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The diagnosis and treatment of peripheral lymphedema: 2016 Consensus Document of the International Society of Lymphology

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This International Society of Lymphology (ISL) Consensus Document is the latest revision of the 1995 Document for the evaluation and management of peripheral lymphedema [1]. It is based upon modifications: [A] suggested and published following the 1997 XVI International Congress of Lymphology (ICL) in Madrid, Spain [2], discussed at the 1999 XVII ICL in Chennai, India [3], and considered/confirmed at the 2000 (ISL) Executive Committee meeting in Hinterzarten, Germany [4]; [B] derived from integration of discussions and written comments obtained during and following the 2001 XVIII ICL in Genoa, Italy as modified at the 2003 ISL Executive Committee meeting in Cordoba, Argentina [5]; [C] suggested from comments, criticisms, and rebuttals as published in the December 2004 issue of Lymphology [6]; [D] discussed in both the 2005 XX ICL in Salvador, Brazil and the 2007 XXI ICL in Shanghai, China and modified at the 2008 Executive Committee meeting in Naples, Italy [7, 8]; [E] modified from discussions and written comments from the 2009 XXII ICL in Sydney, Australia, the 2011 XXIII ICL in Malmö, Sweden, the 2012 Executive Committee Meetings [9],and [F] from discussions at the 2013 XXIV ICL in Rome, Italy, and the 2015 XXV ICL in San Francisco, USA, as well as multiple written comments and feedback from Executive Committee and other ISL members during the 2016 drafting.

The document attempts to amalgamate the broad spectrum of protocols and practices advocated worldwide for the diagnosis and treatment of peripheral lymphedema into a coordinated proclamation representing a "Consensus" of the international community based on various levels of evidence. The document is not meant to override individual clinical considerations for complex patients nor to stifle progress. It is also not meant to be a legal formulation from which variations define medical malpractice. The Society understands that in some clinics the method of treatment derives from national standards while in others access to medical equipment and supplies is limited; therefore the suggested treatments might be impractical. Adaptability and inclusiveness does come at the price that members can rightly be critical of what they see as vagueness or imprecision in definitions, qualifiers in the choice of words (e.g., the use of "may... perhaps... unclear", etc.) and mentions (albeit without endorsement) of treatment options supported by limited hard data. Most members are frustrated by the reality that NO treatment method has really undergone a satisfactory meta-analysis (let alone rigorous, randomized, stratified, long-term, controlled study). With this understanding, the absence of definitive answers and optimally conducted clinical trials, and with emerging technologies and new approaches and discoveries on the horizon, some degree of uncertainty, ambiguity, and flexibility along with dissatisfaction with current lymphedema evaluation and management is appropriate and to be expected.

We continue to struggle to keep the document concise while balancing the need for depth and details. With these considerations in mind, we believe that this 2016 version presents a Consensus that embraces the entire ISL membership, rises above national standards, identifies and stimulates promising areas for future research, and represents the best judgment of the ISL membership on how to approach patients with peripheral lymphedema in the light of currently available evidence. Therefore, the document has been, and should

continue to be, challenged and debated in the pages of Lymphology (e.g., as Letters to the Editor) and ideally will remain a continued focal point for robust discussion at local, national and international conferences in lymphology and related disciplines. We further anticipate as experience evolves and new ideas and technologies emerge that this "living document" will undergo further periodic revision and refinement as the practice and conceptual foundations of medicine and specifically lymphology change and advance.

Key words: Consensus, lymphedema, diagnosis, treatment, ISL, International Society of Lymphology

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General considerations

As a fundamental starting point, lymphedema is an external (and/or internal) manifestation of lymphatic system insufficiency and deranged lymph transport Some members prefer to define peripheral lymphedema as a symptom or sign resulting from underlying lymphatic disease. It is defined as an illness by the International Classification of Diseases from the World Health Organization. Lymphedema may be an isolated phenomenon or associated with a multitude of other disabling local sequelae or even life-threatening systemic syndromes. Its nature may be acute, transitory, or chronic. In its purest form, the central disturbance is a low output failure (mechanical insufficiency) of the lymphvascular system; that is, overall lymphatic transport is reduced. This derangement arises either from congenital lymphatic dysplasia (primary lymphedema) or anatomical obliteration, such as after radical operative dissection (e.g., axillary or retroperitoneal nodal sampling), irradiation, or from repeated lymphangitis with lymphangiosclerosis (secondary lymphedema) or as a consequence of functional deficiency (e.g., lymphangiospasm, stasis, and valvular insufficiency in primary or secondary lymphedema. Nonetheless, the common denominator is that the lymphatic system (whether vessels, nodes, interstitium, etc, or combinations) transport has fallen below the capacity needed to handle the presented load of microvascular filtrate including plasma protein and cells that normally leak from the bloodstream into the interstitium. Swelling is produced by accumulation in the extracellular space of excess water, filtered/ diffused plasma proteins, extravascular blood cells and parenchymal/stromal cell products. This process culminates in proliferation of parenchymal and stromal elements with excessive deposition of extracellular matrix substances and adipose tissue. High output failure (dynamic insufficiency) of the lymph circulation, on the other hand, occurs when a normal or increased transport capacity of intact lymphatics is overwhelmed by an excessive burden of blood capillary filtrate. Examples include hepatic cirrhosis (ascites), hypoalbuminemia associated with nephrotic syndrome (anasarca), right heart failure, and deep venous insufficiency of the leg (peripheral edema). Although the final pathway is the manifestation of tissue edema whenever lymph formation exceeds lymph absorption, the latter entities should properly be distinguished from lymphedema, which is characterized by decreased lymphatic transport. In some syndromes where high output lymphatic transport failure is longstanding, a gradual functional deterioration of the draining lymphatics may supervene and thereby reduce overall transport capacity.

