GUIDELINES OF THE SOCIETÁ ITALIANA DI LINFANGIOLOGIA:

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Together with the Institutions

*From the **Consensus Document of the International Society of Lymphology** to the Guidelines of the Società Italiana di Linfangiologia.. Diagnostic-therapeutic guidelines not only for lymphedema, but also for the treatment of more complex lymphedema-related lymph and chyliferous vessel diseases.*

On Friday December 5, 2003, an "open" Session took place in Genoa of the University Master Course on Lymphology, with the participation of many authoritative experts from all over Italy and abroad (Belgium, Korea). It was the 1st Domestic Training Course on the "Guidelines for the Diagnosis and Treatment of Lymphedema" accredited by the Ministry of Health under the Continuing Education in Medicine Program (ECM). Its novelty was that it did not just address general and specialist physicians, who were primarily invited to attend the course, but also other healthcare professionals concerned, such as physiotherapists, qualified nurses, healthcare educators, podologists. Many patients were also present in the crowded Anatomy Amphitheater of S. Martino Hospital.

The event, under the patronage of Regione Liguria, was organized by Società Italiana di Linfangiologia (SIL) with the collaboration of SIAPAV, Lombardy Section, and SIFCS, Liguria Section.

Many distinguished authorities also took part: Prof. Paolo Elia Capra, Health Director, Prof. Virgilio Bachi, Director of the Surgery Department, and Prof. Mario Casaccia (both Honorary Chairmen of the event), as well as many members of the National Scientific Committee, speakers and discussants, patient testimonials (most of them former patients!). Throughout the morning session, exciting papers were presented, all of them harmoniously and also unexpectedly integrated to provide interesting in-sight to the discussion of the Consensus Document proposals, rhythmically illustrated by Prof. Francesco Boccardo from Genoa and Dr. Sandro Michelini from Rome, who have been delegated by SIL to draw up the Guidelines which were presented to the audience for discussion.

The Guidelines illustrated below are the result of this debate. Through a seamless institutional and conceptual process, they are a practical "translation" of the Consensus Document drawn up by the International

Society of Lymphology (ISL), as recently updated and published in *Lymphology*, only wrapped up in a customized packaging to meet specific social-health needs of our country.

This contribution, which is open to interdisciplinary and inter-societal collaboration with other more or less similar domestic and international initiatives, is to be considered, jointly with ISL's Consensus Document, as a "living document." It will be periodically updated and adjusted to all new information expected to be produced by Evidence-Based and Problem-Oriented Medicine, through the analysis of the International Scientific Literature, which is indeed the necessary foundation of these Guidelines, as well as of all those generally meant to apply to all other Medical and Surgical disciplines.

Società Italiana di Linfangiologia

"EBM Guidelines on the Diagnosis and Treatment of Lymphedema"

Evidence-Based (Updated And Methodologically Validated Information from the Medical Literature)

GENERAL CONSIDERATIONS

Articles about lymphedema are often introduced with the misleading statement that the pathophysiology of the disease is unclear and treatment unsatisfactory Yet, the general principles of the pathophysiology of lymphedema are known, although the detailed pathogenesis is still open to question. On one hand, the central disturbance is a *"low output failure"* of the lymphatic 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, iliac-inguinal or retroperitoneal nodal dissection), from repeated lymphangitis with lymphangiosclerosis or as a consequence of functional deficiency (e.g., lymphangiospasm, paralysis and valvular insufficiency) (secondary lymphedema). The common denominator, nonetheless, is that lymphatic transport has fallen below the capacity needed to handle the presented load of microvascular filtrate including plasma protein and cells that normally leak from the bloodstream into the interstitium. "High output failure" of the lymph circulation, on the other hand, occurs when a normal or increased transport capacity is overwhelmed by an excessive burden of blood capillary filtrate. Examples include hepatic cirrhosis (ascites), nephrotic syndrome (anasarca), and deep venous insufficiency of the leg (post-thrombophlebitis syndrome). Failure to control lymphedema may lead to repeated infections (dermato-lymphangio-adenitis-DLA), progressive elephantine trophic changes in the skin, and, on rare occasions, even the development of a highly lethal angiosarcoma (Stewart-Treves syndrome).

