Lymphatic Education
& Research Network

Standardized Approach for the Diagnosis and Management of Lymphedema (LE) and Lymphatic Diseases (LD)

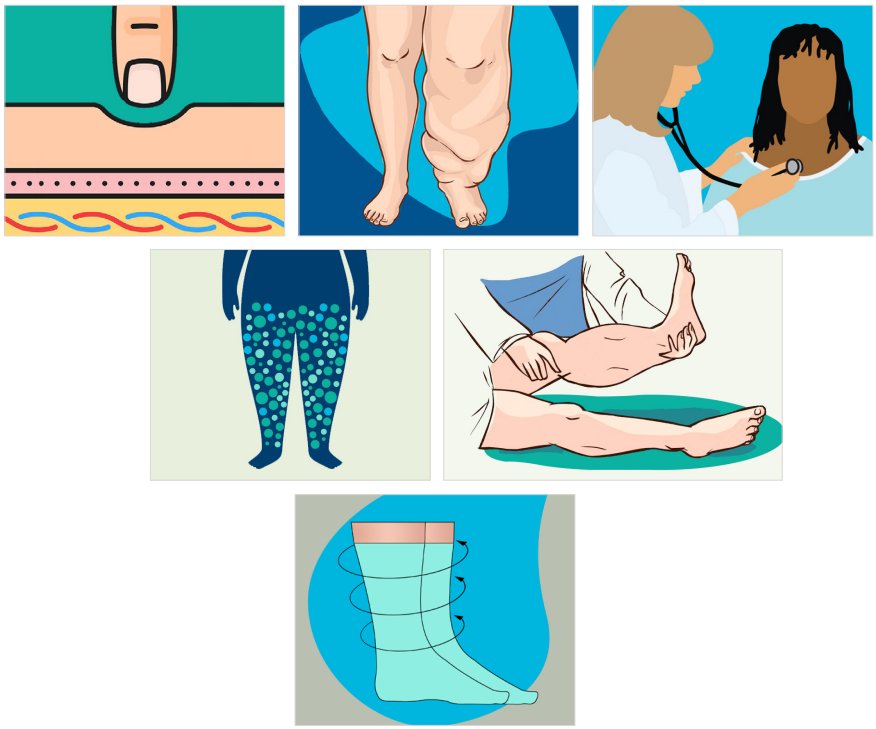

TABLE OF CONTENTS

AUTHOR CONTRIBUTIONS

SECTION 1: PRIMARY AND SECONDARY LYMPHEDEMA AND LIPEDEMA

Overall Introduction

Melissa Aldrich, MBA, PhD, *Center for Molecular Imaging, The Brown Foundation Institute of Molecular Medicine, UT Health, Houston, TX*

Louise Koelmeyer BAppSc(OT), PhD, *Australian Lymphoedema Education, Research & Treatment (ALERT) Program, Faculty Medicine, Health & Human Sciences, Macquarie University, Sydney, Australia*

Kay Pham, MD, *Department of Psychiatry and Behavioral Sciences, Texas A&M Health School of Medicine, Bryan, TX*

Kimberly Steele, MD, PhD

A. Clinical Features & Diagnosis

History and Physical Examination; Staging of Lymphedema; Staging of Lipedema

Sarena Banas, PT, DPT, CLT, *Oncology-Lymphedema Team Leader, Good Shepherd Penn Partners, Philadelphia, PA*

Assessment Tools In the Diagnosis of Lymphedema and Lipedema

Jasmine Zheng, MD, CLT, FAAPMR, *Director of Cancer Rehabilitation, Assistant Professor, Department of Physical Medicine, and Rehabilitation, University of Pennsylvania, Philadelphia, PA*

Imaging

Deborah Rabinowitz, MD, *Director Vascular Anomaly Center at Nemours Children's Health Delaware; Clinical Associate Professor in Pediatrics and Radiology at Sidney Kimmel College of Medicine at Thomas Jefferson University, Philadelphia, PA*

Diagnosis: Primary Lymphedema

Vaughan Keeley, PhD, FRCP, *Consultant Physician in Lymphoedema, University Hospitals of Derby and Burton NHS Foundation Trust Lymphoedema Department, Derby, UK*

On behalf of the EU VASCERN paediatric and primary lymphoedema (PPL) working group.

Secondary Lymphedema

Rebecca Prusinski, PT, DPT, WCS, CLT-LANA, *Good Shepherd Penn Partners, Penn Therapy & Fitness, Philadelphia, PA*

B. Treatment Options for Lymphedema

Conservative Management: Primary Lymphedema

Rebecca Prusinski, PT, DPT, WCS, CLT-LANA, *Good Shepherd Penn Partners, Penn Therapy & Fitness, Philadelphia, PA*

Conservative Management: Lymphedema Risk Reduction and Surveillance for High-risk Patients

Robin Kauffman, PT, CLT-LANA, *Good Shepherd Penn Partners, Penn Therapy & Fitness, Bryn Mawr, PA*

Complete Decongestive Therapy

Robin Kauffman, PT, CLT-LANA, *Good Shepherd Penn Partners, Penn Therapy & Fitness, Bryn Mawr, PA*

Management and Surveillance of Head and Neck Lymphedema

Roman Skoracki, MD, FRCSC, FACS, *The Ohio State University, Department of Plastic Surgery, Columbus, OH*

Genital Lymphedema

Shelley DiCecco, PT, PhD, CLT-LANA, *Department of Physical Therapy, PCOM Georgia, Suwanee, GA*

Surgical Management of Lymphatic Disease: Introduction

Lead on Surgical Methods section: Min-Jeong Cho

Overseeing author: David Chang, MD, *Section of Plastic and Reconstructive Surgery, Department of Surgery, The University of Chicago, Chicago, Illinois*

Surgical Methods for Primary Lymphedema

Min-Jeong Cho, MD, *Department of Plastic and Reconstructive Surgery, The Ohio State University Wexner Medical Center, Columbus, OH*

Surgical Methods for Secondary Lymphedema

Mark Schaverien, MD, *Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX*

C. Management of Cellulitis As a Complication of Lymphedema

Vaughan Keeley, PhD, FRCP, *Consultant Physician in Lymphoedema, University Hospitals of Derby and Burton NHS Foundation Trust Lymphoedema Department, Derby, UK*

On behalf of the BLS/LSN guidelines on the management of cellulitis in the lymphedema group.