A reduced lymphatic circulatory capacity then develops in the face of increased blood capillary filtration. Examples include recurring infection, thermal burns, and repeated allergic reactions. These latter conditions are associated with "safety valve insufficiency" of the lymphatic system where the lymph load increases over "normal" flow to eventually become overwhelmed and this can be considered a mixed form of edema/lymphedema and as such are particularly troublesome to treat.

Peripheral lymphedema associated with chylous and non-chylous reflux syndromes is an infrequent but complex condition that requires specific diagnostic measures and treatment methods. There are other complicating diagnoses (e.g., genetic with Turner or Noonan syndromes or arterial/ venous malformations) which require additional considerations.

In the treatment of "classical" lymphedema of the limbs (that is, peripheral lymphedema), improvement in swelling can usually be achieved by non-operative therapy. Because lymphedema most often becomes a chronic, generally incurable condition, it generally requires, as do other chronic disorders, lifelong care and attention along with psychosocial support. The continued need for therapy does not mean a priori that treatment is unsatisfactory, although often it is less than optimal. For example, patients with diabetes mellitus continue to need drugs (insulin) or special

diet (low calorie, low sugar) in order to maintain metabolic homeostasis. Similarly, patients with chronic venous insufficiency require lifelong external compression therapy to minimize edema, lipodermatosclerosis and skin ulceration (treatments may be preventative if initiated early). Compliance and adherence of the patient is also essential to an improved outcome. With chronic venous insufficiency, poor patient compliance may be causally associated with progressive skin ulceration, hyperpigmentation, and other trophic changes in the lower leg. Similarly, failure to control lymphedema may lead to repeated infections (cellulitis/ /lymphangitis), progressive elephantine trophic changes in the skin, sometimes crippling invalidism and on rare occasions, the development of a highly lethal lymphangiosarcoma (widely known as Stewart-Treves syndrome).

The particular setting of examination, diagnosis, and treatment (clinic, hospital, properly designed teams, etc.) as well as patient condition (ambulation, portability, fragility, etc.) can all impact individualized patient care and treatment.

Prevention/Early Identification and Treatment

The recent promulgation of lists of risk factors for secondary lymphedema has become a highlighted issue due to publications of "do's and don'ts". These are largely anecdotal and not sufficiently investigated. While some precautions rest on solid physiological principles (e.g., avoiding excessive heat on an "at risk" limb, not having chemotherapy administered into the limb unless medically necessary, or trying to avoid infections), others are less supported. Consistently, a BMI >25, axillary node dissection, radiation to the axilla, and appearance of cellulitis following operation are more firmly supported as true risks. It must be noted that most published studies on incidence of secondary lymphedema of the extremities report less than 50% chance of developing lymphedema with nodal basin operations, irradiation, and taxane-based chemotherapy (substantially less with more conservative treatments, e.g., lumpectomy with sentinel lymph node biopsy). Therefore, standard use of some of these "don'ts" for risk reduction of lymphedema may not be appropriate and possibly subjects patients to therapies which are unsupported until a point in the future when evaluation and prognostication evidence has demonstrated more clearly specific risks and the corresponding preventative measures.

The concepts of "primary" and "secondary" prevention (including risk reduction) are receiving increased attention. Operative imaging techniques to lessen lymphatic system impact by identifying lymphatic vessels to avoid during procedures as well as performing prophylactic lymphaticvenous shunts in high-risk patients are being explored. Exercise, self-MLD, and education for prevention of secondary lymphedema are also undergoing investigation. Radiation treatment techniques are continually evolving to reduce and isolate secondary damage. Further research is needed, and all such techniques will have to be tempered by the actual risk of developing lymphedema in specific populations based on emerging incidence evidence.

Recently, the question of when to monitor a patient has emerged for patients undergoing cancer treatment. Prospective surveillance models (PSM) have been developed to address early detection of lymphedema leading to earlier and more efficacious treatment. The prospective surveillance model involves a preoperative cancer treatment assessment where baseline limb volume and functional mobility measurements are established (some clinics with the availability of bioimpedance spectroscopy may utilize that to detect early changes in tissue fluid accumulation).

Patients are then followed in a prospective manner (e.g., 3 month intervals for the first year during and post-cancer treatment and then less frequently). Followup visits include psychosocial support and reassessment of limb volume and functional mobility to offer a comparison to baseline measures to enable identification of meaningful change associated with sub-clinical onset of lymphedema. Sub-clinical lymphedema is measurable at low diagnostic thresholds (3–5% volume change from baseline in swelling not due to weight change — i.e. determined by measuring both limbs) and may initially present in only one segment of the limb. Identifying subclinical lymphedema facilitates early, conservative intervention and may reduce the likelihood that the condition will progress to a chronic advanced stage. Identifying and treating lymphedema at an early stage offers greater treatment success and potential cost savings with conservative management programs including compression garments, education for self-care, self-MLD (and/or partner/caregiver-MLD), psychosocial support and exercise. Early identification may also offer the opportunity for lymphaticvenous shunts in appropriate situations to offer a potential life-long avoidance of further treatment.