EPIDEMIOLOGY

According to data obtained from the International Literature—which correspond to the official data published by the World Health Organization in 1994 - the incidence of lymphedema worldwide amounts to 140 million cases (about one person out of 20). Almost half of lymphedemas are of primary origin, characterized by congenital lymphangio-dysplasia. Other 40 millions have a parasitic origin (the most common forms are caused by Filaria Bancroft infection), and they are mainly present in tropical and subtropical areas (India, Brazil, South-Africa). Some other 20 million cases are of post-surgical origin, mainly lymphedemas secondary to breast cancer treatment. The other 10 million cases are mostly caused by functional problems due to lymphatic circulation overload (especially after deep venous thrombosis of the leg and also in the so called Mayall Syndrome, namely artery-venous hyperstomy due to hyper-lymphogenesis).

With regard to the Italian situation, the results of domestic epidemiological research have shown that primary lymphedemas are more frequent than secondary ones. Lymphedemas of the upper limbs are mostly of secondary nature, whereas lymphedemas of the leg are mainly of primary origin. Females are more affected than males, and the most affected age group is the 3rd to 4th decade of life.

The incidence of more or less manifest lymphangitis as a complication of lymphostasis is very high (practically in the almost totality of cases), so much so that a prolonged antibiotic treatment is almost always required, for therapeutic as well as prophylactic purposes. In particular, out of 945 patients observed during an epidemiological study conducted by the Società Italiana di Linfangiologia, practically from all Italian regions and also from abroad (mainly from Europe), primary lymphedemas have been detected in 57% of globally considered cases, while primary lymphedemas of the arm amounted to 11% and of the legs amounted to 72%. With regard to the upper limbs, from an etiopathogenetic point of view, in the great majority of cases, lymphedema was due to axillary lymph node hypoplasia. Upon specific diagnostic investigations, even in lymphedema cases triggered by lymphangitis or traumas, an underlying lymphatic-lymph node hypoplasia—a condition which predisposes to the onset of lymph stasis in the affected limb—has been demonstrated. In almost all primary lymphedemas of the leg, lymphangio-adenodysplastic impairment has been detected, with hypoplasia and inguinal-crural lymph node fibrosclerosis in 93% of cases, and with lymphatic-chylous gravitation reflux, even in the external genitalia, due to valvular incontinence or failure of ectasic and incompetent vessels, in the remaining 7% of cases. The clinical onset of these forms of lymphedema has most frequently been spontaneous, without any apparent cause; conversely, in some cases it followed lymphangitis or trauma. Secondary lymphedemas have been diagnosed in 43% of patients. Most upper limb lymphedemas (98%) were secondary to axillary lymphoadenectomy and/or radiation therapy for breast cancer treatment, whereas in 2% of cases upper limb lymphedema ensued after the resection of axillary lipomas, axillary lymph node biopsies, or axillo-supraclavicular radiation therapy for lymphoma treatment. Secondary lymphedema in the leg was most frequently observed following uterine cervix carcinoma (46%), followed by lymphedemas as a consequence of urological tumor surgery (39%) (prostate, penis carcinoma, testicular seminal carcinoma), melanoma treatment (6%), Hodgkin lymphoma, and also after resection of lipomas from the thigh (3%), varices surgery (2%), and surgery for inguinal and crural hernia (1%).

Another important outcome of the assessment of approximately 200 women with arm lymphedema secondary to breast cancer treatment is that lymphedema developed in 20-25% of the women who had undergone mastectomy or quadrantectomy with axillary lympho-adenectomy, a percentage which went up to 35% when they were also treated with radiation therapy. These figures are in line with those found in the international literature. However, owing to the high incidence of secondary lymphedema, it is necessary to point out that lymphostasis prevention is possible, through early diagnosis, as well as timely treatment. This is very important, not only for the severe psychological implications and physical disability related to this disease, but also for the possibility to prevent severe and recurring lymphangitic complications and, in particular, the likely, although rare, onset of lymphangiosarcoma out of secondary lymphedema.