D. Lipedema

Introduction; Diagnosis; Imaging; Treament of Lymphedema

Russell Ashinoff, MD, FACS, *The Institute for Advanced Reconstruction & The Plastic Surgery Center, Red Bank, NJ*

Continued ➤

SECTION 2. COMPLEX LYMPHATIC AND VASCULAR ANOMALIES

A. Clinical Features and Diagnosis; B. Management of Vascular and Other Complex Malformations for Overlapping Vascular and Lymphatic Conditions; C. Management of Protein-losing Enteropathies, Chylothorax, Chyloperitoneum, Management of mTOR Inhibitors/Other Pharmacotherapies for Lymphatic Malformations and Complex Vascular Lesions; D. Interventional Therapies

Ionela Iacobas, MD, *Medical Director, Texas Children's Hospital/Baylor College of Medicine, Houston, TX*

SECTION 3. CONSULTATIVE SERVICES FOR LYMPHATIC DISEASES

A. Genetics (Screening for Known Genes and Mutations, Genetic Counseling to Patients and Families)

Salma Adham, MD, *Vascular Medicine Department, Centre Hospitalier Universitaire de Montpellier, Montpellier,* France

B. Mental Health

Introduction; Physical Effects; Psychological Effects; Social Effects; Psychotherapeutic Considerations; Psychopharmacologic Considerations; Limitations in the State of Evidence

Kay T. Pham, MD, *Department of Psychiatry and Behavioral Sciences, Texas A&M Health School of Medicine, Bryan, TX*

Alexander M. Kaplan, MD, MPH, *Regional Medical Director [Austin Region], Associate Director of Research at Family Care Center, Georgetown, TX*

SECTION 4. GUIDELINES FOR COMMUNICATION IN LYPMHEDEMA AND LYMPHATIC DISEASES

A. Introduction; B. Communications Functions (Managing Uncertainty, Exchanging Information, Making Decisions, Building Relationships, Enabling Self-Management, Responding to Emotions, Supporting Hope, Providing Validation); C. Conclusion

Bryan Anthony Sisk, MD, MSCI, *Washington University School of Medicine, St. Louis, MO*

Anna Michele Kerr, PhD, *Assistant Professor, Ohio University Heritage College of Osteopathic Medicine, Dublin, OH*

Shelbie Blake Fishman, BS, *MD Candidate (Third-Year Medical Student), Washington University School of Medicine, St. Louis, MO*

SECTION 5. FINAL REMARKS

William J. Repicci, *President & CEO, Lymphatic Education & Research Network, New York, NY*

ACKNOWLEDGMENTS

The VASCERN PPL Working Group Patient Pathway for Primary Lymphedema

Nele Devoogdt a, Sarah Thomis a, Florence Belva b, Hanne Buciek Hove c, Janine Dickinson d, Caroline Fourgeaud e, Guido Giacalone b, Tonny Karlsmark c, Heli Kavola f, Vaughan Keeley g, Manuela Lourenço Marques h, Sahar Mansour i, Christoffer V Nissen c, Susan Nørregaard c, Michael Oberlin j, Tanja Planinšek Rušigaj k, Sinikka Suominen f, Kirsten Van Duinen d, Stéphane Vignes e, Robert Damstra d.

AFFILIATIONS

a Centre for Lymphedema, Dept. of Vascular Surgery, University Hospitals Leuven, Leuven, Belgium

b Lymphedema Centre, AZ Sint-Maarten, Mechelen, Belgium

c Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

d Expert Center for Lymphovascular Medicine, Nij Smellinghe Hospital, Drachten, The Netherlands

e Department of Lymphology and Reference Center for Rare Vascular Diseases, Cognacq-Jay Hospital, Paris, France

f Department of Plastic Surgery, Helsinki University Hospital, Helsinki, Finland

g Derby Lymphedema Service, University Hospitals of Derby and Burton NHS Trust, Derby, UK

h Associação Nacional de Doentes Linfáticos (andLINFA), Lisbon, Portugal

i Department of Lymphovascular Medicine, St. George's University Hospitals NHS Foundation Trust, London, UK

j European Centre for Lymphology, Földi Clinic, Hinterzarten, Germany

k Dermatovenereological Clinic, University Medical Centre, Ljubljana, Slovenia

VASCERN, the ERN on Rare Multisystemic Vascular Diseases, gathers the best European expertise to help patients with rare vascular diseases.

The Pediatric and Primary Lymphedema Working Group (PPL WG) is one of those groups, and it covers primary lymphoedema in children and adults, and secondary lymphoedema in children up to 18 years of age.