Staging of lymphedema

Most ISL members rely on a three stage scale for classification of a lymphedematous limb with an increasing number recognizing Stage 0 (or Ia) which refers to a latent or subclinical condition where swelling is not yet evident despite impaired lymph transport, subtle alterations in tissue fluid/composition, and changes in subjective symptoms. It may exist months or years before overt edema occurs

(Stages I–III). Assessment of early fluid changes can be accomplished using bioimpedance spectroscopy or tissue dielectric constant analysis. Stage I represents an early accumulation of fluid relatively high in protein content (e.g., in comparison with "venous" edema) which subsides with limb elevation. Pitting may occur. An increase in various types of proliferating cells may also be seen. Stage II signifies that limb elevation alone rarely reduces the tissue swelling and pitting is manifest. Later in Stage II, the limb may not pit as excess subcutaneous fat and fibrosis develop. Stage III encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, alterations in skin character and thickness, further deposition of fat and fibrosis, and warty overgrowths have developed. It should be noted that a limb may exhibit more than one stage, which may reflect alterations in different lymphatic territories.

These Stages only refer to the physical condition of the extremities. A more detailed and inclusive classification needs to be formulated in accordance with improved understanding of the pathogenic mechanisms of lymphedema (e.g., nature and degree of lymphangiodysplasia, lymph flow perturbations, and nodal dysfunction as defined by anatomic features and physiologic imaging and testing) and underlying genetic disturbances, which are gradually being elucidated. Recent publications combining both physical (phenotypic) findings with functional lymphatic imaging as well as those classifications which propose inclusion of disability grading, assessment of inflammation, and even immunohistochemical changes determined by biopsy of nodes/vessels may be forecasting the future evolution of staging. In addition, incorporation of genotypic information, expanded from what is available even in current screening, would further advance staging and classification of patients with peripheral (and other) lymphedema.

Within each Stage, a limited but nonetheless functional severity assessment has utilized simple volume differences assessed as minimal (>5-<20% increase in limb volume), moderate (20–40% increase), or severe (>40% increase). Some clinics prefer to use > 5–10% as minimal and >10-<20% as mild. Volume differentials are most commonly determined using circumferential measurement due to wide availability and low cost. A flexible nonstretch tape is preferred and the truncated cone formula is utilized for calculating volume. Water displacement volumetry is used in some clinics for arm or lower leg volumes although there are some practical limits (e.g., size of limb, measuring areas near the root of the limb, and hygiene issues). Perometry provides high accuracy by using infrared light beams to estimate limb volume but the equipment cost is significant for smaller clinics and the hand and foot are not included.

Clinicians also incorporate factors such as extensiveness, occurrence of erysipelas attacks, inflammation, and other descriptors or complications into their own individual severity determinations.

Some healthcare professionals focus on disability rating utilizing the World Health Organization's guidelines for the International Classification of Functioning, Disability, and Health (ICF). Quality of Life issues (psychosocial, social, emotional, physical disabilities, etc.) may also be addressed by individual clinicians and groups, and note that these can positively or negatively impact therapy and compliance (maintenance).

Diagnosis

An accurate diagnosis of lymphedema is essential for appropriate therapy. In most patients, the diagnosis of lymphedema can be readily determined from the clinical history and physical examination. In other patients, confounding conditions such as morbid obesity, lipohyperdystrophy, endocrine dysfunction, venous insufficiency, unrecognized trauma, and repeated infection may complicate the clinical picture. Moreover, in considering the basis of unilateral extremity lymphedema, especially in adults, solid organ tumors (primary and/or metastatic), lymphomas, and soft tissue sarcomas which may obstruct or invade more proximal lymphatics need to be considered. For these reasons, a thorough medical evaluation is indispensable before embarking on lymphedema treatment. Co-morbid conditions such as congestive heart failure, hypertension, thyroid abnormalities, cerebrovascular disease including stroke, and vascular malformations may also influence the diagnosis and therapeutic approach undertaken.

Imaging

If the diagnosis of lymphedema is unclear or in need of better definition for prognostic or therapeutic considerations, consultation with a clinical lymphologist or referral to a lymphologic center if accessible is recommended. Commonly, ultrasound techniques are first used to assess and rule out venous disease in many centers (although this is also used in some centers to assess lymphedema). The diagnostic tool of isotope lymphography (also termed lymphoscintigraphy — for both vessels and nodes — or more commonly lymphangioscintigraphy despite its reference only to the vessels) has proved extremely useful for depicting the specific lymphatic abnormality. Where specialists in nuclear medicine are available, lymphangioscintigraphy (LAS) has

largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. Although LAS has not been strictly standardized (various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous or subfascial injections, one or more injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques), the images, which can be easily repeated, offer remarkable insight into lymphatic structural abnormalities and (dys)function. The etiology is not necessarily determined from the image alone. LAS has been used frequently in newborns and children obtaining reproducible, pre-clinical diagnostic images.

