymphoedema (eg, ilio-inguinal nodal sclerosis). [59] There is some controversy where some experts believe that all lymphedema and lymphatic malformations are genetically derived and propose to define lymphedema as an abnormality of lymph drainage where the predominant effect is on the tissue territory drained.

Nevertheless, primary lymphedema includes all those manifestations of lymphedema that represent an inherited condition: a disease-causing mutation of any of the genes involved in the development of the lymphatic system, can result in a familial distribution of primary lymphedema. Representative identified genetic mutations can affect *FLT4*[60-62], *FOXC* [16, 61], and *GJC2* [63, 64]

All these forms of genetically determined lymphedema have a prevalence of 1/6000 to 1/10000 live births and today are collectively classified as “primary” lymphedema.
Such conditions have been reported among multigeneration families where the lymphedema is the major clinical sign as primary phenotype and shows an autosomal dominant pattern of inheritance; various genes strongly associated with this pattern of inheritance have been demonstrated with variable expression and variable age at onset. [38, 60, 65]

Milroy’s disease is one example of an inherited lymphoedema . Many of the family cohorts examined demonstrate a gene mutation at the locus 5q35.3: the gene mutated is *FLT4,* which encodes for the VEGFR3 receptor. [15, 60, 65] Milroy’s disease is an inherited germ line mutation, whereas most asymmetrical and regionally limited genetic disorders (e.g. malformations) are due to a somatic mutation. In this situation, some tissue (e.g. skin) may be unaffected while the adjacent tissue (skin) may carry the mutation, an example of “mosaicism."

Although a family history was thought to be a prerequisite for diagnosis of (Nonne) Milroy syndrome (or FLT4-related lymphedema), the description of “de novo FLT4 mutations” in five sporadic patients. [66] (and incomplete penetrance estimated at 90%) suggests that FLT4 inactivating mutations are even found in sporadic cases. [62]

Nevertheless, the 'hereditary' type of primary lymphedema accounts for the minority of cases, while the 'sporadic' type represents the majority. (Table 2)

Table 2. Hereditary lymphedemaa.

Chromosomal aneuploidy
Turner syndrome
Klinefelter syndrome
Trisomy 21
Trisomy 13
Trisomy 18
Triploidy
Dysmorphogenic–genetic disturbances
Klippel–Trenaunay–Weber syndrome
Noonan syndrome
Nonne–Milroy hereditary lymphedema
Meige lymphedema
Neurofibromatosis type I (von Recklinghausen)
Distichiasis lymphedema
Lymphedema–hypoparathyroidism syndrome

(Adapted from Greenlee) [38]

There are also various terminologies for this group of lymphedema but we emphasize the term 'primary' in preference to 'essential' or idiopathic' as recommended by the ISL concensus document 2009. [4]

There is some concern about the current definition of the primary lymphedemas, as such. In fact, it is very likely that some may represent post-natal obliterations of lymph collectors and lymph nodes, thus mimicking congenital and prenatal pathology. True malformations, by definition, are present at birth. Although the term `primary' should indicate an intrinsic defect, there are some lymphoedemas, e.g. ilio-inguinal nodal sclerosis, that are designated as primary because the pathogenesis is not well-understood.

Primary lymphedemas have been historically classified into three groups depending on the age of onset: congenital (before age 2), praecox (between age 2 and 25, but most typically of pubertal onset) and tarda (after age 35). Gender distribution is variable.

There is also some objection to classifying all lymphedema 'tarda' as a primary disorder on the basis of the conventional spectrum based on the age of the onset. The arbitrary age of 35 used to separate 'tarda' from 'precox' is not clinically useful because this classification does not imply a mechanism or pathogenesis.

Lymphoedema-distichiasis syndrome[67-69] caused by mutations in the FOXC2 gene also includes congenital heart disease (5%) and congenital distichiasis (100%) but lymphoedema never manifests before puberty and the onset may be delayed until the 5th decade.[16] Therefore, terms like tarda and precox are outdated terms, potentially misleading as sole criteria for classification.

III. Definition – Special Consideration

Gene Mutation as Etio-pathogenesis of Lymphedema

The first gene identified as causative for human lymphoedema was FLT4 (encoding the VEGFR3 receptor) in 1998.[15, 65, 71, 72] This was found to be mutated in some cases of Milroy disease (MD), a congenital onset form of lymphoedema with swelling of the feet and lower limbs, but few other associated clinical features.[62] Soon after, the gene for Lymphoedema Distichiasis Syndrome (LDS) was mapped and subsequently identified as the developmentally important transcription factor FOXC2. [16, 61, 72, 73] LDS has pubertal onset lymphoedema of the lower limbs, but is a syndromic condition where distichiasis

(aberrant eyelashes originating from the meibomian glands) and varicose veins are prominent clinical signs, with an increased incidence of congenital heart disease and cleft palate.

Identification of further genes was then a slow process. The extremely rare syndrome Hypotrichosis-Lymphoedema-Telangiectasia syndrome (HLTS) was shown in 2003 to be caused by mutations in SOX18 [74], while in 2009 CCBE1 was identified as the gene underlying autosomal recessive Generalised Lymphatic Dysplasia/Hennekam Syndrome. [75, 76]

Recently, the gene GJC2 was discovered independently by Ferrell et al. [63] This codes for connexin 47, and appears to affect gap junctions. The predominant phenotype for mutations in this gene is late onset 4 limb involvement, but there is a wide diversity in age of onset and extent of limb involvement .[77] Two genes very recently identified are GATA2 and KIF11. [64, 78]

Over the last twelve years, seven genes for human lymphatic disease have been discovered. The identification of more genes is important for several reasons. Their discovery uncovers proteins of significance in the lymphatic developmental pathway, and in the maintenance of lymphatics in the adult. FOXC2 and SOX18 are now known to play pivotal roles in lymphangiogenesis, but this was only made apparent after the identification of their pathogenic role in primary lymphedema.

Recent studies on CCBE1 have identified it as crucial for lymphangiogenesis. [79] At a clinical level, identification of a mutation confirms the diagnosis and allows full characterisation of the phenotype, e.g incidence of congenital heart disease in LDS. The ability to give accurate recurrence risks, provide information about the natural history of the disease, and offer the possibility of prenatal diagnosis to families with severe forms of lymphatic dysplasia, is extremely important. By understanding the mechanism of disease, and in particular the molecular changes in the protein, opportunities are presented for a more targeted treatment.

Clinical Implementation of Genetic Mutation

Primary lymphedema represents the major clinical sign among FLT4-related lymphedema known as Nonne-Milroy syndrome and in FOXC2-related lymphedema known as distichiasis syndrome. But in other disorders, the lymphedema may remain a minor clinical manifestation within a complex syndrome in which other abnormal function dominates the clinical presentation, involving the liver (e.g., Cholestasis-lymphedema syndrome)[80], bone marrow (e.g. Emberger syndrome) [64], or gut pathology and developmental delay (e.g. Hennekam syndrome).[75]

Not all gene mutations will result in a phenotype that reflects a major impact on lymphatic function. A minor impact among patients with primary lymphedema has been also reported for *HGF* and *MET* genes, [81] representing a simple association between some nucleotide changes and lymphedema phenotype. Each mutation (four in the HGF and two in the MET gene) was found in only one proband; two of these probands had lymphedema and lymphangiectasia.

Due to incomplete penetrance, some individuals of the same family can remain as (healthy) carriers of the genetic mutation and do not develop the disease. Several non-identical conditions can be associated with the lymphedema (e.g. FOXC2 mutation to determine premature truncation of FOXC2 protein). These phenomena are closely associated with the activity of (unknown) modifier genes that act according to a model of genetic susceptibility. [16]

However, when the mutation results in defective development to varying degrees, the individual is no longer a 'healthy' carrier. Within some families, the lymphoscintigraphy shows various loco-regional lymph transport abnormality in healthy looking limb, suggesting defective development even in the absence of oedema. This 'sub-clinical' condition of lymphedema suggests the potential risk of such varying degrees of developmental error to trigger clinically significant lymphatic transport insufficiency later in the life when the triggering conditions are met. This unique group of subclinical presentation merits special consideration in the realm of lymphedema prevention.

Secondary lymphedema includes all those manifestations of lymphedema occasioned by acquired lymph transport abnormalities and, hence, triggered by an external event such as a parasite infection, trauma, radiation therapy, tumors or inflammatory processes) .[82, 83] However, very recent data suggests that secondary lymphedema is not exclusively due to enviromental insult but can be linked to a heritable factors according to a model of genetic susceptibility [84]; a single heterozygous mutation of the gene GJC2 [84] has been found to promote lymphedema in some women undergoing medical treatment and surgery for breast cancer and, in one case, a familial GJC2 mutation was associated to two sisters treated for breast cancer-related lymphedema.

Perspective on Edema (venous versus and lymphatic)

The antiquated view that venous capillaries are normally in a state of sustained absorption is still widely taught as an established fact. This view has now been disproved by a) measurement of all four Starling forces in the same tissue, b) direct measurement of fluid exchange at venous capillary pressures and c) experimental and theoretical proof that extravascular colloid osmotic pressure is inversely related to filtration rate.