Figures 1, 2, and 3: Illustrations by Hiroo Suami, MD, PhD, Associate Professor, ALERT (Australian Lymphoedema Education, Research, and Treatment)

Figures 7–11: LymphEd, LLC

Editorial and Design: Phyllis Fried; Kimberley Steele, MD, PhD; Sara Sapp, MS; MDM Graphic Design

ABBREVIATIONS/KEYWORDS

ACT	Acceptance and Commitment Therapy
ADLs	Activities of Daily Living
ARM	Axillary Reverse Lymphatic Mapping
BCRL	Breast Cancer-related Lymphedema
BF	Biological Female
BIS	Bioimpedance Spectroscopy
BM	Biological Male
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDT	Complete Decongestive Therapy
CLT	Certified Lymphedema Therapist
COE	Centers of Excellence
DLT	Decongestive Lymphatic Therapy
DVT	Deep Vein Thrombosis
FDA	Food and Drug Administration
GLE	Genital Lymphedema
HCP	Health Care Professional
HNL	Head and Neck Lymphedema
ICG	Indocyanine Green
ISL	International Society of Lymphology
IVC	Inferior Vena Cava
KTS	Kippel-Trenaunay Syndrome
LA	Lymphatic Anomaly
LANA	Lymphology Association of North America
LATL	Laser-Assisted Tumescent Liposuction
LD	Lymphatic Diseases
LDS	Lymphedema Distichiasis Syndrome
LE	Lymphedema
LE&RN	Lymphatic Education & Research Network
LS	Lymphatic System
LVB	Lymphovenous Bypass
LYMPHA	Lymphatic Microsurgical Preventing Healing Approach
MBCT	Mindfulness-based Cognitive Therapy
MCT	Medium-chain Triglycerides
MLD	Manual Lymphatic Drainage
MRI	Magnetic Resonance Imaging
MRL	Magnetic Resonance Lymphangiography
mTOR	Mechanistic Target of Rapamycin
MTL	Microcannula Tumescent Liposuction
NCI	National Cancer Institute
NIH	National Institute of Health
QoL	Quality of Life
RCT	Randomized Controlled Trial
SAL	Suction-Assisted Lipectomy
SSRIs	Selective Serotonin Reuptake Inhibitors
STS	Sodium Tetradecyl Sulfate
SVC	Superior Vena Cava
TCAs	Tricyclic Antidepressants
TDE	Thoracic Duct Embolization
TPN	Total Parenteral Nutrition
VLNT	Vascularized Lymph Node Transfer

INTRODUCTION

Authors: *Melissa Aldrich, MBA, PhD; Louise Koelmeyer, BAppSc(OT), PhD; Kay Pham, MD; Kimberly Steele, MD, PhD*

Welcome to the *Standardized Approach for the Diagnosis and Management of Lymphedema (LE) and Lymphatic Diseases (LD).* This comprehensive guide has been meticulously crafted by experts in the field of lymphatic medicine, in collaboration with the Lymphatic Education & Research Network (LE&RN).

We aim to provide healthcare professionals with a clear and unified framework for the assessment, diagnosis, and treatment of lymphedema (LE) and various lymphatic diseases (LD). In doing so, we strive to ensure that individuals at risk of or living with lymphedema or lymphatic diseases across the globe receive the highest standard of care, with a focus on early detection, effective intervention, and improved quality of life. This document is a product of extensive research, clinical expertise, and a shared commitment to advancing the understanding and management of lymphatic conditions. We invite you to explore this resource and embrace the opportunity to enhance the lives of those living with these often-underrecognized conditions.

As the prevalence of lymphedema and lymphatic disease continues to rise globally, it becomes increasingly imperative to establish consistent and evidence-based practices for their diagnosis and management. lymphedema and lymphatic disease, often overlooked in the past, can have profound effects on an individual's health and well-being. They not only lead to physical symptoms and complications but also impose a substantial emotional and economic burden on patients and healthcare systems. By implementing standardized protocols and guidelines, we aim to address these challenges comprehensively, ensuring that every patient, regardless of their geographical location or medical provider, receives timely and effective care. This document represents a significant milestone in our collective journey toward improving the lives of those affected by lymphedema and lymphatic disease.

The human body comprises eleven essential systems that play critical roles in maintaining overall health, including the circulatory, respiratory, integumentary, endocrine, gastrointestinal (digestive), urinary, musculoskeletal, nervous, reproductive, immune, and lymphatic systems.

Yet the lymphatic system (LS) is the only body system that currently fails to offer patients early diagnosis and appropriate therapy options that are safe, effective, and tolerable[1]. This paradox has an even greater impact when one considers that the lymphatic system bridges the functionality of two critical components to human health, namely, the circulatory and the immune systems.

The lymphatic system consists of a complex network of vessels throughout the body as well as primary and secondary lymphatic organs such as the bone marrow, thymus, spleen, lymph nodes, and mucosa-associated lymphatic tissue. The lymphatic system works in conjunction with the blood vasculature playing a key role in health by returning excess fluids and proteins from tissues to the circulation. Fluid (protein, waste, foreign bodies, lipids) that seeps out of the blood vasculature through the capillaries into the interstitial space (the space between cells) must be collected by the lymphatic system, which is a one-way system of vessels starting with terminal lymphatics and progressing through larger lymphatic vessels to lymph node basins (located throughout the body) and the lymphatic and thoracic ducts (TD) located in the upper chest, where the lymph fluid collected along the route empties into the venous circulation.

When the lymphatic system is impaired due to congenital anomalies or is secondarily damaged by trauma, cancer, chemotherapy, radiation, or surgical injury, it leads to serious consequences such as edema, lymphedema, and potentially cardiac failure. Further, immune cells cannot efficiently circulate in the body to conduct immunologic surveillance, resulting in the affected body part becoming prone to recurrent infection, or cellulitis[2].