Recommendation: No final data are yet available on lymphedema epidemiology in Italy and in the world, in particular on primary lymphedema. As to secondary lymphedema, comparable data have been reported in the literature, not only on its diagnosis, complications, and prevention, but also on its incidence, prevalence, time of onset, risk factors. Grade B recommendation.

CLASSIFICATION

Lymphedemas are generally divided into primary or congenital, and acquired or secondary lymphedemas. Primary lymphedemas are further distinguished into connatal, namely already present at birth; early onset lymphedemas, if they develop before 35 years of age; late onset lymphedemas, if they develop after 35. In the connatal group of lymphedemas, a further distinction is made between sporadic and heredofamilial forms, mostly to be considered as more or less complex malformation syndromes either linked or not with genetic anomalies. C. Papendieck's Classification is generally followed to identify the type of dysplasia

underlying the various forms of congenital lymphedema: LAD I (lymphangiodysplasia—dysplasia of the lymphatics); LAD II (lymphadenodysplasia—lymph node dysplasia); LAAD (lymphangioadenodysplasia—dysplasia of the lymphatics and lymph nodes). The term dysplasia includes agenesis, hypoplasia, hyperplasia, fibrosis, lymphangiomatosis, hamatomatosis, valvular insufficiency. Secondary lymphedemas may be distinguished into post-surgical, post-trauma, post-lymphangitis, and parasitic lymphedemas.

Recommendation: In secondary lymphedemas, in particular in post-traumatic and post-lymphangitic forms, but also in those developed after surgery and/or radiation therapy, a constitutional predisposition is almost always observed (congenital dysplasia of the lymphatics and/or lymph nodes.) Grade B recommendation.

STAGING

For lymphedema staging, generally, a three stage scale is used, even if the 2nd and 3rd stage can each be subdivided into two sub-stages, thus ending up with a 5 stage scale. This staging includes primary as well a secondary lymphedemas, clinically overt and sub-clinical lymphedemas. Through proper diagnostic investigations, an initial lymph flow impairment can promptly be detected and clinical disease progression monitored, irrespective of lymphedema nature. The staging of lymphedema is based on clinical and diagnostic-instrumental criteria: e.g., extension of edema, clinical progression of disease during the day and changes due to decubitus, number and severity of lymphangitic complications, edema thickness, and disease-related skin changes. Stage IA includes patients who have undergone surgery and are at risk of developing lymph stasis in the extremity homolateral to the site of primary disease (for example, the arm homolateral to the surgical and/or radiation therapy site in breast cancer treatment). At this stage, there is no clinical evidence of lymphedema yet, however a slower lymph flow is detected by lymphoscintigraphy, with initial dermal back flow.

Finally, severity of the clinical picture based on volume difference can be assessed as minimal (>20% increase) in limb volume, moderate (20-40% increase), or severe (>40% increase).

Recommendation: Stage 1: a) no edema but presence of lymphatic impairment (following mastectomy with axillary lymphadenectomy with equal extremities in volume and thickness). b) Mild edema, reversible with limb elevation and night rest. Stage 2: Persisting edema which subsides only partially with limb elevation and night rest. Stage 3: Persisting edema (no spontaneous regression with limb elevation) and progressing disease (acute erysipeloid lymphangitis). Stage 4: Fibrolymphedema (initial lymphostatic verrucosis) with "column-shaped" limb. Stage 5 - Elephantiasis with severe deformation of the affected extremity, marked and extended sclerodermic pachydermitis and lymphostatic verrucosis.