Therefore in the steady state the blood capillary produces a constant but dwindling fluid filtration with no reabsorption. This means that the lymphatic system is responsible for draining all microvascular fluid filtered except for periods of transient reabsorption lasting no more than a few minutes after which the blood capillary reverts to a state of filtration.[22, 23]

This means that lymphatic failure is responsible for all forms of peripheral oedema, the mechanisms for which are a) only lymphatic failure (in the face of normal microvascular filtration) ie lymphoedema, b) a failure of lymph drainage to compensate for high microvascular filtration (increased capillary pressure, reduced plasma colloid oncotic pressue (COP) or increased microvascular permeability from inflammation) or c) lymphatic failure resulting from sustained increased microvascular filtration exhausting (so lymphoedema dissolves when high microvascular fluid filtration is corrected) and/or permanently damaging lymph drainage capacity (so lymphoedema remains even when high microvascular fluid filtration is corrected).

Therefore in circumstances of venous disease where corrective venous surgery is undertaken, eg EVT(endovascular therapy), but oedema fails to resolve then lymphoedema is the explanation. The message to phlebologists is always to consider lymphatic failure in any clinical circumstance where oedema exists.[85]

IV. Diagnosis - General Consideration

General Guideline

As a part of the diagnostic procedure, systemic causes of edema (e.g. heart failure, hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema) should be excluded. In addition to a complete history and physical examination, some tests should be ordered especially for the "tarda" subgroup of patients; for them, lymphedema is diagnosis of exclusion and lymphoscintigraphy alone is insufficient to make a full diagnosis. [87-90]

Duplex ultrasonography should be included with scintigraphy in all forms of lymphedema including congenital, for differentiation from edema of mixed etiology. [91, 92] In some genetic forms of primary lymphedema such as Milroy disease and lymphoedema distichiasis syndrome venous valve failure (venous reflux) frequently co-exists indicating the close relationship between venous and lymphatic development. [86]

Nevertheless, there is a danger of identifying an 'incidental' venous pathology with the assumption that the venous abnormality is the cause of chronic edema and thereby neglecting the lymphatic component. Vein surgery in edema can have significant negative effects if the state of the lymphatics is not known. Therefore, both, venous and lymphatic systems should always be evaluated together when investigating chronic oedema.

Proper diagnosis should allow appropriate clinical and laboratory staging [93] of the disease for the assessment of progress of the condition and its response to treatment. Diagnosis should include a proper assessment of clinical and subclinical infections in the early and latent stages; such evaluation should be repeated aggressively not only for timely treatment but also for effective prevention of various conditions such as tinea pedis.

Diagnostic evaluation should include appropriate assessment of patient compliance since the outcome of successful management is totally dependent on this crucial factor.

Lymphedema among children is chiefly of primary origin. Their lymphedema can be part of a syndrome if there are other concomitant phenotypic abnormalities and if a genetic defect is recognizable. However, recognition relies upon careful personal and family history and physical examination in the initial phases.

Clinical evaluation will not be complete without documentation for lymphedema stage [4-7, 93-95] Stage 0 through Stage III, classification of severity of edema (volume): Mild – Moderate – Severe, proper description on the skin and subcutaneous tissue changes, and functional assessment of limb affected by lymphedema. WHO guidelines for International classification of Functioning, Disability and health and Quality of Life issues can be used as a reference on this complex condition of social, emotional, physical disabilities. [96-98]

Clinical Evaluation

Evaluation of patients with presumed primary lymphedema must include a detailed history and clinical evaluation along with a thorough physical examination. [91-93] History should include age at onset, travel to tropical countries and history of all causes that could result in secondary lymphedema including the medications with edema causing potential (e.g. antipsychotics, anti parkinsons, cyto coxics, bisphonates). History of temporary edema of the affected limb or other areas must be noted and a detailed family history of limb swelling should also be recorded.

Signs and symptoms of primary lymphedema should be documented. These include non-pitting edema, skin changes such as “peau d’orange, pinkish-red skin discoloration,

hyperkeratosis, dermatitis, eczema, ulceration, varicosity, lymph vesicles, drainage of fluid, clear or milky, or yellow discoloration or other abnormalities of the nails. The presence of Stemmer sign[99] (skin fold of toes or fingers can barely be lifted), squaring of the toes, or puffiness of the forefoot (buffalo hump) should be noted.

The presence of venous, arteriovenous, or capillary malformations, or any tissue overgrowth eg increased/decreased leg length[100, 101], increase in fat or muscle bulk should be recorded. Finally, any complications, such as cellulitis, lymphangitis, malnutrition, immunodeficiency or, rarely, suspicion for malignancies (lymphangiosarcoma) must be documented.

Diagnostic Tests - General Principle

Basic initial diagnostic procedures for primary lymphedema should mimic those for early-stage secondary lymphedema (e.g. routine volumetry, symptoms of the patients) to establish an early diagnosis in 'at-risk' patients .

An appropriate combination of non- to minimally- invasive tests typically should be able to provide all the information necessary to insure an adequate diagnosis and lead to the correct multidisciplinary, specifically targeted and sequenced treatment strategy. The tests and the information they can provide are indicated below.

Non-invasive evaluations

Basic/Essential tests [67, 106-110]

- Plain X ray
- Duplex ultrasonography[86, 92, 102]
- MRI with/without contrast [103-105]
- CT scan [106, 107]
- Radionuclide Lymphoscintigraphy[108-110]

Optional tests

- Ultrasonographic lymphangiography [11]: investigational for the reconstructive surgery candidate patient
- MR lymphangiography[111, 112]: investigational for the reconstructive surgery candidate patient
- Microscopic fluorescent lymphangiography [113, 114]: investigational for the phlebolymphedema
- Indocyanine green imaging[115, 116]
- Indirect lymphography[117] using water soluble contrast agents

- Whole body blood pool scintigraphy (WBBPS) [118]
- Volumetry[119]
- Bio-impedance Spectroscopy [120]
- Air plethysmography[121]

1. Plain x-rays

X-rays of bones will identify limb length discrepancies, bone abnormalities or phleboliths in patients with combined LMs and VMs. Bone scanogram is specifically designed for the assessment of bone length.

2. Duplex ultrasonography (DUS)

DUS should include evaluation of the deep and superficial and local vasculature and the supra-fascial structures. Venous duplex studies should confirm any associated venous anomalies (valvular incompetence, obstruction, ectasia or aneurysms) and/or exclude venous obstruction as etiology or contributing factor to lymphedema.

The ultrasound evaluation of subcutaneous tissue tickness is a useful parameter to evaluate lymphoedema and its response to treatment.
The suprafascial and the subfascial thickness of the edematous tissue is demonstrable through high resolution echography (and/or CT scan) and tissue compressibility [122, 123]. These are useful measurements that allow periodic assessment of the response to therapy and are useful in monitoring a patient's progress and determining prognosis.

In patients with lymphedema, thickening of the cutaneous, epifascial and subfascial compartments has been ultrasonographically observed. This contrasts with MRI observations, where the subfascial compartment was shown to be unaffected.[20] High frequency ultrasound (20 MHz) reveals characteristic patterns of cutaneous fluid localization in various types of edema.

In lymphedema, there is a distinctively uniform pattern of distribution. This imaging technique has applications both in differential diagnosis and in therapeutic monitoring, although further refinement may become necessary to better characterize the spectrum of subcutaneous fibrosis that can be encountered in lymphedematous skin.[124, 125]

3. MRI and CT

MRI with or without contrast is indicated for further detailed evaluation of tissue overgrowth, pelvic pathology obstructing lymph drainage or malformations among the

patients with a combined form of vascular malformations (e.g. Klippel-Trenaunay Syndrome). [53, 54]

In lymphedema, the images reveal a characteristic distribution of edema within the epifascial compartment, disclosing a honeycomb pattern along with thickening of the skin. In venous edema, both the epi- and subfascial compartments are affected, while in lipedema, there is fat accumulation without fluid. [126, 127]

Magnetic resonance imaging is also helpful in the identification of lymph nodes, enlarged lymphatic trunks, and in the differentiation of the various causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI may complement the functional assessment provided by lymphoscintigraphy. At times, these complementary sources of information are necessary to establish the diagnosis and to make the requisite therapeutic decisions. [103]

4. Radionuclide Lymphoscintigraphy (LSG)[128-131]

Scintigraphy is a functional study that complements the anatomical information provided by lymphangiography. There are no standardizations nor is there a gold standard as yet.

LSG, performed with injection of 99mTc-labeled human serum albumin or 99mTc-labeled Sulphur Colloid subcutaneously into the first and second web-space of the toes or fingers, is the test of choice to confirm or exclude lymphedema as the cause of chronic limb swelling.

Movement of the colloid from the injection site, transition time to the knee, groins or axilla, absence or presence of major lymphatic collectors, number and size of vessels and nodes (e.g. popliteal nodes), the presence of collaterals and reflux, symmetric activity with the opposite side are recorded and used for interpretation . [132] Semiquantitative assessment has been reported, and most recently, the technique of quantitative assessment of transit time from the foot to the knee was also validated [(101-105)].

LSG remains the gold standard for lymphatic function evaluation since the LSG is the only test that can clearly indicate lymphatic function. Radionuclide lymphoscintigraphic findings provide the proper clinical and/or laboratory staging that may be essential for proper clinical management.