LAS provides dynamic images of both lymphatics and lymph nodes in the peripheral and central system as well as semi-quantitative data on radiotracer (lymph) transport, and it does not require dermal injections of blue-dye (as often used for example in axillary or groin sentinel node visualize(correctly termed lymphadenoscintigraphy). Blue dye injection is occasionally complicated by an allergic skin reaction or serious anaphylaxis. Moreover, clinical interpretation of lymphatic function after vital dye injection alone ("the blue test") can be misleading. Direct oil contrast lymphography, which is cumbersome and occasionally associated with minor and even major complications, is usually reserved for complex conditions such as chylous reflux syndrome and thoracic duct injury, where LAS can provide at least preliminary diagnostic images for screening. Non-invasive duplex-Doppler studies and occasionally phlebography are useful for examining the deep venous system and supplement or complement the evaluation of extremity edema. Other diagnostic and investigational tools used to elucidate lymphangiodysplasia/lymphedema syndromes (including newborns and children) include magnetic resonance imaging (MRI) — including MR lymphography (MRL) and MR angiography techniques, computed tomography (CT), CT lymphograms, 3-D oil contrast lymphography, CT-SPECT, ultrasonography (US), indirect (water soluble) lymphography (IL), near infrared fluorescent imaging (NIRF) (also known as ICG lymphography) and fluorescent microlymphangiography (FM). NIRF has been increasingly used in some centers for examining the superficial lymphatic system and in the operative setting. Both peripheral MRL and NIRF are becoming more widespread in use around the world despite limitations for imaging the deeper lymphatic system. DEXA (dual-energy X-ray absorptiometry or biphotonic absorptiometry) may help classify and define a lymphedematous limb but its greatest potential use may be to assess the chemical composition of limb swelling (especially increased fat deposition, which by its added weight can lead to muscle hypertrophy). IL and FM are best suited to depict initial lymphatics and more superficial collectors and accordingly have limited clinical usefulness albeit valuable in research investigations. US has found practical value in depicting the "dance" of the living adult worms in scrotal lymphatic filariasis, and it is also increasingly used to highlight tissue alterations.

Genetics

Genetic testing has become practical and commercially available to screen for a number of specific hereditary syndromes with discrete gene mutations such as lymphedema-distichiasis (FOXC2), some forms of Milroy disease (FLT-4), and hypotrichosislymphedema-telangiectasia (SOX18), as well as a variety of chromosomal abnormalities.

Other genes identified include: Generalized Lymphatic Dysplasia (Hennekam syndrome) (CCBE1, FAT4), Inherited Lymphedema Types 1C (GJC2) and 1D (VEGFC), Lymphedema-Choanal Atresia (PTPN14), Emberger (GATA2), oculodento-digital syndrome (GJA1), lymphedema-lymphangiectasia (HGF), and hereditary lymphedema III (PIEZO1). The future holds promise that such testing for other known mutations and chromosomal defects, as well as newly discovered ones, combined with careful phenotypic descriptions, will become routine to classify familial lymphangiodysplastic (correctly lymphdysplastic since nodes can also be involved) syndromes and other congenital/genetic dysmorphogenic disorders characterized by lymphedema, lymphangiectasia, and lymphangiomatosis. Algorithms have been developed to assist clinicians in phenotyping and directing genetic analysis.

There are many other clinical syndromes with lymphedema as a component. Some of these have genes identified [Noonan (PTPN11, KRAS, SOS1, and others); microcephaly-chorioretinopathy-lymphedema-mental retardation (MCLMR) (KIF11); Proteus syndrome (AKT1); Clove (fibroadipose hyperplasia (PIK3CA); Park-Weber syndrome (capillary malformation-arteriovenous malformation) (RASA1); and lymphatic related hydrops fetalis (LRHG) (EPHB4)] while others still have no known associated genes. It is important to consider that the number of de novo germinal variations in these genes is increasing. In addition, recent and ongoing research is exploring a possible genetic (and epigenetic) basis underlying increased risk of developing secondary lymphedema after treatment involving injury to the lymphatic system.

Newer genetic techniques such as genome-wide association studies (GWA study, or GWAS), whole genome sequencing (WGS), and whole exome sequencing (WES) are rapidly advancing genetic analysis. A targeted Next

Generation Sequencing panel examining all known genes associated with lymphedema is currently the most common choice for analyzing hereditary forms of lymphedema. As costs decrease, more patients will undergo such analysis and more single, multiple, and interacting variants will be identified to help classify individuals with genetic defects related to the lymphatic system. These more refined classifications may impact diagnosis (perhaps allowing proactive rather than reactive care), future treatments (targeted therapy), and quality of life as precision medicine is applied to lymphatic diseases. These newer techniques will also contribute to prenatal diagnosis and, combined with multimodal imaging, to the early diagnosis and potential treatment of congenital lymphatic conditions.

Biopsy/Lymph Node Exam

Caution should be exercised before removing enlarged regional lymph nodes in the setting of longstanding peripheral lymphedema as the histologic information is seldom helpful, and such excision may aggravate distal swelling. Fine needle aspiration with cytological examination by a skilled pathologist is a useful alternative if malignancy is suspected. Use of sentinel node biopsy in the axilla or groin for staging malignancy such as breast and melanoma appears to have substantially lessened the incidence of peripheral lymphedema by discouraging removal of normal lymph nodes; however, an increased number of sentinel nodes taken may reduce this protective effect.

Treatment

Therapy of peripheral lymphedema is divided into conservative (non-operative) and operative methods. Applicable to both methods is an understanding that meticulous skin hygiene and care (cleansing, low pH lotions, emollients) is of the utmost importance to the success of virtually all treatment approaches, as is patient education and training. Basic motion exercises of the extremities (muscle pumping exercises), especially combined with external limb compression and preferably performed as daily life activities (walking, yoga, bicycling, and climbing stairs) are useful. Limb elevation (specifically bed rest if indicated) is also helpful to the appropriate patient undergoing treatment. Newer studies have indicated that more vigorous exercise can be undertaken under the proper conditions, and strong evidence is now available on the safety of resistance exercise in controlled trials for breast cancer-related lymphedema. Evidence has not been published on how soon after the operation exercises (and what type) should be initiated, and this area needs further study. As previously stated, even widely used treatment methods have yet to undergo sufficient meta-analysis of multiple studies which have been rigorous, well-controlled, and with sufficient followup. Satisfactory studies comparing different methods of treatment do not exist, and advocates of all methods report that earlier treatment is optimal for the best results. It is also worth considering that a combination of therapies may be best for some patients, but these combinations are even less frequently studied in comparison trials. Use of various treatment options is appropriate for neonates and children with careful consideration from the treatment team. Treatments can take place in the outpatient setting, a day hospital, or during hospitalization as judged appropriate by the medical team for each patient.