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: generalized edema with increased thickness, depending on its higher or lower fibrosclerotic tissue component, no pitting, even in early disease stages, Stemmer sign (e.g., lack of skin plication at the root of the second toe), dystrophic skin lesions (post-lymphangitic sequelae, lymphostatic verrucosis, lymphorrhoea, chylorrhea, etc.) frequent dermato-lymphangio-adenitis (DLA) complications. Further, lymph node examination is also useful, in order to detect any associated acute or chronic lymphadenopathy. In more complex forms of angiodysplasia, featuring arteriovenous hyperstomy (Mayall Syndrome) or congenital arteriovenous macro and microfistulas (Klippel Trenaunay or Klippel Trenaunay Servelle Syndrome), the clinical picture may feature the following: gigantism with elongation of the extremities, more or less marked foot dysmorphism, flat or map-like Port-wine stain angiomas, hyperhydrosis of the foot plant. However, there are also spurious forms, which are more difficult to diagnose, owing to prevailing lymphedematous components. Also, in some patients, confounding

conditions such as morbid obesity, venous insufficiency, occult trauma, and repeated infection may complicate the clinical picture. Moreover, in considering the basis of unilateral or bilateral extremity lymphedema, especially in adults, an occult tumor needs to be considered. For these reasons, a thorough and integrated medical evaluation is indispensable before embarking on lymphedema treatment. Co-morbid conditions such as congestive heart failure, hypertension, and cerebrovascular disease including stroke may also influence the therapeutic approach undertaken.

If the diagnosis of lymphedema is unclear or in need of better definition for prognostic considerations, consultation with a clinical lymphologist or referral to a lymphologic center is recommended.

Imaging

Lymphangioscintigraphy is the first choice test for lymphedema diagnosis, in order to confirm the nature of lymph stasis and to identify its cause (either obstacle or reflux), to evaluate the extension of disease (dermal back flow), any higher or lower damage to deep vs. surface lymphatic circulation, and drainage through lymph nodes. Therefore, the study of both deep and surface lymph circulation is useful, by proper tracer injection into specific drainage sites of both systems. This is a non invasive, easily repeatable procedure, even in newborn babies. With this imaging technique, even IA stage—not yet clinically manifest— lymph stasis can be detected, thus playing a fundamental role in secondary lymphedema prevention. This investigation technique is also useful in following up on the outcome of various lymphedema treatments and, in particular, of lymphatic microsurgery. Lymphography is a modern investigation technique which is essential when studying complex congenital or acquired conditions of chyliferous vessels, the cisterna chyli, and the thoracic duct. Under the most modern facilities, it is performed in the operating room, under local anesthesia, with microsurgical preparation of the lymphatics. Ultrasonography, CT, and MRI are useful diagnostic tools to define complex syndromes featuring angiodysplasia and lymphedema associations, as well as to investigate the organic obstructive origin, if any, of lymphedema secondary to a tumor. In particular, for lymphedemas of the extremities, High Resolution Ultrasonography (with linear 10-14 MHz probes) depicts any increased sub- and suprafascial thickness, and its subsequent reduction after treatment. It is also useful to measure tissue compressibility and to highlight different echogenic features depending on the prevailing tissue component (e.g., water vs. tissue fibers). Hence, US is quite useful to monitor treatment outcome and for prognosis purposes. Lymphangio-MRI, in particular, using the fatty-tissue subtraction technique, provides useful information in advanced obstructive lymphedema conditions, featuring dilated lymphatics swollen with lymph. Investigations of venous circulation with Color-Doppler Ultrasound—commonly employed for the instrumental assessment of an edematous limb—, Phleboscintigraphy, and Phlebography (if required, based on the Ultrasound examination outcome) are essential. Investigations of arterial circulation may also become necessary in pan-angiodysplasia conditions associated with lymphedema. In all these cases, in addition to Color-Doppler Ultrasound, digital arteriography may also be useful. Indirect Lymphography, Fluorescent Microlymphography, Hudack—McMaster Lymphochromic Test, flow and lymph pressure measurement, as well as Laser Doppler may all provide useful information on anatomic and functional conditions of blood micro-circulation (Laser Doppler), as well as of initial lymphatics and lymphatic collectors. However, their clinical use is limited.

Genetic Testing

Genetic testing is almost becoming practical to define a limited number of specific hereditary syndromes with discrete gene mutations such as lymphedema-distichiasis and some forms of Milroy disease. The future holds promise that such testing combined with careful phenotypic descriptions will become routine to classify familial lymphangiodysplastic syndromes and other congenital/genetic-dysmorphogenic disorders characterized by lymphedema, lymphangiectasia, and lymphangiomatosis. Recent studies have shown the association between lymphedema and anomalies of chromosomes 5, 16, 18, and 21.