Guidelines 6.2.0 of the American Venous Forum on lymphoscintigraphy and lymphangiography

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.2.1	We recommend lymphoscintigraphy for the initial evaluation of patients with lymphedema	1	B
6.2.2	We suggest lymphoscintigraphy, using visual interpretation of the images with a semiquantitative scoring index, to document response to treatment of lymphedema	2	B

Adopted from [131]

LSG, along with clinical evaluation, is the most essential component for the diagnosis of primary lymphedema. LSG is extremely useful for identifying the specific lymphatic abnormality and has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG can easily be repeated with minimal risk. Data and images obtained from the study identify lymphatic (dys)function, based on visualization of lymphatics, lymph nodes, and dermal backflow as well as semi-quantitative data on radiotracer (lymph) transport.

However, the LSG has not been standardized with regard to the various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection site, epi-or sub-fascial injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques. [133]

5. Newly developed Tests - Indocyanine green lymphography

Fluorescent lymphography using Indocyanine green [134, 135] has recently been shown to be a relatively easy and non invasive means of assessing superficial lymphatic function in secondary lymphoedemas. This water soluble compound has been used in assessment of hepatic function, for ophthalmic angiography and other clinical indications for over 50 years. Not only can it help in information provision regaring lymphovenous shunts but also as a diagnostic tool in the assessment of lymphatic function generally.

Patterns and signs in primary lymphoedemas have yet to be elucidated but its simplicity, non invasive and non radioactive nature mean it presents an alternative to traditional lymphoscintigraphy at least for superficial lymphatic functional assessment.

Invasive evaluations

'Invasive' tests are seldom needed for the actual diagnosis but are occasionally needed for differential diagnosis; Further studies with invasive tests such as direct puncture percutaneous lymphangiography can be generally deferred to later stages if there is need for refining the diagnosis or if surgical or other invasive therapeutic measures are considered. Otherwise, these should be reserved for road mapping in subsequent therapy if needed.

On some occasions an invasive study is required to provide more information for an accurate differential diagnosis. These tests and the information they provide are indicated below;

- Direct puncture percutaneous lymphangiography
- Standard (ascending) lymphangiography, optional for reconstructive surgery candidate patients, where indicated
- Fine needle aspiration biopsy of lymph node
- Skin biopsy in cases of suspected sarcoma, skin cancer or differential diagnosis of warty lesions

Conventional oil contrast lymphangiography, especially if coupled with CT scan, is still advantageously employed in selected patients with chylous dysplasia and gravitational reflux disorders in order to define more clearly the extension of the pathologic alterations and sites of lymphatic and chylous leakage. These are the only diagnostic investigations that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy, etc. [136, 137]

Clinical and Laboratory Staging

There have been substantial efforts over several decades to provide proper clinical staging of the lymphedema in conjunction with proper classification. There are many different staging systems[93-95], including a three staging system (Stage 1 through 3) proposed by the International Society of Lymphology (ISL); more recently, Stage 0 has been added to this schema.

Most of the currently available staging systems reflect only tissue turgor and limb shape, etc and neglect other critical clinical information (e.g. number of major joints with changes in tissue composition) as well as socioeconomic status to reflect quality-of-life (QoL) properly.[93-98]

Therefore, many new proposals were made to compensate for such discrepancies; these include the Lymph CEAP classification by Europeans and U.S.-based combined staging of two separate Clinical and Laboratory staging based on the lymphoscintigraphic findings.[93-95, 138] But none of the current staging systems are able to meet the mandate as contemporary guidelines for improved management of lymphedema in different stages.

V . Treatment - General Consideration

General Guideline

Patient involvement in management is essential, especially for home maintenance. Patients should be encouraged to be aware of the nature of the disease and should be properly guided on how to be actively involved actively in self-management.

The treatment of children with lymphedema must be chiefly conservative, utilizing decongestive lymphedema therapy including compression therapy, directed exercises, massage and skin care. In the neonate, initial observation alone may be sufficient, as delayed lymphatic development and maturation can result in spontaneous improvement. The role of parents is crucial in providing the necessary input.

Proper management of various co-morbid conditions such as congestive heart failure, obesity, sleep apnoea, granulomatous disease, neurological disability and chronic arthritis is essential for the safe management of lymphedema since these co-morbid conditions will influence the therapeutic approach taken. Also calcium channel blocking agents should be avoided as they impair lymphatic pumping.[139] Medications that stimulate sodium retention, such as NSAIDs, should be similarly avoided.

The ultimate goal of treatment is to improve the physical characteristics of the affected limb or area as well as the QoL, [96-98, 140] thus achieving,

- Better social adaptation and a socially useful life,
- Better functional adaptation with physically normal activity, and
- Better psychological adaptation despite a psychologically unacceptable physical deformity.

Contemporary management of chronic lymphedema is now based on Decongestive Lymphatic Therapy (DLT).[141-145]

VI . Treatment - Physical & Pharmacological Therapy

Decongestive Lymphatic Therapy (DLT) based on compression therapy-

DLT is now well established as the treatment of choice for lymphedema regardless of the underlying etiology (primary or secondary) or its clinical stage. DLT consists of compression (bandaging, garments, intermittent pneumatic compression) therapy, movement exercises, manual lymphatic drainage (MLD), in addition to basic skin care, and education for risk reduction. Appropriate management of subjective symptoms and psychosocial management should also be included in the treatment regimen.

Compression bandage-based DLT with or without sequential intermittent pneumatic compression (SIPC)-based mechanical compression therapy[146-149], is the single most important component of DLT.
In the initial management phase of lymphedema, short stretch bandaging should be adopted, together with exercises and meticulous skin care, guided by specifically trained staff. The type and level of the bandaging and garments are still under evaluation. [150] This is an empirical strategy to control the edema and does not result in a "cure".

The maintenance phase after initial decongestion should be based on a practical combination of compression garments (e.g. tailored round or flat knitted garments depending on the stage and extent of the lymphedema), self management (e.g compression bandage or velcro-devices and/or self massage), skin care and exercises to continue to reduce lymph formation, promote uptake of fluid and their contents from the interstitium and maintain lymph transport. This phase requires life-long commitment. [150]

However, the specific mechanism of action and the optimal dosing of compression requires more research. Less bulky bandages and velcro-band devices than the widely used mulatilayer-multicomponent bandages allow better movement and show superior outcomes.[151, 152] Recent experimental data support the view that there is an optimal pressure range for reducing edema, corresponding to a pressure range around 30 mm Hg for the upper and 50-60 mm Hg for the lower extremties.[153] Higher pressures may be counterproductive. The main goal is to prevent edema and fibrosis. If this can be reached by lower compression pressure individually, then lower compression is appropriate and may help to improve compliance.

These findings from studies in postmastectomy arm lymphedema[154] and in patients with chronic venous edema in the lower extremities [155] excluding extreme fibrotic and elephantiastic indurations need to be confirmed by further investigations comparing the dose (pressure) with more outcome parameters than just volume reduction.[150] Due to the pressure drop of inelastic material this concept of an optimal pressure range has important implications concerning the timing of bandage changes. Bandages changed in

daily intervals should not be applied with the same high pressure compared to bandages changed once or twice weekly.

In a recent study it was shown that self-adjustable velcro-band devices, applied by lymphedema patients themselves may reduce edema even more effectively than inelastic lymph bandages. [152] This may be explained by the fact that the patients avoided unacceptably low and high pressures during self-application and self-readjustment.
MLD has not been fully scientifically documented and remains to be confirmed with objective data.[156, 157, 158]

However, MLD has become an indispensable treatment modality. The MLD component of DLT is believed to reduce lymphatic congestion effectively by physiologic stimulation of a poorly functioning lymph-transporting system thereby encouraging interstitial fluid entry into the initial lymphatics. In addition to improving lymphodynamics during treatment sessions and immediately after, it may also reduce the fibrosclerosis of the involved soft tissues, although this effect is conjectured but not established. [159-161]

DLT can be applied with minimal risk of complication and morbidity and can improve disease status in the majority of patients, regardless of the underlying etiology. It is more effective when started in the earlier (fluid) stages of lymphedema, and when utilized in the compliant, motivated patient who is commited to life-long therapy. In the later stages of lymphedema, the efficacy of DLT is very much limited to the maintenance of the current stage of lymphedema at best and, possibly, prevention of progression and of complications. DLT is therefore, not curative but may stabilize disease or even prevent progression, and it produces a satisfactory outcome in the majority of cases. This is especially true when the patient is compliant and maintains a self-motivated home treatment schedule with a life-time commitment.

DLT is often the only effective treatment in 'advanced' lymphoedema.
SIPC can be used as an adjuct treatment modality and using a mechanical pumping device, is particularly useful in those cases where lymphedema is treated by passive physical therapy (e.g. elderly, patients in bed, with serious disabilities, etc.) in whom spontaneous/isotonic physical exercise is highly compromised or absent, and to maintain results (home self therapy). Optimal settings concerning pressures, pattern and timing sequences of the pressure in such pumps need further clarification.[162, 163]

Proper occupational therapy can augment the selected muscle exercises, often forgotten by the patients in most important clinical stages.[97, 98.] Psychological support is also extremely important in the lymphedema patient and is helpful for maintenance of compliance, especially for children and family members.