Non-operative Treatment

Physical therapy and adjuvants

a. Complex Decongestive Therapy (CDT) also known as Combined Physical Therapy (CPT) or Complex Decongestive Physiotherapy (CDP) (among others) is backed by longstanding experience and generally involves a two-stage treatment program that can be applied to both children and adults for most areas of the body. The first phase consists of skin care, a specific light manual massage (manual lymphatic drainage-MLD) and sometimes deeper techniques with patients classified above Stage I, using muscle pumping exercises, and compression typically applied with multilayered bandage wrapping. Phase 2 (initiated promptly after Phase 1) aims to conserve and optimize the results obtained in Phase 1. It consists of compression by a low-stretch elastic stocking or sleeve, skin care, continued "remedial" exercise, and repeated MLD as needed.

Prerequisites of successful combined physiotherapy are the availability of physicians (i.e., clinical lymphologists), nurses, physiotherapists, occupational and other therapists specifically trained, educated, and experienced in this method. In addition, factors such as the acceptance of health insurers to underwrite the cost of treatment, willingness of biomaterials industry to produce and provide high quality affordable products, and an understanding of the holistic needs of each patient impact success. Compressive bandages, when applied incorrectly, can be harmful and/or useless.

Accordingly, such multilayer wrapping should be carried out only by professionally trained personnel. Multiple manufactured devices/garments to assist in

compression (i.e., pull on, velcro-assisted, quilted, etc.) may relieve some patients of the bandaging burden and perhaps facilitate compliance with the full treatment program, and some clinics find that patient self-care and risk reduction strategies help maintain edema reduction (although neither of these has undergone rigorous study).

CDT may also be of use for palliation as, for example, to control secondary lymphedema from tumor-blocked lymphatics. Treatment is typically performed in conjunction with chemoor radiotherapy directed specifically at producing tumor regression. Only theoretically, massage and mechanical compression could mobilize dormant tumor cells; however lymph flow does not stop after a cancer diagnosis and only diffuse carcinomatous infiltrates which have already spread to lymph collectors as tumor thrombi might be mobilized by such treatment. Because the longterm prognosis for such an advanced patient is usually dismal, any reduction in morbid swelling is decidedly palliative.

A prescription for elastic garments (custom made with correctly-obtained specific measurement if needed) to maintain lymphedema reduction after CDT is essential for long-term care. Preferably, a physician (sometimes with assistance of highly-skilled specialists) should prescribe the compression garment to avoid inappropriate usage in a patient with medical contraindications such as arterial disease, painful postphlebitic syndrome or occult visceral neoplasia. Generally the highest compression level tolerated (~20–60 mmHg) by the patient is likely to be the most beneficial. Some clinics prefer to use only flat-knit garments while others use both flat and round-knit garments (or combination). Sometimes patient selection, choice, physical ability as well as cost need to be taken into consideration particularly when assessing mobility and future compliance.

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

b. Compression garments alone have been successfully used for treatment particularly in breast cancer-related lymphedema at first indication of fluid build-up and minimal volume change as well as in early Stage I. Data on the use for later stages are very limited.
c. Massage alone. Performed as an isolated technique, classical massage or effleurage generally does not appear to be of benefit. Moreover, if performed overly vigorously, massage (classical or others, not MLD) may damage lymphatic vessels or their attachment to surrounding tissues.

There are several published studies demonstrating the utility of MLD monotherapy in specific populations (i.e., early breast cancer-related lymphedema and newly established and/or mild lymphedema without adipose or fibrosis tissue deposition) but there is a need for more robust studies to generate convincing evidence. This is counterbalanced against several systematic reviews with metaanalysis concluding that MLD (in breast cancer-related arm lymphedema) has no or very little additional effect on compression therapy.

There are some published reports supporting the use of manual lymph drainage as a monotherapy for lymphedema prevention after cancer surgery.

d. Intermittent pneumatic compression. Pneumomassage is usually a two-phase program. After external compression therapy is applied, preferably by a sequential gradient "pump," form-fitting low-stretch elastic stockings or sleeves are used to maintain edema reduction. Newer devices that simulate manual massage and design improvements for area of coverage, ease of use, and sequence/actions may increase patient compliance particularly for those who cannot complete both phases of CDT (e.g., exercise with compression). Displacement of edema more proximally in the limb and genitalia and the development of a fibrosclerotic ring at the root of the extremity with exacerbated obstruction of lymph flow need to be assiduously avoided by careful observation. Combining pneumatic compression with manual lymph drainage has been suggested but not sufficiently evaluated.
e. Thermal therapy. Although combinations of heat, skin care, and external compression have been advocated for and successfully used by practitioners in Europe and Asia for thousands of patients, the role and value of thermotherapy alone without compression in the management of lymphedema remains unclear and further rigorous studies are needed. Studies have shown that under bandaging the skin temperature slowly rises, and it is proposed that this lower level thermal therapy is helpful. Some centers use far infrared light as an adjunct to bandaging and report improved outcomes.
f. Elevation. Simple elevation (particularly by bed rest) of a lymphedematous limb often reduces swelling, particularly in Stage I of lymphedema. If swelling is reduced by antigravimetric means, the effect should be maintained by wearing of a low-stretch, elastic stocking/sleeve during daytime.
g. Low level laser. Reports with small numbers of patients and small meta-analysis have demonstrated efficacy of low level laser use for patients with lymphedema. More

robust changes are noted with reduction of pain and mobility of tissue than just pure lymphedema volume reduction. More studies with larger numbers of patients in diverse settings are needed to confirm these findings.

h. Aquatic therapy/ water-based exercise programs have gained some success due to the natural compression of water when exercising and improvements to skin condition. Not all patients (particularly those with wounds or skin issues) are candidates for aquatic therapy.

i. For appropriate patients, adjuvant devices such as ultrasound or shockwaves may be useful to help break up fibrous tissue, although no large patient series have been published.