Biopsy

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

Immunohistochemical Investigations

Interesting immunohistochemical investigations have recently been conducted on lymphatics-lymph node material taken during lymphatic microsurgery and on the interstitial matrix. These studies have yielded valuable information on lymphedema physiopathology. In particular, dysfunctions of lymphatic vessel walls and of lymph nodes have been identified and classified. They progressively develop and evolve in parallel with lymphedema progression and, more specifically, proportionally with lymphedema duration. These observations have confirmed that, for a proper treatment of this disorder, whenever lymphatic drainage is lacking or obstructed, it is essential to resume its good functioning, as soon as possible. In this way, successful and long-lasting results will be obtained, through the preservation of a good autonomous lymphatic pump performance linked with smooth muscle fibrocells that are normally present in lymphatic pre-collectors and collectors, as well as in lymph node capsules. With disease progression, smooth muscle cells are gradually lost and replaced by non-dynamic fibrosclerotic tissue.

Recommendation: Lymphoscintigraphy, High Resolution Ultrasonography and Color Doppler Ultrasound are employed in the first level of diagnosis. Ultrasonography, CT, MRI and lymphography in the second level of diagnosis; phlebography, arteriography, genetic testing, and biopsy in the third level. Grade A.

TREATMENT

Therapy of peripheral lymphedema is divided into conservative (non-operative) and operative methods.

Non-operative Treatment

A) *Physical therapy*

1 - **Combined Physical Therapy (CPT).** This methodology generally involves a two-stage treatment program: the first phase consists of skin care, manual lymph drainage, range of motion exercise and compression, typically applied with multi-layered bandage-wrapping. Phase 2 (initiated promptly after Phase 1) aims to maintain and optimize the results obtained in Phase 1. It consists of skin care, compression by a low-stretch elastic stocking or sleeve, continued “remedial” exercise, and repeated manual lymph drainage, as needed. Prerequisites of successful combined physiotherapy are the availability of physicians (i.e., clinical lymphologists), nurses, and therapists highly trained and educated in this method. Compressive bandages, when applied incorrectly, can be harmful and/or useless. A prescription for low stretch elastic garments (custom made with specific measurement if needed) to maintain lymphedema reduction after CPT is essential for long-term care. Failure of CPT is confirmed only when intensive non-operative treatment in a clinic specializing in management of peripheral lymphedema and directed by an experienced clinical lymphologist has been unsuccessful.

2 - **Uniform and/or Intermittent Pneumatic Compression**. Pneumomassage is usually a three-phase program: treatment of lymph nodes proximal to the extremity, to prepare them and avoid engorgement; external compression therapy, using appropriate pressure values depending on the clinical stage of lymphedema; compression stockings or sleeves or multilayered bandaging are then used to maintain edema

reduction.

3 - **Manual Lymph-drainage** Mostly performed according to the conventional methods of the German and Belgian schools. The various massage techniques may also be combined, on a case by case approach. Not to be performed too vigorously, in order to avoid damage to lymphatic vessels and lymph nodes.

B) *Drug therapy*

1 - **Benzopyrones (b**.): these drugs include Coumarine and its derivatives (alpha-B.) and Bioflavonoids and their derivatives (gamma-b., Diosmine, Rutine, Esperidine, Quercetine, etc.)

Alpha-b. act as follows:
- Increase capillary tone
- Reduce capillary permeability to proteins
- Increase the number of macrophages
- Promote macrophage proteolytic action
- Stimulate lymphangion propulsion action
- Inhibit prostaglandin and leukotriene synthesis

Therefore their effects are as follows:
- Interstitial fluid reabsorption
- Gradual regression of fibrosis promoted by macrophage proteolysis
- Reduction of chronic inflammation with subsequent lower incidence of acute episodes and less tendency to fibrotic edema development.

Natural Coumarines, to be administered in 8 mg/die dosage for 60 days, have shown to be therapeutically effective in improving subjective symptoms, in functional recovery of the lymphedematous extremity, in reducing edema thickness, promoting bulk reduction after physical and/or microsurgical treatment, without toxic effects to the liver.