There are however a few theoretical, relative contraindications to each component of the DLT: MLD with the risk of intravascular cancer metastases/thrombosis during the manipulation; and high pressure bandaging to the patient with advanced cardiac failure; and in advanced peripheral arterial disease of the limb.

Guidelines 6.3.0. of the American Venous Forum on lymphedema: medical and physical therapy

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.3.1	To reduce lymphedema we recommend multimodal complex decongestive therapy that includes manual lymphatic drainage; multilayer short-stretch bandaging; remedial exercise; skin care; and instruction in long-term management	1	B
6.3.3	To reduce lymphedema we recommend treatment daily, a minimum of 5 days per week, and continue until normal anatomy or a volumetric plateau is established	1	B
6.3.4	To reduce lymphedema we suggest compression pumps in some patients	2	C
6.3.5	For maintenance of lymphedema we recommend an appropriately fitting compression garment	1	A
6.3.6	For maintenance of lymphedema in patients with advanced (stages II or III) disease we recommend using short-stretch bandages during the night. Alternatively, compression devices may substitute for short-stretch bandages	1	B
6.3.7	For remedial exercises we recommend wearing compression garments or bandages	1	C
6.3.8	For cellulitis or lymphangitis we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci. Examples include cephalexin, penicillin, clindamycin, cefadroxil	1	A
6.3.9	For prophylaxis of cellulitis in patients with more than three episodes of infection we recommend antibiotics with superior coverage of Gram-positive cocci , particularly streptococci, at full strength for 1 week per month, Examples include cephalexin, penicillin, clindamycin, cefadroxil	1	C

Adopted from [164]

Pharmacological Treatment

Pharmacological trials of oral pharmaceutical treatments encompassing coumarin and derivatives, hydroethylrutosides, calcium dobesilate, escin extracts, 0-(beta-hydroxyethyl)-rutosides and MPFF found that such drugs may help lymphedema treatment by reducing protein and extracellular fluid accumulation[165] , stimulating lymph contractility and flow[166], and reducing protein concentration and fibrotic induration in tissues by stimulating proteolysis.[167, 168]

However, the investigation on the effect of oral pharmaceuticals based on three clinical trials with coumarin have shown conflicting results.[168-170]

The first study investigating two dosages, 90 mg (n = 23) and 135 mg (n = 30) over 12 months showed at the end that both groups experienced similar reduction in percentage of the limb.[169] The second study used a cross over design to compare the 6-month phase of coumarin (400 mg) to the 6 month phase of a placebo (n = 138).[170] Results demonstrated edema worsening in both treatment and placebo phases. The third study used the same cross over design as above and results demonstrated that the amount of edema of the legs was reduced from 25 percent to 17 percent above normal and that nearly one third of the edema fluid was removed from the legs. During the six months of the placebo period, the amount of edema of the legs was unchanged from 24 percent above normal.[168]

The 0-(beta-hydroxyethyl)-rutosides were studied in 6 months randomized, double-blind, cross-over trial performed on 26 patients with postmastectomy lymphedema of the arm, and 14 with lymphedema of the leg. The active drug significantly reduced the volume and circumference of the limbs. Patients reported increased comfort and freedom of movement, a reduction of their bursting pains, heaviness and tension, and an increased mobility of their limbs. [171]

From the 15 selected trials of the effect of pharmacological treatment in the reduction of limb lymphedema, the authors of the last Cochrane review were not able to perform a meta-analysis due to the heterogeneity of study designs. Consequently they did not draw conclusions about the effectiveness of these drugs in reducing limb volume, pain, or discomfort in lymphoedematous limbs . [172]

Despite the use of benzopyrone remaining an unsettled issue in view of its hepatic toxicity and it is currently not approved for clinical use in the U.S. or in the U.K., a combined approach [173] implementing conventional physical therapy, medical treatment using benzopyrones[174], and various physical [175] and surgical treatments remains the favored approach.

However the literature [176] indicates that better use of pharmacogenomic knowledge (screening patients for genetic polymorphisms) could significantly reduce the risk of benzopyrone associated hepatotoxicity by limiting the use of benzoprones (particularly coumarin) to those with a functional non polymorphic CYP2A6, a liver enzyme responsible for the metabolism of coumarin to non cytotoxic metabolites rather than o hydroxy-phenylacetaldehyde which is cytotoxic.

VII . Treatment - Surgical/Operative Therapy

General Overview

There are four different surgical approaches to the treatment of primary lymphedema.. Each surgical approach has distinctively different indications for the various stages of primary lymphedema.

- Reconstructive surgery with various microsurgical lympho-venous anastomoses [177-180]: this is best utilized in the early stages of lymphedema prior to the development and progression to the fatty fibrous stages where lymph vessels may show signs of fibrotic (functional) changes - clinical stage I & II (early stage)

- Reconstructive surgery with autologous free lymph nodes transplant surgery[(177, 180)]: is best utilized in patients with lymphadenodysplasia - clinical stage II & III. It remains a controversial procedure whose efficacy has not yet been fully established .
- Debulking/Ablative (excisional) surgery[12, 181-184]: is best utilized when there are massive limb changes and when there is significant fibrotic induration. It is the least prefered approach of all of the surgical strategies - clinical stage III & IV (end stage)
- Circumferential suction-assisted lipectomy [122, 123,185, 186]: is a lipo-remediation techniques to remove adipose tissue when the patient is in the adipo-fibrous (mid) stage and DLT and MLD etc., have failed - clinical stage II & III. This procedure has been reported to be effective in secondary lymphedema, but its utility in primary lymphedema with regard to its timing and to potential risks in truncular lymphatic malformation (LM) is not established[187, 188] Its safety has not been proven, especially in cases of co-existing when extratruncular LM [189, 190] .

These surgical interventions require specialized techniques and experience as well as specific followup to achieve optimal outcomes. Those wishing to utilise these techniques should receive specific training with the relevant expert groups.

Lymphatic-venous anastomosis for reconstruction [191-194] involves various technical aspects including the interposition of an autologous vein graft between lymphatics above and below the lymphatic obstruction. This technique is used in those cases involving the lower limbs, where surgically non-correctable disease exists (interpositioned vein grafted shunt or lymphatic-venous-lymphatic anastomosis - LVLA). [192]

Dilemma and Controversy

The first indication for additional surgical therapy is a well-documented, steady progression of the disease, despite maximum of MLD-based DLT for a mimimum a six month to two year period.[195, 196] Howver, two years of maximum therapy is generally considered to be too long and conservative before being declared a "treatment failure." Due to medicolegal and medicoethical issues involved in the treatment of primary lymphedema, while DLT remains first line treatment, two years is the generally accepted time period for the confirmation of a failed treatment by the IRB (Institutional Review Board).

There remains significant controversy regarding this waiting period before considering reconstructive surgery. A delay of surgery for more than one year will increase the risk of surgical failure due to chronic lymphatic damage. Therefore, this waiting period should be shortened as much as possible especially in compliant patients who stand to benefit the most from lymphatic reconstruction.

Surgical therapy for primary lymphedema should remain a treatment option as supplemental therapy in patients who have a non- to poor- response to DLT and/or compression therapy. This is especially true in the U.S. where rigid criteria for treatment indications are influenced by medical-legal-ethical conflicts. Within the good response group of patients in whom lymphedema relapses after DLT, notwithstanding the use of elastic garments, there are patients who can be excellent surgical candidates with outcomes similar to those in the early stage, treatment failure/non-responding group.

Patient compliance with life-long DLT therapy following surgical treatment is the single most important factor in ensuring successful surgical management of lymphedema unless microsurgery is applied early enough as a preventive approach.[197, 198] In addition, the prevention and treatment of systemic and local infection such as cellulitis and erysipelas is equally important to prevent further injury to already jeopardized lymph vessels following successful reconstructive surgery.[199] There is also a research indicating that the lymph stasis is a cause of poor immune response, and therefore increased risk of infection. This implies that improving the lymph flow with surgery decreases risk of infection.[200]

The role of reconstructive surgery in early stage lymphedema and excisional surgery in late stage lymphedema remains a decision for the multidisciplinary management team. Full integration with DLT-based therapy can deliver effective control of the condition in both in early and late stage lymphedema. Life-long compliance and follow up is neccessary for successfully treatment including postoperative DLT and compression garments.

Reconstructive Surgery - Lymphatic Microsurgery

1. General Principles

Reconstructive surgery to restore lymphatic function with newly created lympho-venous or lympho-lymphatic bypass, lympho-lymphatic venous segmental reconstruction, or free lymph node transplantation of a damaged lymph-transport system to enhance lymph flow is more theoretically sound than DLT, with a definite chance of 'cure' in early stage lymphedema.