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

Drug therapy

a. Diuretics. Diuretic agents are of limited use during the initial treatment phase of CDT and should be reserved for patients with specific co-morbid conditions or complications. Long-term administration of diuretics, however, is discouraged for it is of marginal benefit in treatment of peripheral lymphedema and potentially may induce fluid and electrolyte imbalance. Diuretic drugs may be helpful to treat effusions in body cavities (e.g., ascites, hydrothorax) and with protein-losing enteropathy as well as in those patients in palliative care. Patients with peripheral lymphedema from malignant lymphatic blockage may also derive benefit from a short course of diuretic drug treatment.

b. Benzopyrones. Oral benzopyrones, which have been reported to hydrolyze tissue proteins and facilitate their absorption while stimulating lymphatic collectors, are neither an alternative nor substitute for CDT. The exact role for benzopyrones (which include those termed rutosides and bioflavonoids) as an adjunct is still not definitively determined including appropriate formulations and dose regimens. Coumarin, one such benzopyrone, in higher doses has been linked to liver toxicity particularly in some patients with specific liver enzyme defects.

c. Antimicrobials. Antibiotics should be administered for bona fide superimposed acute lymph stasis-related inflammations (cellulitis/lymphangitis or erysipelas). Typically, these episodes are characterized by erythema, pain, high fever and, less commonly, even septic shock. Mild skin erythema without systemic signs and symptoms does not necessarily signify bacterial infection. If repeated limb "sepsis" recurs despite optimal CDT, the administration of a prophylactic penicillin or broad spectrum antibiotic is recommended (continuance depends on medical risk/benefit assessment). Fungal infection, a common complication of extremity lymphedema, can be treated with antimycotic drugs. In most instances, washing the skin using a mild disinfectant followed by antibiotic-antifungal cream is helpful. Short-term use of anti-histamines and steroids in selected patients with inflammation has also been utilized by some practitioners.

d. Filariasis. To eliminate microfilariae from the bloodstream in patients with lymphatic filariasis, the drugs diethylcarbamazine, albendazole, or ivermectin are recommended. Killing of the adult nematodes by these drugs (macrofilaricidal effect) is variable and may be associated with an inflammatory-immune response by the host with aggravation of lymphatic blockage. Short and long-term efficacy of antibiotics (e.g., penicillin or doxycyclin) separate from general skin hygiene in patients with lymphatic filariasis to prevent elephantine trophic changes remains to be determined to gain wider acceptance.

e. Mesotherapy. The injection of hyaluronidase or similar agents to loosen the extracellular matrix is of unclear benefit and may actually be harmful.

f. Immunological therapy. Efficacy of boosting immunity by intraarterial injection of autologous lymphocytes is unclear and needs independent, reproducible evidence. Recent proposals for the use of anti-inflammatory pharmaceuticals have not yet demonstrated efficacy and may face drawbacks if administered long-term.

g. Diet. No special diet has proved to be of therapeutic value for most uncomplicated peripheral lymphedema. In breast cancerrelated lymphedema and in obese patients, weight reduction has been shown to help. Restricted fluid intake is not of demonstrated benefit for peripheral lymphedema. In chylous reflux syndromes (e.g., intestinal lymphangiectasia), a diet as low as possible or even free of long-chain triglycerides (absorbed via intestinal lacteals) and high in short and medium chain triglycerides (e.g., MCT absorbed via the portal vein) is of benefit especially in children. Specific vitamin supplements may be needed in very low or no fat diets. Some clinics suggest diets (e.g., enriched with omega 3's) that may lower inflammation, but evidence is not currently robust.

h. In complicated patients with lymphatic system overgrowth (lymphangiodysplasia) associated with lymphedema, specialized centers may utilize pharmacotherapeutic options such as octreotide, OK-432, rapamycin, or other anti-proliferative agents (these treatments are particularly used in newborns and children).

Psychosocial rehabilitation

The magnitude of the relationships between negative psychological and psychosocial factors and lymphedema has been documented as a cause of nonadherence to self-management as well as diminution in quality of life. Psychosocial support, quality of life assessment-improvement program, and a patient self-efficacy assessment are integral components of any lymphedema treatment.

Operative Treatment

Operations designed to alleviate peripheral lymphedema by enhancing lymph return have gained increased acceptance worldwide but in advanced stages usually require long-term combined physiotherapy and/or other compression after the procedure to maintain edema reduction and ensure vascular/shunt patency. These microsurgical procedures currently provide the closest chance for a cure of lymph flow disorders. In carefully selected patients following full evaluations, these procedures act as an adjunct to CDT or are undertaken when CDT has clearly been unsuccessful (or has removed the fluid component). Recent research has also focused on a preventive aspect in high risk patients (in limited reports). Imaging is indispensable to identify functional vessels or nodes to manipulate.

As with physical methods above, proponents report that greater success is found in those patients with early (Stage I) lymphedema (with the notable exception to liposuction, which is usually performed in later stages).