Gamma-b actions include the following:
- Reduction of endothelium permeability to protein macromolecules
- Capillary filtration reduction
- Venule tone increase

Hence, its effects are as follows:
- Stabilizing action on interstitial connective tissue and on the capillary wall
- Prostaglandin and leukotriene production inhibition.

2. **Antibiotics**: antibiotics are used during the acute phase (beta-hemolytic streptococcus therapy), for treating dermato-lymphangio-adenitis (DLA), and as a preventative prophylactic treatment against acute lymphangitis episodes (long-acting penicillin)
3. **Antimycotic drugs**: they are used to treat fungal infection of the extremities (flucanozole, etc.)
4. **Dietylcarbamazine:** To eliminate microfilariae from the bloodstream in patients with lymphatic filariasis and also for healthy carriers.
5. **Diuretics**: normally prescribed at low dosages and for short periods, specially when lymphedema is associated with phlebedema or other disorders such as heart and kidney disease, ascites, chyliferous vessels disorders, etc. They fail to remove the interstitial protein component, hence they have only a symptomatic and no etiologic effect.
6. **Diet:** In obese patients, reducing caloric intake combined with a supervised exercise program is of distinct value in decreasing limb bulk. Restricted fluid intake is not of demonstrated benefit. In chylous

reflux syndromes, a diet low in lipids and the exclusive intake of medium-chain triglycerides (MCT) which are absorbed via the portal vein, without overloading the chyliferous vessel system, has proved to be of great benefit especially in children.
Therefore, there is a wide range of pharmacologic and therapeutic principles available. Which one is to be selected depends on etiopathogenic and physiopathologic features of each type of lymphedema.

The use of vascular endothelial lymphedema-specific growth factors (VEGF-C and VEGF-D) is still under investigation and waiting for final trials for both primary and secondary lymphedema.

C) *Psychosocial rehabilitation*

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

Recommendation: The various non operative therapeutical methods must be applied in a combined and integrated manner, on a case by case basis, and depending on the clinical stage of lymphedema. Grade B.

Operative Treatment

Surgical techniques employed in the past to treat lymphedema would focus on bulk reduction of the affected limbs by a debulking-resection operation (cutolipofascectomy, total surface lymphangectomy, Thompson's operation, etc.). However, these were only symptomatic treatments: since they would not remove the cause of lymph flow obstruction, they were reducing lymphedema only temporarily, while they would require long hospitalization periods, and would frequently be accompanied by infections, delayed wound healing, loss of sensitivity, residual and progressing edema of the ankle and foot, as well as extensive retracting and disfiguring scars. Following the advent of Microsurgery, functional and causal therapeutic solutions for lymphedema were investigated and implemented aiming at draining the lymph flow or reconstructing the lymphatic pathways where they had been obstructed or were missing. Fine, repairing techniques were employed with direct intervention on the very lymphatic structures. Microsurgery techniques have yielded positive and long-lasting results in the treatment of primary lymphedemas — including those in children — as well as in secondary lymphedemas following cancer treatment, involving lymph node resection in some 'critical' areas, such as in the armpit and the groin. Direct intervention on lymphatic-lymph node structures was first performed by multiple antigravitational ligatures of incompetent lymphatic and chyliferous vessels according to Servelle and Tosatti, to treat gravitational reflux lymphochyledema; Kinmonth (bridge) procedure was also employed, featuring the anastomosis of iliac-inguinal lymph nodes with an ileum segment, after mucosa removal from its mesenteric pedicle. However, with the progress made in surgical equipment design, armamentarium and techniques, two microsurgery methods have been developed for a “conservative and functional” treatment of lymphedema, namely derivative and reconstructive microsurgery. Derivative microsurgery techniques aim to resume lymph flow at the obstruction site, through a lymph-venous drainage in which lymph nodes or, directly, lymphatics are employed: Lymph node-Venous Anastomosis (LNVA), Lymphatic-Capsular-Venous Anastomosis (LCVA), End-to-end Lymphatic-Venous Anastomosis (EE-LVA), End-to-side Lymphatic-Venous Anastomosis (ES-LVA). Most recently, multiple, end-to-end and end-to-side lymphatic-venous anastomoses are most commonly employed, which are fashioned directly with the use of major veins or their collaterals, depending on the anatomic picture at the time of surgery, and performed at 1/3 midportion of the forearm volar surface and in the inguinocrural region for the arm and leg, respectively. Conversely, with reconstructive microsurgery techniques, the lymphatic flow is resumed by overcoming the obstruction site either through a direct anastomosis of afferent and efferent lymphatics, or through the implant of autologous or venous segments between collectors down and upstream the obstruction: Lymphatic-lymphatic Anastomosis (LLA), Segmental Lymphatic Vessel Autotransplantation (SLAT), Lymphatic-Venous- Lymphatic-Plasty or Lymphatic-Venous- Lymphatic Anastomosis (LVLA), Free