The LM as the cause of primary lymphedema accompanies an extremely variable number of lymph vessels and lymph nodes by the various forms of dysplasias such as lymphangio-dysplasia, lymphadeno-dysplasia, and lymphangio-adeno-dysplasia (Papendieck's classification), and variations among the lymph nodes and lymph-transporting system (e.g. aplasia, hypoplasia and hyperplasia). [34, 201]

Therefore, proper candidates for reconstruction are much more rare among the primary lymphedemas due to such variation within the lymph nodes and lymph-transporting system (e.g. aplasia, hypoplasia and hyperplasia). [193, 194]
Nevertheless, excellent results have been reported even in primary lymphedema, with claims that there are many candidates with suitable lymph vessels for the reconstruction with the condition of lymphadeno-dysplasia than lymphangio-dysplasia. [193, 194]

Reconstructive surgery outcomes are also known to be much more variable and generally not as effective as those seen when performed to treat secondary lymphedema, where a surgically correctable lesion is often found along the major lymphatics and collectors. Excellent results have been reported even among the primary lymphedema, with claims that there are many candidates with suitable lymph vessels for reconstruction with a prevailing condition of lymphadenodysplasia rather than lymphangiodysplasia.[34, 201] However, many others failed to confirm these same observations and this issue remains to be supported with further evidence.

Lymphatic surgical reconstruction is known to be technically demanding, requiring microsurgical techniques that are often available only at specialized centers where lympho-venous procedures are routinely performed. These demands have hampered the widespread proliferation and acceptance of lymphatic reconstruction as the first-line treatment of lymphedema. This is especially true in the primary lymphedemas, despite the theoretical potential for disease reversal. Only a handful of institutions throughout the world continue to devote the effort and resources required to maintain an active lymphatic surgical reconstruction center. Access to these techniques is extremely limited.

2. Candidate Selection & Indication

Early stage lymphedema should be considered as an ideal candidate for reconstructive surgery, since there is a significant risk of from progression of disease to fibrotic changes in the lymphedema patient. There remains significant controversy regarding a suitable waiting period before considering reconstructive surgery.

A delay of surgery for more than one year will increase the risk of surgical failure due to chronic lymphatic damage. Moreover, functional magnetic resonance imaging demonstrates improvement of cortical alterations in patients after early microsurgical treatment of reversible congenital lymphedema. [202]

Therefore, the timing of lymphatic reconstruction remains most crucial and this waiting period should be shortened as much as possible. Thus, indications for lymphatic reconstructive surgery may be summarized as follows: failure to respond to proper therapy at clinical stage I or II; progression of the disease to advanced stages, despite proper treatment; chylous-reflux combined with extremity lymphedema; multiple recurrences of local or systemic infection; poor tolerance- *physically, mentally and socioeconomically*- of DLT-based conservative treatment.

A policy for lymphatic reconstruction that limits the candidates to those who fail DLT-based therapy will result in further damage to the lymphatic system and, subsequently, a higher likelihood of procedure failure. Therefore the wider inclusion criteria above are preferred.

In fact, the majority of candidates for lymphatic reconstruction have already had significant damage to lymph-transporting vessels caused by long-term lymphatic hypertension. Postoperative maintenance of DLT following successful reconstructive surgery is essential to maintain good long term outcomes. Without appropriate DLT assistance to partly damaged lymph vessels, even flawless technical surgical successes become futile.[89, 90]

A majority of patients have very poor compliance and do not maintain postoperative DLT that is required for the long term success of delayed surgery. Postoperative DLT totally depends upon patient compliance. Patient compliance is absolutely necessary for successful lymphatic surgery . [89, 90]

Due to the variety of such barriers, reconstructive lymphatic surgery has remained an adjunctive therapy. Yet in most cases, when optimally performed, it can result in effective treatment of primary lymphedema.

Ablative Surgery - Excisional Surgery

Ablative (cytoreductive) surgery is based on excisional techniques to reduce fibrosclerotic overgrowth, while liposuction can obliterate the epifascial compartment by removal of overgrown adipose tissue.

Several operations [182-104, 203-205] to treat lymphedema have been introduced throughout the decades (e.g. Charles procedure[204], Homan's procedure[183]), but have ultimately been abandoned by the majority of vascular surgeons due to the associated morbidity and poor long term results. More recently however, modifications of the original techniques have resulted in significant improvements in morbidity with improved outcomes (e.g. Modified Auchincloss/Homan procedure).[203]

Once the lymphedema advances to an irreversible stage, it has a tendency to progress steadily despite aggressive DLT with or without complementary compression therapy.

When the lymphedema progresses to its late end stages (stage III and IV of chronic lymphedema), the majority of patients will have an increased risk of recurrent local and systemic sepsis. In addition, due to the progressive deformity of the affected limbs, proper DLT becomes technically difficult. Therefore, once the multidisciplinary team admits its failure to arrest lymphedema progression toward the end stages with DLT and with evidence of steady deterioration despite maximum treatment, excisional surgery can be offered as a supplemental measure of last resort to improve the efficacy of available DLT.[11, 12]

Evaluation of potential candidates for palliative excisional surgery should be performed when the clinical stage of chronic lymphedema reaches the end-stages of lymphedema (stage IV or late stage III) and accompanied by;

- increased difficulty in providing effective DLT due to a highly disfigured limb and/or failure to be able to wrap adequately with a bandage for exercise therapy.
- increased frequency and severity of local and systemic sepsis.

Indications for ablative surgery include;

1) failure to implement proper care at clinical stage III or IV (end stage)
2) progression of the disease to end stages in spite of maximum available treatment
3) increased frequency and/or severity of local and/or systemic sepsis.[19, 20]

However, compliance with maintenance DLT postoperatively becomes a major critical issue for long term success of excisional surgery. Without adequate postoperative DLT;

excisional surgery alone cannot maintain the initial excellence of the surgical achievements and is highly likely to fail in the long term.[12]

Ablative Surgery - Circumferential suction-assisted lipectomy

The current application of liposuction is a selective removal of excessive adipose tissue alone, when this complicates secondary lymphedema of the upper limb following breast cancer treatment, or in other secondary causes of limb lymphedema. [185, 186]

Therefore, the patient most likely to benefit from this procedure is one who has a unique condition of an excess fat accumulation as a manifestation of the lymphedema, although control of the hydrostatic component of lymphedema is mandated continuously with conventional bandage-based and /or stocking– based compression armsleeve therapy before and after the liposuction..

For primary lymphedema, which has an entirely different pathogenesis as a truncular LM, the efficacy of liposuction has not been proven. After all, the target for the suction ablation of swollen arm is the adipose tissue and NOT the lymphedematous tissue . However, it has been claimed there is no risk of additional damage by the liposuction to the remaining lymphatic system. [185, 186]

The clinical course of primary lymphedema, mostly affecting the lower extremity as a truncular LM, is not same as that of secondary lymphedema affecting of the extremity; there is no clear evidence of selective overgrowth of the adipose tissue among this group. When the condition of 'pitting' edema progresses to 'non-pitting', the whole tissue becomes fibrosclerotic with very limited amount of fat tissue available for liposuction to improve local swelling.

Therefore, liposuction cannot be utilized in end stage primary lymphedema as a replacement for the currently employed excisional surgery.

Furthermore, primary lymphedema as a clinical manifestation of truncular LM is associated with significant risk for combined extratruncular LM. When coexisting extratruncular LM is stimulated by the liposuction, its its mesenchymal cell characteristics will cause it to grow rapidly and make the condition worse. [149]

Guidelines 6.4.0 of the American Venous Forum on principles of surgical treatment of chronic lymphedema

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.4.1	All interventions for chronic lymphedema should be preceded by at least 6 months of non-operative compression treatment	1	C
6.4.2	We suggest excisional operations or liposuction only to patients with late stage non-pitting lymphedema, who fail conservative measures	2	C
6.4.3	We suggest microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema, if performed early in the course of the disease	2	C

Adopted from [206]

VIII. Special Issues

Elephantiasis

General concept

Elephantiasis is a unique condition that characterizes the end stage of lymphatic impairment, with profound dermal as well as soft tissue changes. According to the International Society of Lymphology [4], elephantiasis is classified as Stage III (in a Stage 0 to III clinical classification of lymphedema) where "…pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed."

Elephantiasis reflects the most advanced clinical stage of lymphedema without regard to the underlying cause; while the presentation of tissue fibrosis, fat deposition and skin lesions may vary widely the clinical stage retains its designation due to the limb disfigurement.
All of these patients present a long history of limb swelling without proper treatment for many years and often complicated by secondary infection/cellulitis, slowly progressing to this debilitating and disfiguring chronic manifestation.

Lymph stasis may result –among others- in altered adipocyte metabolism and proliferation. Thus, localized adipose tissue enlargement could accompany primary lymphedema if remains untreated. If primary lymphedema is combined with morbid

obesity, clinical symptoms could appear in a more advanced form therefore overweight status is considered as an important secondary trigger factor. [207-210]

The two most striking characteristics of this end-stage condition of lymphedema have been fully described by Moritz Kaposi [211] long before the etiopathogenic factors were known: the relationship between elephantiasis and recurrent inflammatory attacks and the tissue changes. Elephantiasis occurs "after a series of short-term paroxystical inflammatory episodes… (that) after five to ten years lead to hypertrophy of the skin and subcutaneous tissue".

The majority of elephantiasis is caused by infection, especially in the global health context of lymphatic filariasis. Primary lymphedema can also progress to the condition of elephantiasis if untreated[212] and infection is allowed to supervene.