An estimated 10 million Americans live with lymphedema (LE)[3]; more than human immuno-deficiency virus (HIV)[4], Parkinson's[5], multiple sclerosis[6], muscular dystrophy[7], and amyotrophic lateral sclerosis (ALS)[8] *combined.* Normal structure and function of the lymphatic system can be altered by congenital diseases such as primary lymphedema, lymphatic malformations or by trauma, cancer, radiation, or surgical injury resulting in secondary lymphedema. Every day, children are born with incurable lymphatic anomalies (LA), leading to life-

altering and sometimes fatal complications[9]. Up to 30% of breast cancer survivors suffer from debilitating lymphedema[10], as are those treated for prostate[11], ovarian[12], head and neck[13] cancers, and melanoma[14]. U.S. Veterans suffering trauma, infection[15], or burn pit exposure are also at risk[16]. Lymphatic dysfunction has been further demonstrated to play a key role in the pathophysiology of common chronic diseases, including obesity, diabetes, hypertension, heart failure (HF)[17] inflammatory bowel disease[18], asthma, chronic liver disease (CLD), chronic kidney disease (CKD), HIV, sepsis, hepatitis, coronavirus disease (COVID-19), neuro-degenerative disease, glaucoma, transplant rejection, and autoimmune disease. In developing countries, filariasis is the most common cause of lymphedema. In developed nations, breast cancer and cancer treatment are usually the precipitating factors. Evidence suggests that, particularly in the case of breast cancer-related lymphedema (BCRL), implementing a prospective surveillance model of care for screening, early diagnosis, and intervention can reverse or impede the progression of lymphedema from the subclinical to the clinical phase, ultimately ;the goal of preventing advancement to the irreversible chronic phase[19].

Despite its critical importance, the lymphatic system has often been underappreciated, mainly due to its largely invisible nature. This has resulted in individuals at risk of or living with lymphatic disease suffering without timely and accurate diagnoses and treatments. However, there is now a growing awareness of the significance of lymphatic medicine, thanks to the efforts of a passionate community, including those living with lymphedema or lymphatic disease, their family and friends, researchers, clinicians, and patient advocacy organizations such as LE&RN. The field of lymphatic medicine has never been more poised for major growth as government and private sector funding agencies internationally are finally recognizing its importance. Accepting the status quo in the early detection and treatment of lymphedema and lymphatic disease is not acceptable and we must do better through dissemination of knowledge, experience, and education.

This document, developed in collaboration with clinical specialists across the globe, is a standardized approach for the diagnosis and management of lymphedema and lymphatic disease. Its purpose is to provide healthcare professionals with guidelines for preventive measures and delivering consistent and effective care to individuals living with lymphatic disease, in alignment with the mission objectives of LE&RN's Centers of Excellence (COE). **By promoting knowledge dissemination, sharing experiences, and advancing education, we aim to improve early detection and treatment of lymphatic diseases, ultimately enhancing the well-being of millions of individuals affected by these conditions.**

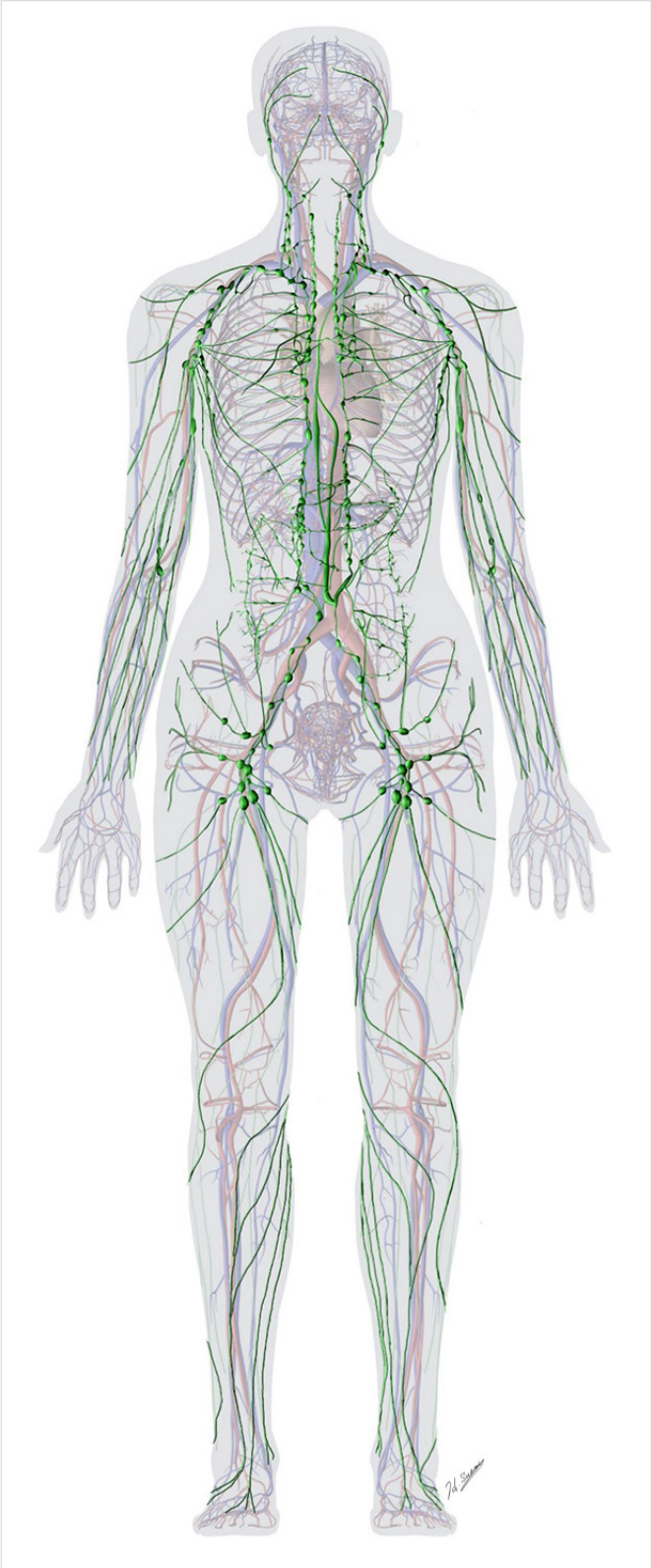

Figure 1. The Lymphatic System

SECTION 1: PRIMARY AND SECONDARY LYMPHEDEMA AND LIPEDEMA

A. CLINICAL FEATURES & DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION

Author: *Sarena Banas, PT, DPT*

A thorough medical history and physical examination are important in the evaluation of the patient with a possible diagnosis of lymphedema (LE), lipedema, or other lymphatic disease (LD). Indeed, it is key to the next steps in the management of your patient to determine immediately whether the patient is presenting with signs and symptoms of lymphedema vs. lipedema. The patient may present with similar symptoms of pain, swelling, and heaviness in the affected limb that could represent either primary or secondary lymphedema, lipedema, other lymphatic diseases, or possibly even other diseases associated with the LS.