Worldwide, surgical resection (in several forms) is the most widely used operative technique to reduce the bulk of lymphedema (especially in genitalia cases). Liposuction to reduce excess fat deposition is becoming more widespread with surgeons in multiple countries now performing the procedure.

In some specialized centers, operative treatment within specific guidelines may now be a preferred approach depending on the treatment team training and availability of various treatments.

It is noted that there is no clear clinical differential for choosing which of these different techniques to use for treating individual patients and no head-to-head comparisons or randomized studies of the techniques. In addition, many centers also use combinations of operative procedures (along with added non-operative methods) in their approach to treating patients making determination of individual treatment effects more difficult to evaluate.

Microsurgical procedures

This operative approach is designed to augment the rate of return of lymph to the blood circulation. The surgeon should be well-schooled in both microsurgery and lymphology and utilize appropriate imaging tools to document efficacy. In general, microsurgical procedures must be performed with special caution in children. Experience with these procedures suggests that improved and a longer lasting benefit is forthcoming if performed early in the course of lymphedema before damage to the lymphatic wall and impaired lymphatic contractility have occurred.

a. Derivative methods. Lymphaticvenous (or lymphovenous) anastomoses (LVA) are currently in use at multiple centers around the world. These procedures have undergone confirmation of long-term patency (in some cases more than 20 years) and some demonstration of improved lymphatic transport (by objective physiologic measurements of long-term efficacy). Multiple lymphaticvenous anastomoses in a single surgical site with both the superficial and deep lymphatics, allow the creation of a positive pressure gradient (lymphatic-venous) and evade the phenomenon of gravitational reflux without interrupting the distal peripheral superficial lymphatic pathways. Some centers also practice lymph nodal-venous shunts as a derivative method.
b. Reconstructive methods. These sophisticated techniques involve the use of a lymphatic collector (LLA) or an interposition vein segment (LVLA) to restore lymphatic continuity in lymphedema conditions due to a locally interrupted lymphatic system. Autologous lymph vessel transplantation mimics the normal physiology and has shown long-term patencies of more than 10 years. This procedure generally has been restricted to unilateral peripheral lymphedema of the leg due to the need for one healthy leg to harvest the graft but it has also been utilized for bilateral upper extremity lymphedema where two healthy legs are available for lymphatic harvesting.

Vascularized Lymph Node Transplantation

Transplantation of superficial lymph nodes from an uninvolved area together with the vascular supply (VLNT) to the site of lymphadenectomy for cancer has been proposed both as a preventive and therapeutic approach to limb lymphedema.

Long-term followup data on risk and efficacy is scant along with the influence of adjunctive physical methods. There have been several reports of lymphedema developing in the donor area. While imaging has demonstrated blood flow to the transplanted nodes, sparse data have been published on lymph flow through the transplanted nodes. Further research showing long-term efficacy and improvement in techniques to avoid donor site lymphedema are needed. Some surgeons combine this procedure with

liposuction and postoperative compression claiming favorable outcome, which makes it difficult to evaluate the surgical procedure per se.

Liposuction

Liposuction (or suction-assisted lipectomy) using a variety of methods has been shown to completely reduce non-pitting, primarily non-fibrotic, extremity lymphedema due to excess fat deposition (which has not responded to non-operative therapy) in both primary and secondary lymphedema (and more limited studies in lipedema). Even patients with signs of fibrosis can benefit from the procedure when using power-assisted liposuction, which facilitates breaking down fibrosis especially in leg lymphedema. Similar to conservative treatment, long-term management requires strict patient adherence with dedicated continuous wearing of low-stretch elastic compression garments, which may be challenging in warmer climates and pose financial considerations. This operation and followup are very different from cosmetic liposuction and should be performed by an experienced team of surgeons, nurses and physiotherapists to obtain and sustain optimal outcomes.

Newer investigations have focused on combining microsurgery with lymph vessel sparing liposuction in an effort to alleviate the need for continual compression.

Surgical Resection

The simplest operation is "debulking," that is, removal of excess skin and subcutaneous tissue of the lymphedematous limb. The major disadvantage is that superficial skin lymphatic collaterals are removed or further obliterated. It can also be associated with significant scarring, risk of infection, and difficult wound healing. After intensive CDT, redundant skin folds may require excision. Debulking has been reported to be useful mainly in treatment of the most severe forms of fibrosclerotic lymphedema (elephantiasis) and in cases of advanced genital lymphedema. Caution should be exercised in removing enlarged lymph nodes or soft-tissue masses (e.g., lymphangiomas) in the affected extremity as lymphedema may worsen thereafter. Operations including the Charles and Thompson procedures are seldom used when other options are available.

Tissue Engineering/Lymphatic (Re)Vascularization

The implantation of tubes to transport lymph or engineered tubes/devices to promote new substitute lymphatic growth have not yet documented long-term value in large studies, and these techniques are continuing to undergo investigation.

Omental transposition, enteromesenteric bridge operations, and implantation of threads to promote perilymphatic spaces (substitute lymphatics) have not shown long-term value and should be avoided without further published evidence.

Specialized Considerations

Chylous and other reflux syndromes are special disorders which may benefit from CT- or MR-guided sclerosis, interventional radiology techniques, or operative ligation of visceral dysplastic lymphatics, and/or lymphatic to venous diversion to close and decompress leaking lymphatic vessels after delineation by multimodal imaging. Assessment in children and even pre-natal care is expanding.

There has been recent work with implantation of silicone tubes as artificial lymphatics, and new developments in coatings and techniques may produce added improvements.