The clinical signs are the distinctive dermatological findings of severe epidermal and dermal changes, with dermal fibrosis, hyperkeratotic, verrucous, papillomatous, nodular lesions displaying a cobblestone-like appearance. Warty skin overgrowths are sources of bacterial and fungal colonization and skin abrasions and moist environment causes recurrent cellulitis/infections.

Lymphatic filariasis is still the most prevalent cause of secondary lymphedema worldwide and remains an endemic disease in more than 80 countries . About 1.39 billion people live in areas at risk.[214] The most common presentation of elephantiasis is in lower limb and/or genital involvement with the secondary lymphedema of filarial infection.
The current classification of **e**lephantiasis is based on tropical [208] and non-tropical elephantiasis of secondary origin; the various conditions that cause non-tropical/nonfilarial elephantiasis are grouped separately as elephantiasis nostras verrucosa (ENV); Morbid obesity [213] , chronic venous insufficiency, recurrences of lower extremity cellulitis/lymphangitis and/or chronic soft-tissue infection are known to cause ENV . Alternative terms for this disorder include lympho- static verrucosa, lymphostatic papillomatosis cutis, elephantiasis crurum papillaris et verrucosa and mossy foot and/or leg.

Among the other lymphatic disorders that produce elephantiasis is podoconiosis, a common but neglected tropical disease.[215]
Podoconiosis is a non-infectious geochemical elephantiasis caused by exposure of bare feet to irritant alkalic clay soils. It is found in at least 10 countries in tropical Africa, Central America and northwest India, where such soils coexist with high altitude, high seasonal rainfall and low income. Podoconiosis develops in men and women working barefoot on irritant soils, with signs becoming apparent in most patients by the third

decade of life". [216] It is estimated that more than 4 million people are affected worldwide [215].

Management

Specific publications concerning management of elephantiasis in primary disorders of the lymphatic system refer only to case reports. Larger series where late stage lymphedema are considered are difficult to interpret due to the wide range of clinical presentations found in this group of patients; sometimes authors employ classifications using volume excess while others will take into account the degree of fibrosis and skin changes and/or limb deformity.

Elephantiasis is the result of a long-lasting, untreated condition. Independent of its origin, elephantiasis can be prevented be early recognition of lymphedema for appropriate treatment with prevention of aggravating factors. Therefore, the treatment should focus on prevention of developing this condition. Simple measures like adequate hygiene of the skin is a cornerstone to elephantiasis prevention. [217] and early diagnosis is essential.

All patients with primary lymphedema must have proper skin care, which is the most useful conservative treatment available, together with physical treatment and compression. In patients with elephantiasis, of all the treatment modalities available, skin care is the most important,since infection is responsible for the progression of initial stages of lymphedema to elephantiasis. [218]

Aggressive treatment of skin lesions is mandatory to reduce disease progression. Warty skin overgrowths are sources of bacterial and fungal colonization and, if adequate care does not prevent skin abrasions and moist environment, they may also benefit from local surgical excision. In severe cases, aggressive treatment of skin lesions by surgical excision is mandatory followed by compression therapy to reduce disease progression. [210]

In addition, aggressive weight control is an essential step to prevent further aggravation of primary lymphedema to progress to its end stage. [207] Lifelong administration of antibiotics should be considered in primary elephantiasis as recommended for filarial patients,[4] at least until further scientific evidence contraindicates its use. [219]

Compression treatment can obtain significant volume reduction and partial regression of skin lesions. As compression therapy by custom-made garments is mandatory to maintain limb girth in long-term treatment, sometimes additional surgical procedures are required to resect redundant skin and achieve a favorable limb shape in orderto avoid ineffective

compression therapy becasue of the irregular limb contour .[212] Many publications suggest good results after reduction surgery in genital elephantiasis. [220-222]
However, this resection surgery is accompanied by significant morbidity and complications, and postoperative compression therapy is mandated to maintain the initial surgical outcome. [11, 12, 205]

Patients with end-stage lymphedema and elephantiasis are not suitable candidates for lymphovenous bypasses since all the lymphatic vessels are already damaged by persistent lymphostasis beyond the level of functional recovery, with massive irreversible skin and tissue changes.[193] Circumferential suction-assisted lipectomy is effective to remove adipose tissue of lymphedemaous arms and legs.[223-225] However, when the lymphedema reaches the stage of elephantiasis, with profound soft tissue and epidermal changes , this method is rendered much less useful, since most of the adipose tissue is replaced by fibrotic tissue through the protracted process of progressive dematolipofibrsclerosis.

When elephantiasis is combined with hyperkeratotic lesions, some studies show efficacy of oral etretinate therapy[226, 227] in flattening the hyperkeratotic,verrucous and papillomatous lesions . Etretinate has more recently been replaced by acitretine, which has similar potency with less severe side effects. [228]

Phlebolymphedema

Definition

Phlebolymphedema (PLE) represents a unique clinical condition of 'combined insufficiency' of both venous and lymphatic systems, ie, simultaneous chronic venous insufficiency (CVI) and chronic lymphatic insufficiency (CLI), with various causes . [138, 229, 230]

Primary phlebolymphedema is mostly caused by 'congenital' malformation affecting the venous and lymphatic systems simultaneously; they are a combined condition of venous and lymphatic malformation (as the outcome of defective development during various stages of embryogenesis. The CLI of primary PLE is a diffuse condition of lymphedema caused by a truncular LM [92, 187] from the outset in the majority of patients, together with the CVI caused by the VM. [45, 231]

This combined condition of VM and LM often represents one aspect of the clinical manifestation of Klippel-Trenaunay Syndrome (KTS) [53, 232] as its vascular malformation components. KTS is characterized by having both vascular malformation components as well as non-vascular anomaly of congenital origin affecting the soft tissues and skeletal system. [233, 234]

Secondary phlebolymphoedema is much more frequent than the primary form.
In contrast, the pathophysiology of secondary PLE is not as complicated as the primary condition; this 'acquired' condition begins with CVI due to various causes, often as a part of post-thrombotic syndrome following deep vein thrombosis (DVT).
Often this condition is the outcome of the advanced stages of CVI, complicated by non-healing venous stasis ulcer. It may also be frequently observed in morbid obesity .[235, 236]
CVI results in lymphatic dysfunction leading to CLI as its culmination.[237, 238]
Hence, the CLI of secondary PLE is generally limited to a regional/local condition as a complication of CVI following chronic recurrent infection /inflammation and reactive fibrosis.[239, 240]
Microlymphangiopathy may be demonstrated in all these cases .[114, 241, 242]
Therefore, proper assessment of this 'dual' outflow system failure (CVI + CLI) warrants a correct understanding of the interrelationship between the venodynamics and lymphodynamics.

Pathophysiology-Hemodynamics

Although the venodynamics and lymphodynamics are based on distinct hemodynamic mechanisms, the venous and lymphatic systems are a mutually dependent dual outflow system of the circulation. Therefore, they are one 'inseparable' system and the insufficiency or overload of one or both systems allows the other to play an auxiliary role to compensate in fluid return.[243]

However, both systems are 'mutually complementary' ONLY when they are functioning normally. When one of the two systems loses its normal function (e.g. chronic venous hypertension, lymphedema), such mutual interdependence generates a new problem for the other. In other words, failure of one system gives an additional burden/load to the other system. Long term single system failure results in total failure of this 'inseparable' dual system, resulting in the unique clinical condition of PLE.

When CVI results in an excessive fluid load at the tissue level, it increases afterload on the capillary, creating additional load for the lymphatic system. When this overload exceeds the maximum capacity of normal lymphatic compensation, it results in CLI. CLI becomes more prominent especially in a compromised lymphatic drainage/transport system due lymphatic dysfunction of various etiologies of primary (e.g. hemolymphatic malformation) and secondary origin (e.g. surgery and radiotherapy associated with cancer treatment).
In the Bonn Vein Study (Pannier 2007) [244] 8.1 % of the C4 patients and 11.1 % of the C5 patients showed a significant positive Stemmer´s sign of the toes indicating phlebolymphedema

Nevertheless, ‘primary’ PLE is still a relatively under-recognized condition. It is the most common manifestation of the 'hemolymphatic' malformation (HLM) consisting of a VM and LM, often as the clinical condition of the KTS. When an AVM [245] is further combined with VM and LM, known as Parkes-Weber Syndrome, primary PLE becomes much more difficult to manage. [246, 247]

Clinical Evaluation

The basic evaluation of VM and LM as a cause of primary PLE should include a thorough history and physical examination; the combination of DUS , MRI/CT and LSG is generally sufficient to confirm the clinical diagnosis of combined VM and LM.[55,]

Assessment of PLE should be extended to further assessment of the extent and severity of the CVI and CLI, since these will determine the variable clinical manifestations.
Simultaneous evaluation of both venous and lymphatic systems is mandated for all primary PLE cases. A variety of laboratory tests is available for assessment of venous and lymphatic system and these are sufficient to provide the necessary hemodynamic information for proper management . [248]

The assessment of the extent and severity of the CVI should begin with DUS and may include various plethysmographic studies in addition to ascending/descending phlebography, in order to identify the etiology (e.g. marginal vein). [55]

The most common VM to cause CVI leading to primary PLE is the ‘lateral embryonic vein' represented by marginal vein (MV) . [249, 250] This is one form of truncular VM lesion developed during the later stage of embryogenesis. MV causes severe venous reflux and venous hypertension due to the absence of venous valves as a part of defective development. [251, 252]

The second most common VM to cause the CVI is deep vein dysplasia (e.g. iliac vein agenesis, hypoplastic femoral vein) or defective vein (e.g. web, stenosis, vein valve agenesia, aneurysm, ectasia) with venous outflow obstruction and reflux to cause venous hypertension. [253, 254]

An extratruncular VM lesion as a VM component among KTS patients seldom causes CVI alone, but when it is thought to be involved in the development of CVI and contributing to PLE, investigation to exclude other VM components of the KTS is necessary. [255, 256]

In evaluation of CLI, the functional status of the lymphatic system should be determined first with LSG as the initial baseline investigation, in order to delineate excessive fluid accumulation in the tissues of the limb or affected lymphatic territories. Additional tests are also required when the extratruncular LM is involved in KTS.