The Patient's History

Upon initially evaluating a patient that you suspect may have a lymphatic disease, the following questions should be addressed as a part of the comprehensive history of the presenting illness:

1. When did the symptoms first begin?
2. What has been the duration of these symptoms?
3. What are the symptoms reported?
4. How does the patient describe their pain/discomfort?
   - *Lipedema is often called the "painful fat syndrome" because individuals living with lipedema describe painful hard nodules (fat) under the skin.*
   - *However, individuals living with lymphedema report that their pain is diffuse, causing a tightness and/or heaviness of the entire extremity.*
5. What makes the symptoms better? What makes the symptoms worse?
6. How have the symptoms progressed?
   - *Lipedema in the advanced stages may progress to developing symptoms of lymphedema.*
7. Any prior history of treatment for the symptoms? And, what was the outcome of the treatment?
8. Does the patient have a significant past medical history, such as recurrent infections, deep vein thrombosis (DVT), trauma, cancer, or cancer treatment, including chemotherapy or radiotherapy?
9. Does the patient have a cardiac or renal history or any medication changes that could affect diagnosis and treatment?
10. Does the patient have a significant surgical history, such as tumor resection, axillary lymph node dissection, or vascular procedures?

The Patient's Physical Exam

The most pertinent components of the physical examination should include evaluation of the skin, soft tissue, vasculature, and lymph nodes, documentation of any surgical scars or evidence for trauma, as well as a comprehensive assessment to identify any other areas on the body that may be swollen.

Differential Diagnosis: Lymphedema or Lipedema

Key points to consider when examining your patient:

- Lipedema is a bilateral condition and is generally symmetrical.
- Lymphedema can be unilateral, but commonly can be bilateral and is asymmetrical in presentation.
- Lymphedema, in its early stages, involves pitting edema, whereas lipedema presents as non-pitting edema.
- Stemmer's Sign—a diagnostic test carried out during a physical exam in which the provider pinches the skin over the dorsum of the base of the second toe. *A positive Stemmer's Sign occurs when the thickened skin is difficult to lift off the underlying tissue and is positive for lymphedema in the early stages.*
- Lipedema does not involve the feet whereas lymphedema can present with very edematous and swollen ankles and feet.
- While skin infections are common in lymphedema, it is not common to see infection in lipedema.

Special attention should be paid to the condition of the skin, the presence of skin pitting, and a comparison of limb circumferences. At the initial onset, the affected extremity may exhibit pitting, which is an indication of excess interstitial fluid moving when pressure is applied to the skin, such as is seen in lymphedema, or non-pitting, such as seen in lipedema. With chronic lymphedema, the skin may have less pitting and instead become thickened and fibrotic.

Additional findings suggestive of venous involvement may include the presence of visibly distended veins, delayed emptying of the superficial veins during elevation of the extremity, and venous telangiectasias.

Table 1. Differential Diagnosis: Lymphedema versus Lipedema

Characteristics	Lymphedema	Lipedema
Limb Involvement	Unilateral or Bilateral	Bilateral
Stemmer Sign	Positive	Negative
Symmetry	Asymmetrical	Symmetrical
Pitting	Pitting in early stages, non-pitting in late stages	Non-pitting
Skin Changes	Present in severe presentation (i.e., papilloma(s) and fibrosis)	None
Stages	0, 1, 2, 3	1, 2, 3, 4
Other Considerations	May have lymphorrhea (leaking of lymph) in severe cases; may have wounds and/or ulcers in setting of venous involvement	Tenderness, easy bruising, hips to ankles distribution/involvement

Staging of Lymphedema

The International Society of Lymphology (ISL) utilizes a staging system that refers to the physical condition of the extremities[20].

STAGE 0: Involves latent or subclinical lymphedema where swelling may not be visibly apparent, but impaired lymph transport and subtle changes in subjective symptoms may be present.

STAGE I: Occurs when high protein fluid accumulates and subsequently subsides with limb elevation. Pitting of the skin may or may not be seen at this early stage.

STAGE II: Represents progressive changes, with limb elevation being inadequate in reducing limb swelling. Pitting is most likely to occur in this stage.

STAGE III: Corresponds to the most severe grade of lymphedema where pitting can be absent and trophic skin changes such as acanthosis, skin pliability and thickness, increased deposition of fat, and fibrosis may be present[20].

Staging guidelines currently only refer to phenotypic findings, but clinicians may consider incorporating other factors such as extensiveness, occurrence of associated complications, lymphatic imaging findings, inflammation, genetic information, degree of disability, and quality-of-life issues.

Figure 2. Stages of Lymphedema

Staging of Lipedema

Lipedema is classified in stages by observational characteristics in the extremities[21]:

STAGE I: Smooth skin; homogenous increase in subcutaneous tissue.

STAGE II: Irregular skin surface, nodular changes of the subcutaneous tissue.

STAGE III: Increased lipedema tissue more fibrotic in texture with numerous large subdermal nodules and overhanging lobules of tissue.

STAGE IV: A pronounced increase in circumference with loose skin/tissue.