Lymphatic- Lymph Nodal Flaps (FLF). With the LVLA technique, also bilateral lymphedemas can be treated, without risk of causing any iatrogenic lymphedema on the harvest site, as could instead happen when harvesting a lymphatic-lymph node specimen. Indications for the various microsurgical techniques depend on the presence of a viable lymphatic-venous pressure gradient in the affected limb. Should lymphostatic deficiency be associated with venous insufficiency (a condition mostly found in the lower extremities: varices, venous hypertension, valvular incontinence), derivative microsurgery is not recommended, while only reconstruction techniques can be applied.

Recommendation: Conventional surgical debulking-resective techniques are to be confined to cases in which it is necessary to remove excess skin and subcutaneous tissue of the lymphedematous limb, following a significant lymphedema reduction with CPT and/or microsurgery. Microsurgical procedures are highly beneficial especially in the early stages of disease: through the resumption of preferential lymph flow pathways in the affected extremity, good results (even healing) can be achieved with Microsurgery. Long term efficacy of lymphatic-venous anastomoses mainly depends on the accuracy of the adopted technique (the use of the operative microscope is essential) and on disease stage. Grade B.

PREVENTION

Prevention of lymphedema secondary to breast cancer treatment with surgery and/or radiation therapy is possible today specially thanks to lymphoscintigraphy, which permits the study — before or after tumor treatment — of the anatomic-functional lymph flow system in the homolateral arm.

In this way, it is thus possible to identify patients at (low, medium, or high) risk of secondary lymphedema onset. Therefore, these patients could successfully benefit from early - rather than late - therapeutic measures which best suit them on a case by case basis, depending on the identified lymph flow damage extension.

This investigation must be performed by subcutaneous (and not intradermal) radiotracer injection into the interdigital folds at the root of the extremity, in order to ensure that there is no tracer escape and, therefore, no false positive results from the test.

The Protocol for Secondary Lymphedema Prevention following breast cancer treatment drawn up by Società Italiana di Linfangiologia provides a list of clinical and lymphoscintigraphic criteria on which preventative measures have been established to be taken before, during, and after surgery, including the option of microsurgical lymphatic-venous anastomosis to be immediately performed together with axillary lymph node resection.

Further, lymphoscintigraphy performed in blood-relatives of patients with primary lymphedema or in patients who have undergone radical lymphadenectomy for cancer treatment at the root of the extremity or complementary radiation therapy, who show no edema in the affected limb, may show a slower radiotracer flow (presence of lymph node stops along the extremity which could not be otherwise displayed). This is a sign of some propensity to developing lymphedema (preclinical studies).

Recommendation: Today, the chances to prevent arm lymphedema secondary to breast cancer treatment are real, through the implementation of a prevention protocol based on clinical criteria, as well as on lymphoscintigraphy outcome. Grade B.

Società Italiana di Linfangiologia

"GUIDELINES - EBM
ON THE DIAGNOSIS AND THERAPY OF LYMPHEDEMA"

Recommendations:

Grade A - Randomized clinical trials, meta-analyses, no heterogeneity

Grade B - Randomized clinical trials also on small populations, meta-analysis also of non randomized trials, some heterogeneity is possible
Grade C- Recommendation based on observational studies and on consensus reached by the authors of these guidelines.