CLI due to primary PLE is mostly due to primary lymphedema caused by truncular LM lesions affecting the lymphatic trunk system (e.g. lymphatic dysplasia: aplasia, hypoplasia, or hyperplasia). Extratruncular LM lesions (eg. lymphangioma) on the other hand, are seldom involved in CLI. However, when present, the extratruncular LM may be evaluated with MRI and or whole body blood pool scintigraphy.[47, 118, 247] Other optional tests may be further included depending upon the overall CVM components (e.g. AVM). (Table 1)

Clinical Management

The general principles of primary PLE management should remain within the guidelines for the management of KTS and its vascular malformation component . However, this combined venous-lymphatic disorder by two independent VM and LM conditions results in an extremely delicate mutual interdependency; their management mandates proper interpretation of this complicated interrelationship between them.

The management of the CVI should have a priority over that of the CLI unless there is a serious complication of the LM component (e.g. leakage with or without sepsis). This is because the degree and extent of negative impact on CLI by the CVI is much more severe than the effect of the CLI on the CVI. Effective control of the CVI often results in much improved CLI condition.

Baseline therapy for the CLI component of primary PLE is compression therapy since the absolute majority of the CLI is limited to the lymphedema. Reinforced gradient compression therapy based on DLT is required to control the CVI and CLI together.

However, lymphedema caused by CLI in primary PLE is more difficult to control than CLI by independent primary lymphedema with no CVI component. The CLI combined with CVI is often more resistant to the conventional treatment based on DLT, and the disease has a distinct tendency to progress. Therefore, aggressive care with a strict prevention regimen (e.g. infection) is warranted even for maintenance compared to the solitary condition of primary lymphedema.

When this truncular LM causing primary lymphedema is combined with the extratruncular LM (lymphangioma), additional treatment with sclerotherapy of the coexisting extratruncular LM is generally required. When such a lesion is present, it has a

direct communication to the lymph transporting system, which produces an additional burden to the truncular LM that already causes the CLI.

Management of the CVI in primary PLE is dependent on its etiology. When the reflux of the MV is the source of CVI, the MV should be treated either with open surgical resection or endovascular obliteration. However, as its precondition, the treatment of the MV warrants a normal deep venous system that can tolerate the sudden influx of diverted blood volume following the obliteration of the MV system. [255-258]

The CVI of primary PLE is occasionally due to deep vein dysplasia, which would require a conservative management unless there is a clear evidence for significant hemodynamic gain by bypass surgery of the hypoplastic or aplastic iliac and/or femoral veins to relieve venous hypertension in patients with chronic indolent venous ulcers.[240, 241]

However, the benefit of surgery over the basic conservative therapy of CVI in patients with primary PLE (e.g. MV resection) should be carefully weighed against the potential deleterious effects on the coexisting LM with a marginally compensated CLI, which would make the clinical condition worse.

Therefore, primary PLE generated by HLM as the vascular malformation component of KTS should be handled by a multidisciplinary team to manage the extremely delicate interdependency between the VM and LM safely.

Conclusion

- PLE can be managed more effectively when open and/or endovascular therapy is added to the basic compression therapy to control the CVI and CLI together.
- Primary PLE with CVI by the reflux of MV can be treated successfully with MV resection, while CVI by deep vein dysplasia with the conventional compression therapy alone in its majority.
- Secondary PLE may show regression after repair of the venous pathology [240]

Lipedema -Differential Diagnosis

Introduction

Lipedema, the most common disorder to be mistaken with lymphedema, is an infrequently recognized clinical entity affecting nearly exclusively women and does not take place in the World Health Organization International Classification of Diseases-10 (WHO ICD-10) as an individual disease. [259]

Definition

Lipedema is a bilateral, symmetrical, 'bike pant' or column-shaped fatty swelling of the legs, whereas arms are less commonly involved.[260-264] This is a female disorder and males usually develop lipedema on the basis of hormonal disturbance, however there is one published case report where a healthy man was diagnosed with lipedema.[265] The general incidence of lipedema among women is estimated to be around 11% .[261]

Pathology and Pathophysiology

Földi and Földi have proposed that microangiopathy in the area of the affected adipose tissue results in higher permeability to proteins and increased capillary fragility leading to spontaneous and minor traumatic injury-induced formation of bruising.[261] Siems *et al* detected nearly four-fold higher levels of plasma vascular endothelial growth factor (VEGF) levels at baseline than normal values of plasma VEGF.[266] VEGF controls angiogenesis and hypoxia is a potent inducer of angiogenesis and this factor may have a role in lipedema formation. The detected high baseline levels of both malonyl dialdehyde (MDA) and protein carbonyls are indicative of severe preexisting oxidative stress and lipid peroxidation. [266] Pit-1 mutation[267] in family members with lipedema and genetic screening of lipedema affected families[268] strongly suggests inheritence. Suga *et al* found robust CD68+ macrophage infiltration in lipedematous adipose tissue with loss of adipocytes due to necrosis and simultaneous proliferation of adipose-derived stem cells (Ki67+ CD34+). These results suggest massive adipogenesis with concomitant hypoxia resulting in necrosis and macrophage recruitment.[269] Lipedema is presumably associated with endocrinological background.[262-264]

However adipocyte metabolism in lipedema is poorly investigated and remains to be elucidated, it may share similarities with obese white adipose tissue pathophysiology. High fat diet could trigger adipocyte hipertrophy and saturated fatty acid release recruits macrophages inducing inflammatory response. [270] High fat diet plays also an important role in stem cell recruitment. [271] Relatively high prevalence of lipedema among congenital analbumenic patients might be explained with abnormal lipid metabolism. [272] Suspected subclinical, later clinical lymphatic insufficiency may further aggravate the enlargement of adipose tissue as seen in animal models. [273, 274]

Clinical Findings

The diagnosis of lipedema is relatively simple using patient history and clinical examination.[260-264] There are striking features to facilitate the recognition of this disproportional obesity. In the early stages of the disorder, the only clues may be the bilateral fat-pads right below the inner sides of the knees and the disappearance of the concave spaces on both sides of the Achilles tendon (ie, the filling of the retromalleolar

sulcus).[261-263] On progression the characteristic stove pipe legs appear however the feet remain spared and the fat deposits begin abruptly above the ankles (cuffing sign) [4,5]. In case of arm involvement fat deposition abruptly ends at wrists leaving hands unaffected. [4,5] In contrast to lymphedema, Stemmer's sign is always negative in pure lipedema and the oedema is hardly or non-pitting .[261-264] Two further leading hallmarks are the 'easy bruising' and aching dysaesthesia. [261-264]
Lipedema, especially in advanced stages, is quite frequently combined with impaired lymphatic or venous function that may strongly modify the original limb shape resembling the features of identical vascular abnormality. [262-264, 275]

Clinical appearance

Földi and Földi proposed 2 two types of lipedema phenotype[3]: columnar and lobar whereas the first type seems to be predominant and can be described as enlargement of portions of the lower limbs as a series of varying conic sections and the combination of the two appearances is also not uncommon.

Classification

In stage I, the skin looks flat, but the subcutis is already enlarged and on palpation feels like 'styrofoam balls in a plastic bag'. In stage II, walnut- to apple-sized indurations develop and the overlying skin has an irregular surface ('mattress phenomenon'). Stage III shows larger indurations and deforming, even lobular fat deposits. The same group recommended a classification concuring with the location of the fat deposits: mainly buttocks (type I), buttocks to knees (type II), buttocks to ankles (type III), mainly arms (type IV) and mainly lower legs (type V). [276]

Schingale distinguishes five types of lipedema presention: type I: adipose tissue increased on buttocks and thighs, type II: the lipedema extends to the knees with formation of fat pads on the inner side of the knees, type III: lipedema extends from the hips to the ankles, type IV: involving the arms and legs, type V: lipolymphedema.[277]

Disease course

Manifestation of lipedema usually starts after puberty or pregnancy; in rare cases it may manifest after menopause.[261-264] In most cases the disease has a progressive course with gradually increasing fat deposition.

General principles of diagnostic tests

In most cases lipedema could be easily diagnosed. However combined forms with lymphatic or venous insufficiency, morbid obesity could be cumbersome, therefore various non- or minimally invasive tests might efficiently assist clinical assessment.