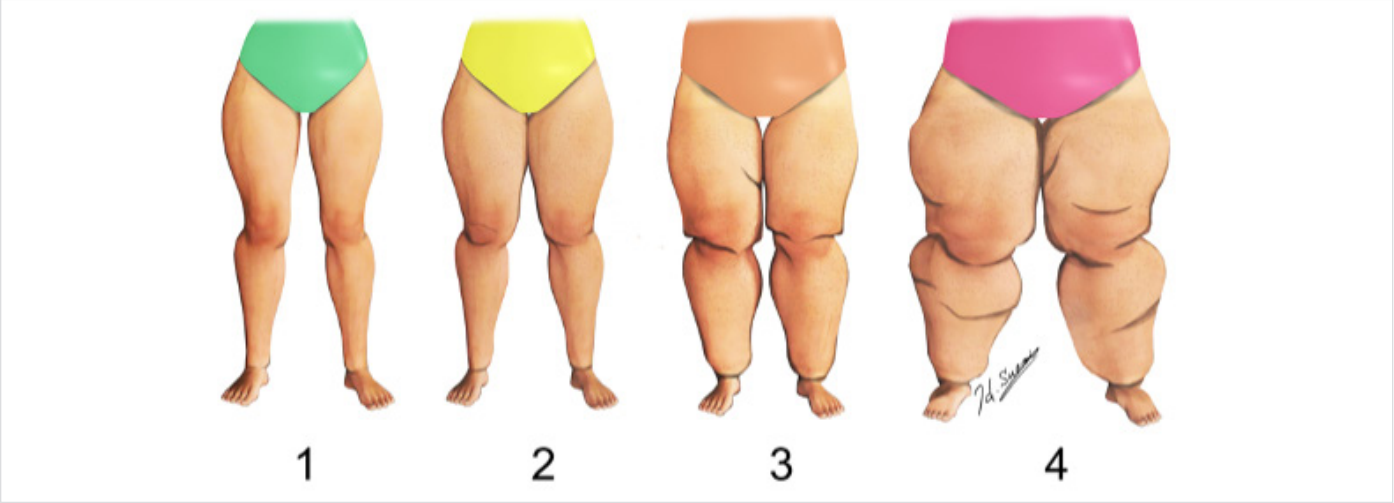

Figure 3. Stages of Lipedema

Diagnosis: A General Overview

Throughout the evaluation of the patient, the following differential diagnoses should be considered in order to conduct a more focused assessment: cancer-related or non-cancer-related lymphedema, lipedema, congenital vascular anomalies with discernment between vascular, lymphatic, and combined disorders, systemic lymphatic disorders, protein-losing enteropathy, lymphangiectasias, lymphaticovenous disease, pediatric lymphatic diseases, filariasis, podoconiosis, and complex lymphatic anomalies such as Gorham's Stout Disease (GSD), Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), Central Conducting Lymphatic Anomaly (CCLA). See *Figure 4* (on next page) for a diagnosis algorithm.

ASSESSMENT TOOLS USED IN THE DIAGNOSIS OF LYMPHEDEMA AND LIPEDEMA

Author: *Jasmine Zhang, MD, CLT, FAAPMR*

In addition to a comprehensive history and physical exam, there are additional tools that can be utilized to further measure lymphedema (LE) and lipedema. These tools can be used to assist in the diagnosis and monitoring of disease progression and response to treatment interventions. Additionally, these tools can be used in surveillance programs; for example, prior to breast cancer treatment, it is optimal to obtain pre-treatment measurements of the upper limbs for a more accurate baseline, as weight fluctuations throughout treatment can obscure lymphedema-driven limb volume changes that occur post-treatment.

Circumferential measurements using a tape measure is a common assessment method, with limb volumes easily calculated from circumference measures by using the truncated cone volume formula[22]. Measurements are completed at standard distances (typically 4 centimeters) apart along the limb using a tape measure. Baseline measurement (for example, before cancer treatment) or the unaffected contralateral limb is used as a reference, with volume differences of 200cc or 5–10% seen as diagnostic.

However, one must be aware that in complex vascular anomalies such as Klippel-Trenaunay Syndrome (KTS), Proteus syndrome, and PIK3CA-related overgrowth spectrum (PROS), individuals may present with visible overgrowth of various body parts in addition to having lymphedema, so the diagnostic criteria would not apply here. In addition, these measurements do not consider changes in fat or muscle mass.

Volume measurements can also be performed via a perometer, a machine that uses photosensors and light-emitting diodes to scan a limb. While it has good reliability, these machines are expensive and thus not readily available in non-research settings[23]. Water displacement is another tool in which the limb under