Società Italiana di Linfangiologia
"GUIDELINES - EBM
ON THE DIAGNOSIS AND THERAPY OF LYMPHEDEMA"
FUTURE PROSPECTS

- PREVENTION OF PRIMARY LYMPHEDEMA
- GENE THERAPY

ANGIODYSPLASIA AND LYMPHEDEMA

Cases of lymphatic dysplasia associated with vascular defects are defined as hemolymphatic malformations. According to the Hamburg classification (1988), congenital vascular malformations are grouped depending on the predominant defect: arterial, venous, lymphatic defects, A-V shunting defects or combined vascular defects. Each of these pictures is then subdivided into truncular and extratruncular forms, depending on the time and site of embryo defect onset.

Lymphatic malformations, classified under extratruncular (limited or diffuse) forms, are conventionally defined as lymphangiomas or lymphangiomatosis.

Truncular forms, which affect the major vessels (aplasia, hypoplasia, dilatation or hyperplasia), may cause lymphedema.

Further, lymphatic malformations may be associated with osteodystrophic syndromes (s.): angio-osteohypertrophic s. (with bone segment elongation), or angio-osteohypotrophic s. (with bone segment shortening). Comprehensive and integrated diagnostic procedures must be implemented with investigations of the arterial, venous, and lymphatic components. CT and MRI are useful to define malformation extent and relationships. Treatment features conservative medical-physical methods, in the mildest cases. Surgical treatment includes derivative and reconstructive lymphatic microsurgery, resection of tissues mostly affected by dysplasia, and antigravitational ligatures of incompetent lymphatics. Alternatively or in association with surgery, there are also treatment options by percutaneous sclerotherapy of lymphangiomatous and lymphangectasic areas and/or embolotherapy of arteriovenous fistulas.

Recommendation: Hemolymphatic malformations, although rare, are due to highly complex vascular defects. They are nosographically classified according to the Hamburg Classification. Comprehensive and integrated diagnostic investigations must be conducted focused on the arterial, venous, and lymphatic components. CT and MRI are used to provide a comprehensive definition of malformation extent and relationships. Therapy features conservative, surgical, sclerotherapic methods, as well as percutaneous embolization, in varying mutual combinations, depending on the specific physiological features underlying each single case. Grade C.

NEONATAL LYMPHATIC DYSPLASIA

Lymphoscintigraphic investigations have recently been conducted on newborn babies with complex

clinical pictures with hydrops, in order to determine the likely lymphatic origin of their malformation.

The task of CPR professionals in these cases is to conduct a primary assessment with treatment of respiratory and heart-blood circulation problems they are faced with from time to time, in order to ensure the survival of the baby, followed by a second, more accurate assessment, and by the final treatment.

Lymphatic circulation investigations by lymphoscintigraphy are part of the procedures of a secondary assessment. Indeed, from a physiopathologic point of view, if hydrops conditions are not due to congestive heart failure or to decreased osmotic plasma pressure and increased capillary filtration, they may well be due to lymphatic malformations (chylothorax, chylous ascites, lymphedema, etc.)

Recommendation: In the assessment of a newborn baby with hydrops, after giving support to his/her life functions, also lymphatic circulation is to be considered as a possible cause of hydrops, an investigation which today is helped by lymphoscintigraphy.

FUTURE PROSPECTS

Among future prospects, there is the possibility to successfully treat primary lymphedema, and, in particular, congenital heredofamilial forms. The chance to prevent lymphedema in the members of a family affected by heredofamilial lymphangiodysplastic syndrome is based on diagnostic procedures, such as lymphoscintigraphy and laser-Doppler ultrasound, which can provide direct and indirect morphological-functional parameters on lymph circulation in the extremities, and disclose lymphatic drainage failure even before any clinical onset of the edema. This “latent” phase of lymphedema is important to identify patients at risk, who will then be referred for preventative medical-physical treatment. On this point, currently ongoing genetic and molecular biology studies are very important.

Finally, investigations are being conducted on the application of gene therapy for the treatment of primary lymphedema.

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- Evidence based (143 References)
- Recommendations