Non-invasive evaluation

Waist-to-Height Ratio
Of the anthropometric measurements waist-to-height ratio is a practical tool for a discrimination between obesity and lipedema.[278]

Waist-to-heigth ratio values (Nauheimer adiposity scale) [278]

< 0,40	underweight
0,40 – 0,45	normal
0,46 – 0,54	overweight
0,55 – 0,63	weak obesity = grade 1 by BMI
0,64 – 0,72	moderate obesity = grade 2 by BMI
0,73 – 0,81	severe obesity = grade 3 by BMI
0,82 – 0,90	massive obesity = grade 4 by BMI
> 0,91	giant obesity = grade 5 by BMI

Streeten Test
After the exclusion of cardiac, renal and venous insufficiency the patient can be subjected to this examination. The person drinks 20 ml water/body-weight kg and remains in an upright position for 4 hours. During this observational period urine is collected. The leg volumetry is scheduled prior and subsequent to test. Normal healthy persons excrete more than 60% of the ingested water and the leg volume does not increase with more than 350 ml/kg.[279] Due to the unpractical and exhausting procedure for the patient this test is hardly used any more.

Capillary Fragility Assessment
Bruising is attributed to increased capillary fragility in lipedema. Capillary fragility is decreased when patients are subjected to efficient decongestion.[280] Another clinical setting compared uncomplicated simple obesity with uncomplicated lipedema from the perspective of capillary fragility measurement and disclosed that the capillaries of lipedematous limbs are much more sensitive to physical injuries (unreported data).

Assessment of Aortic Stiffness in Lipedema
Transthoracic echocardiography and blood pressure measurement revealed that lipedema was associated with higher aortic stiffness compared to healthy individuals. [281]

Pain Perception Assessment

Spontaneous pain was described as pressing and lumpish by most lipedema patients; other sensory and affective pain characterizations were heavy, tearing, distressing, enervating, fierce, unbearable, exhausting and pinching.[282] The pinch test is the most simple method for pain provocation.[261]
In a comparative clinical trial a 10-item questionnaire specifically constructed for an accurate characterization of lipedema as well as a special numerical analogue scale (from 0 to 10) called pain rating scale and Wong Baker Faces scale were applied for pain assessment and clearly showed that decongestion was able to improve pain perception.[283]

Ultrasound Examination
High resolution ultrasonography can distinguish lipedema from phleb- or lymphedema with high sensitivity.[284]

CT, MRI Examination
CT[285] and MRI[286] are indicated for scientific purposes or subtle cases. According to Monnin-Delhom *et al*., computed tomography scan has a sensitivity of 95% and specificity of 100% for the diagnosis of lipedema. [285]

Minimally invasive evaluation:

Lymphoscintigraphy and Fluorescent Microlymphography:
Altered microcirculation with increased permeability results a large amount of interstitial fluid thus increased lymph flow is visualized by lymphscintigraphy in early stages of lipedema. If lipedema remains untreated the increasing amount of interstitial fluid warrants a higher transport capacity of lymphatic conductors. This transitional intensive function exhausts the lymphatic vessels modifying the phenotype from lipedema to lipo-lymphedema as a result of lymphatic insufficiency. [287]
Fluorescent microlymphography displays lymphatic microaneurysms and dilated vessels of the uppermost lymphatic network, indicating that lymph vessels might also be involved in the pathogenesis .[288]

MRI lymphangiography
This examination is capable of the evaluation of various tissue components and simultaneous display of the lymphatic vessels with high precision. [289]

Treatment
Non-surgical treatment
Even if lipedema is not very responsive to dietary restrictions weight control is of paramount importance in lipedema care in order to improve symptoms and to prevent progression. [261-263]

The intensive phase of conservative treatment corresponds to decongestive lymphatic therapy (DLT).[261] The first observational study on the effect of DLT in lipedema showed that the maximally achieved reduction was nearly 10% of the original leg girth. [290] In a clinical study manual lymph drainage (MLD)-based DLT was compared with MLD+sequential intermittent pneumatic compression (SIPC)-based DLT. Each treatment regimen resulted in significant limb volume loss without any difference between the two modalities.[291] In other controlled trials MLD+SIPC-based DLT decreased capillary fragility [280] and pain perception [283], as well.
The maintenance phase aims to preserve volume decrease using medical compression pantyhoses. A dogmatic concept discourages the use of high compression class stockings as lipedematous limbs do not tolerate high pressure. A recent study utilizing chronic venous insufficiency questionnaire (CIVIQ) of 20 items and visual analogue scale (VAS) was able to show that lipedema patients displayed almost the same level of tolerance to 23-32 mmHg (lower) and 34-46 mmHg (higher) pressures. [292]

Surgical treatment
Tumescent liposuction with vibrating microcanulas as surgical approach gives a reliable and long-time benefit including robust volume reduction along with a reduction of oedema and pain to lipedema patients without proven damage of lymphatics. [293]

Prognosis

Early diagnosis and treatment are mandatory for lipedema otherwise gradual enlargement of fatty deposition causes impaired mobility, debilitating condition and further co-morbidities like arthrosis and lymphatic insufficiency. When lipedema is combined with advanced lymphedema interlobar areas may become susceptible for microbial infections that may further progress to cellulitis or septicaemia.

Lipedema has remarkable psychological and psychiatric impact ranging from mild to severe anxiety, depression or even anorexia. [261-264]

IX. Summary

Accurate diagnostic programs and tools and enhanced awareness of the early signs of lymphedema are essential. Primary lymphedema can be managed safely as one of the chronic lymphedemas by a proper combination of DLT with compression therapy regardless of the clinical stage of lymphedema. Treatment in the maintenance phase should include compression garments, self management including the compression therapy, self massage and meticulous personal hygiene and skin care in addition to lymph-transport promoting excercises. Prevention of chronic lymphedema in patients at

risk is critical. Early diagnostic programs and enhanced awareness should be fully integrated.

The management of primary lymphedema can be further improved with proper addition of surgical therapy either reconstructive or ablative. These two surgical therapies can be effective only when fully integrated with MLD-based DLT postoperatively unless reconstructive surgery is peformed as a preventive intervention (e.g. LVA in patients at risk of lymphedema but without clinical signs of swelling).[200]

Excisional surgery is a very effective method to control the progression of lymphedema initially, but ultimately becomes unable to maintain its initial success without additional DLT postoperatively. Liposuction for decompression will also have the same outcome; postoperative maintenance compression is mandated.

Compliance with a long-term commitment of DLT postoperatively is the most critical factor determining the success of any new treatment strategy with either reconstructive or palliative surgery. The future of management of primary lymphedema caused by tuncular lymphatic malformation has never been brighter with the new prospect of gene-oriented management.
"Molecular antidotes" to such pathological overgrowth of lymphangiomatosis such as the Klippel Trenaunay Syndrome should become major players, with a chance for cure, in near future.

Acknowledgment

The authors would like to thank to Professor Wilfried Schmeller (Hanse Klinik, Lübeck, Germany) for his insightful review and essential comments on Lipedema-Differential Diagnosis subchapter, and Professor Tiziana Baroncelli (Vascular center, Prato, Italy) on Diagnostic Evaluation of Lymphedema subchapter.

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Epilogue

We tried to provide general and broad concepts regarding primary lymphedemas. We also tried to leave minimum points of disagreement as possible, thus providing the reader some indisputable points that one can trust and apply to their clinical practice as phlebologists.

Attempt to reduce the length of the document to improve its efficacy of the delivery, might have made the document poorer in new ideas and insights, but all points considered will have a greater strength as recommendations.

B.B. Lee, MD, PhD, FACS
Coordinator

Epilogue

A huge lymphedematous limb in the status of elephantiasis with recurrent lymphangitis I encountered on the first day of internship was my first contact with the vascular pathology. Since then chronic lymphedema has remained my major interest throughout my career as a vascular surgeon with great debt to Professors Carlos Mayall and Mario Degni, two of the greatest Brazilian masters of Lymphology world, I studied since my

surgery residency. Therefore, this unique Consensus has a special meaning to me as a pupil of assiduous studious of the lymphatic system disorders.

This consensus of the UIP on the Primary lymphedema is the refinement of one previously published and shown during the congress of the chapter in Prague in 2011. Some aspects of lymphedema, for example, elephantiasis, were included in this updated version. The modern methodology based on Evidences, recommended by Guyatt et al [1,2], was used taking into account the experience of the authors and publications, especially those comparative studies of good quality.
As a multifaceted disease in its etiology and pathophysiology, the treatment and control also present a corresponding richness.

This set of recommendations now published definitely demystifies the concept that the "Lymphedema has no cure" or "There's nothing to do" used by many doctors, including specialists, to declare the state of their patients with lymphatic pathology. As Prof. Mayall used to say, “The most difficult disease to be treated is not the lymphedema but the prejudice and ignorance that dwells in the minds of many physicians”.

I hope that this phenomenal work will help demystify in definitive the concept that "Lymphedema has no cure" and also remind everyone that the lymph vessels do exist and have an important role in the circulation and it should be respected.
I am proud to have been able to participate in this consensus as the UIP President and also as a collaborator.

I congratulate Professor BB Lee for the excellent coordination work and also all the contributing authors who helped to produce this excellent document that will surely be consulted and quoted by several colleagues and for a long time.
Angelo Scuderi M.D.
President of UIP