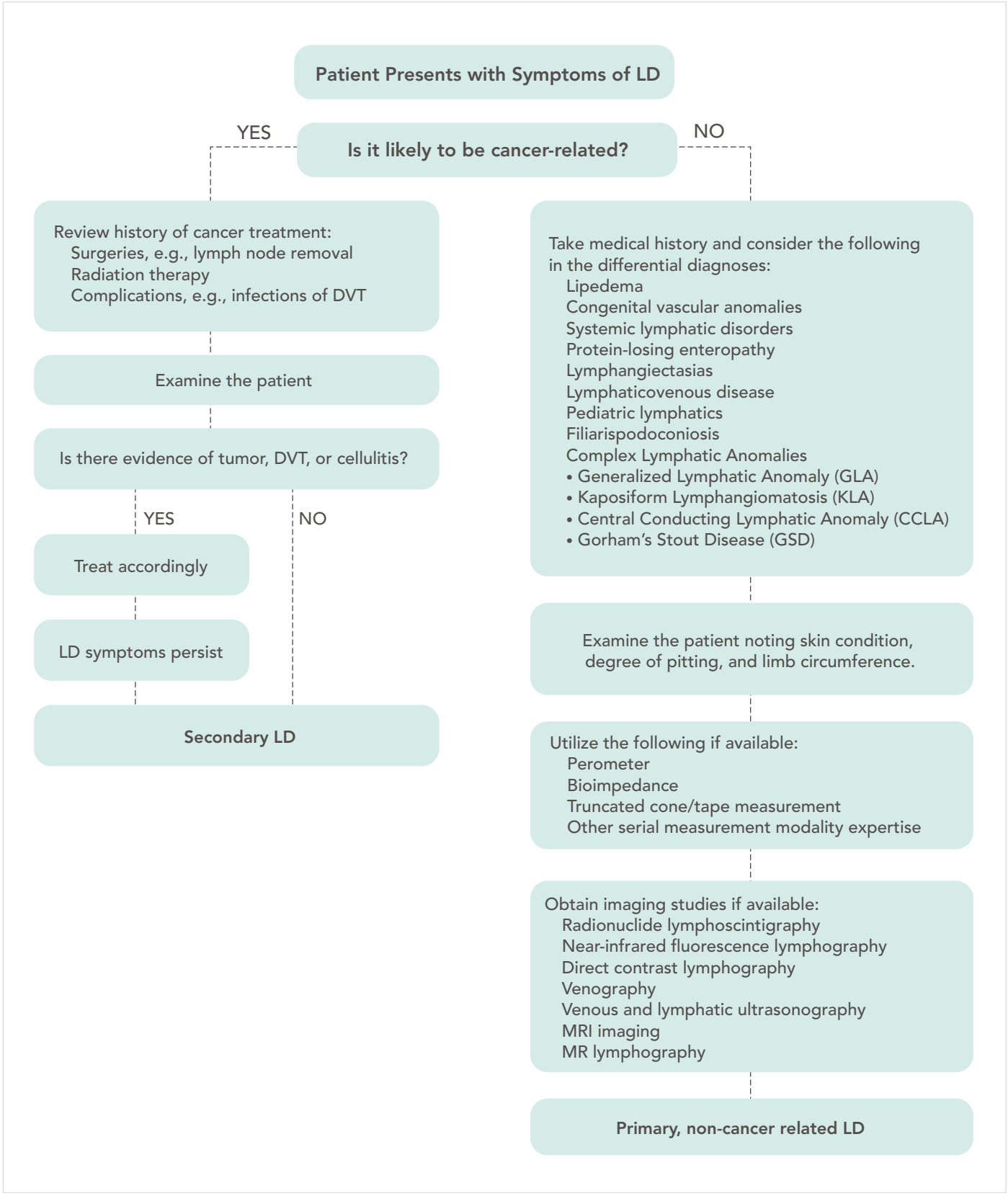

Figure 4. Algorithm in the differential diagnosis of lymphedema, lipedema, and vascular anomalies inclusive of lymphatic anomalies.

evaluation is immersed in a bath and the displaced water volume is measured. This method is time-consuming and requires access to water and a water tank with an outflow[22]. Another method involves bioimpedance spectroscopy (BIS), which has become an increasingly popular method of detecting fluid changes. BIS measures the rate of electrical current transmission through the limb as an indication of subdermal limb fluid levels. Validated mathematical models are used to calculate tissue and fluid measures. A faster transmission rate is measured through the lymphedematous limb, and it has been validated to detect subclinical lymphedema[24–26].

The above methods are not able to differentiate between lymphedema versus lipedema.

However, ultrasound imaging can provide additional details about the characteristics of the soft tissues, giving the provider information about not only whether abnormal edema is present but also whether the abnormalities are more indicative of lymphedema or lipedema. Ultrahigh frequency ultrasound has been able to demonstrate superficial lymphatic channels and the locations of adjacent venules, which has been proven particularly useful for some surgical interventions for the treatment of lymphedema such as lymphovenous bypass or anastomosis.

Ultrasound imaging demonstrating thicker skin and dermal hypo-echogenicity denotes lymphedema, whereas lipedema has been associated with increased thickness of subcutaneous fat and hypo-echogenicity subcutaneous fat[27].

IMAGING

Author: *Deborah Rabinowitz, MD*

Various imaging methods may be used to better characterize aberrant lymphatic vessels and provide a more personalized therapeutic approach. The imaging modalities discussed here are all available at LE&RN Comprehensive Centers of Excellence, Networks of Excellence, and Referral Networks of Excellence, and near-infrared fluorescence lymphography is available at LD Surgery Centers of Excellence.

Radionuclide Lymphoscintigraphy was traditionally the gold standard for diagnosis and confirmation of lymphedema28. A technetium-labeled radionuclide is injected into the interdigital tissues of the affected extremity, and images are obtained as the radiotracer emits gamma rays. The tracer is visualized as it is taken up by the lymphatic system, demonstrating the dynamic flow within the lymphatic system. Delayed tracer movement or dermal backflow confirms the diagnosis of lymphedema with reports of 96% sensitivity and as high as 100% specificity[29] however, does not provide anatomic detail. Planar lympho-scintigraphy can be enhanced with single-photon emission computed tomography (SPECT) imaging, which fuses the flow images with CT images. This adds three-dimensional anatomic detail, however has limited spatial resolution[30].

Near-infrared Fluorescence Lymphography uses indocyanine green (ICG), a non-radioactive dye used safely for over 60 years, to provide real-time imaging of lymphatic vessels and lymph nodes. Advantages of this method include high-resolution images, a safety profile with a 1/10,000 allergy risk, low invasiveness, and suitability for intraoperative imaging. Disadvantages include limitation to superficial tissue and difficulty in imaging individuals with high body mass index (BMI)[31]. Additionally, venography and ultrasonography can be used to identify concomitant venous pathology in individuals with clinical evidence of lymphedema[32].