Extratruncal disease (i.e., lymphatic malformations outside of the main trunks which may or may not be associated with arterial/venous malformations) are often treated with a variety of these surgical procedures (as well as with pharmacotherapy) in highly specialized centers.

Rehabilitation and even habilitation is a particularly necessary component of care.

Treatment Assessment/Followup

In each patient undergoing therapy, an assessment of limb volumes should be made before, during and after treatment. This volume can be measured by water displacement, derived from circumferential measurements using the truncated cone formula, or by perometry. The excess volume (affected limb — unaffected limb) should be measured since limb volumes vary with weight increase/decrease of the patient as well as whether measurements are made in the morning or afternoon. Only measuring the affected extremity can lead to unreliable values. It is desirable, however, that treatment outcomes be reported in a standardized manner in order to compare and contrast the effectiveness of various treatment protocols.

Additional assessments by imaging modalities such as LAS and NIRF to document functional changes in lymphatic drainage, DEXA, US, or MR imaging to determine volume and tissue compositional changes, tonometry/indurometry, bioelectrical impedance BIS or BIA), and tissue dielectric constant (TDC) to examine tissue alterations and fluid changes add scientific rigor to analysis of the outcomes of different treatment approaches.

Health Related Quality of Life (HRQOL) and patient perceptions of self-efficacy assessed by a variety of vali-

dated disease specific instruments and visual analog scales of patients with lymphedema should be used in conjunction with physiological measures to evaluate effects of treatment.

Timing and longevity of assessments is an area that is recognized as a need but there are no good guidelines or model systems in place. Pre-treatment and pre-operative assessment (in the Prospective Surveillance model- Section I) should continue after treatment and likely should be life-long to include HRQOL, self-efficacy, and self-regulation measures. Data on long-term results will be useful in comparing treatment options and success, as well as enable patients to have the opportunity to participate in best-practice decisions.

Molecular Therapy

Despite ongoing basic research and clinical trials, molecular treatments (e.g., administration of VEGF-C or other lymphatic-targeting molecules by various methods) have not yet been significantly translated to the clinic. While the addition of lymphatic growth (or inhibitory) factors is attractive, the applicability of these treatments is uncertain at this time and should be examined carefully in the context of co-morbid conditions (e.g., presence of cancer, cancer treatments, drug regimens). It is also apparent when examining the growth of new lymphatics in the laboratory that for all but the smallest microlymphatics a milieu of growth (and other) factors may be needed for initiation and development of functional macrolymphatics (and even more for the de novo development of a lymph node).

Research agenda

While recognizing and encouraging individual investigators to pursue many different avenues of research, some general directions can be formulated. Diagnostic techniques need to be continually explored and developed, treatment options need confirmation and improvements with a particular focus on personalization, and better delineation of prognosis is necessary. Multinational collaborative studies and innovative clinical research designs in addition to randomized control trials need to be done and are encouraged with the aim of translating new discoveries and potentially improved approaches more rapidly into the clinical arena. Ongoing epidemiologic studies on the incidence and prevalence of lymphedema regionally and worldwide will benefit from the further development and establishment of standardized, secure, intercommunicating database-registries.

Assessment of lymphedema risk and steps for lymphedema prevention in different groups of at risk patients need to be determined.

Studies might include research on minimizing or preventing secondary lymphedema through altered operative/ /nodal sampling techniques (e.g., sentinel node biopsy or precise anatomical knowledge of derivative pathways), vector control (as demonstrated in China) and prophylactic drugs for filariasis, identification of patients with heritable genetic defects for lymphangiodysplasia (lymphedema), and use of massage or compression where lymphatic drainage is subclinically impaired as documented by imaging techniques (e.g., LAS and NIRF).

Research in molecular lymphology including lymphatic system genomics, proteomics, and "systemomics" should be greatly expanded. With the cellular and molecular basis of lymphedema-associated syndromes better defined, an array of specific biologically based treatments including modulators of lymphatic growth and function should become available. Improved imaging techniques and physiological tests need to be devised to allow more precise non-invasive methods to measure lymph flow dynamics and lymphangion activity. Advances in imaging including molecular imaging techniques as well as development of new and improved technologies (e.g., NIRF and photoacoustics) to visualize the superficial and deep lymphatic system and soft tissues need to continue. These may become point of care devices available to all or even encompass wearable sensors for both early detection and treatment assessment possibly sent digitally through a mobile phone or over the internet. Telelymphology consultations and followup linkage of specialized centers to remote areas should enhance future care delivery. As knowledge accrues, the current crude classification of lymphedema should be revisited and modified to include more encompassing clinical phenotype-genotype correlations based on anatomic and functional alterations in the lymphatic or associated affected systems. Accordingly, treatment, whether by designer drugs, gene or stem cell therapy, tissue engineering, physical methods or new operative approaches, should be directed at preventing, reversing or ameliorating the specific lymphatic defect and restoring function and quality of life.

Conclusion

Lymphedema may be uncomplicated or complex but should not be neglected.

Accurate early diagnosis and effective therapy is now available which should be able to shift the focus to a more proactive rather than reactive approach. Randomized trials need to take place. Lymphology itself is now recognized as an important and distinct discipline in which clinicians from diverse specialties can be carefully trained and collaborate

to unravel the intricacies of the lymphatic system, lymph circulation, and related disorders. The emerging era of molecular lymphology and precision medicine tailored to the individual patient is likely to result in earlier recognition of a potential problem, improved understanding, evaluation, and treatment in the lymphology clinic, and in the larger context of clinical medicine.

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