Magnetic Resonance Imaging (MRI): MRI has become an important tool in the imaging armamentarium for both lymphedema, lipedema, and as well, complex vascular and lymphatic anomalies. Non-contrast MR demonstrates the anatomical findings of lymphedema, with characteristic high signal in the subcutaneous tissues/epifascial space on heavily T2 weighted sequences, corresponding to low signal intensity on T1 weighted sequences[33,34]. The central lymphatic vessels, including the thoracic duct, can also be demonstrated on heavily-T2 weighted sequences[34].

Lymphangiography: Lymphangiography (or lymphography) uses known imaging techniques such as X-ray (fluoroscopy), CT or MRI, and specialized dyes that are able to visualize the lymphatic system and detect abnormal anatomy and/or pathology such as lymphatic leaks.

Interstitial MR Lymphangiography (MRL) is performed with the injection of gadolinium (an MRI contrast) into the interstitial tissue of the affected extremity. T1-weighted Images are then obtained at time intervals to demonstrate both the dynamic lymphatic flow and high-resolution anatomic imaging. This demonstrates the function of the lymphatic system as well as dilated lymphatic vessels and dermal backflow35. Interstitial MRL is also used in pre-surgical planning for both lymphovenous anastomosis and vascularized lymph node transfer surgeries[36,37].

Dynamic Contrast-enhanced MR Lymphangiography (DCMRL) is increasingly utilized to visualize the central lymphatic system[34]. Intranodal injection of gadolinium is performed with direct cannulation of groin lymph nodes and injection of gadolinium during time-resolved T1 weighted imaging[38]. Lymphatic flow and anatomy are both visualized with high resolution, allowing for a detailed examination of the central

lymphatic system, the thoracic duct, and the connection with the venous system[5]. This is particularly useful in those living with a complex lymphatic anomaly, who often have both increased lymphatic flow and aberrant anatomy[39]. DCMRL can also demonstrate focal areas of lymphatic leakage in the chest or abdominal cavities, responsible for chylous ascites, chylous pleural effusions, and chylous pericardial effusions[40]. This information can then be used for pre-procedure guidance for planned embolization or lymphovenous bypasses[41]. DCMRL also confers the advantage of visualizing lymphatic masses, chylous effusions, lymphatic malformations, and associated visceral or bony lesions without a second examination. Of note, some centers have begun to utilize CT lymphangiography in lieu of MR, which allows excellent anatomic imaging but does not provide the same dynamic imaging of lymphatic flow[42].

Conventional Lymphangiography: Intra-nodal lymphangiogram with water-soluble contrast and oil-based contrast is typically performed before and during interventions. Water-soluble contrast is difficult to visualize under fluoroscopy and is typically reserved for infants. Oil-based contrast can be visualized under live fluoroscopy and can identify the anatomy and function of the lymphatic system, similar to MR lymphangiography. Oil-based contrast also has a higher viscosity and, therefore, remains within the lymphatic system for a longer period. The cisterna chyli remains radio-opaque and can be targeted and can be calculated with a microcatheter for intervention.

The same contrast agents have more recently been injected into the hepatic and mesenteric lymphatics. The hepatic lymphatics are in the peri-portal space and can be visualized with injection of water-soluble contrast or a small amount of lipiodol. This can be another route to visualize the thoracic duct or identify a lymphatic leak[43]. Mesenteric lymphangiography is performed by inserting a needle into the mesenteric lymph nodes in the mesentery surrounding the bowel. Lipiodol is then injected and can be used to demonstrate mesenteric lymphatic outflow, obstruction, or leakage[44].

DIAGNOSIS OF PRIMARY LYMPHEDEMA

Author: *Vaughan Keeley, MD*

The term **primary lymphedema** covers a group of rare genetic conditions that lead to abnormal functioning and/or development of the lymphatic system[20]. It represents a heterogeneous group that includes sporadic, hereditary, and syndromic forms. The first classification algorithm for primary lymphatic diseases was the *St. George's Classification Algorithm of Primary Lymphatic Anomalies*, developed in 2010[45] and further updated in 2013 and 2020[46,47].

This classification is based on the clinical features, the localization of the edema, and the associated phenotype. According to it, primary lymphedema is divided into five groups:

1) Syndromes
2) Lymphedema with systemic or visceral involvement
3) Lymphedema with a congenital onset (<1.0 year)
4) Lymphedema with a late onset (≥1.0 year)
5) Vascular and lymphatic malformations

Overall, this classification has the objective of providing an accurate diagnosis, as well as facilitating research into the genetic causes of the different phenotypes.

Detailed Information on the Diagnosis of:

Primary Lymphedema

Diagnosis of primary lymphedema can be challenging, and some individuals remain undiagnosed for years. It is important to receive a correct diagnosis as soon as possible after the appearance of the symptoms, in order to consider concomitant medical conditions, facilitate treatment, and reduce the risk of progression[20]. An accurate diagnosis and understanding of the cause of lymphedema are important for the implementation of optimal patient care and management[48].

We recommend the following criteria for referral to an expert center (see *Figure 5*): Patients with edema for more than three months in combination with one of the following: Congenital debut, family history of swelling, genital swelling, systemic involvement (e.g., intestinal lymphangiectasia, pleural effusions, etc.), syndromic forms, recurrent cellulitis.

In the expert center, a more detailed patient history should focus on age of onset, family history, and symptoms (e.g., pain, functional/psychological impact, heaviness). It is, moreover, essential to have information about previous surgical history (e.g., lymphadenectomy, injury, or trauma) and medical history (e.g., cellulitis/erysipelas, cancer, radiation therapy).

Physical examination must include weight, size, and BMI, while in children, a height-weight curve and head circumference should be done. Moreover, the examination should investigate the degree and stage of oedema in different body parts (e.g., legs, arms, genitalia, face) and inspect whether the edema is symmetrically distributed[49].

Lymphedema patients may develop skin problems such as warts, vesicles, papillomatosis, nail abnormalities (up-slanting toenails), and bacterial

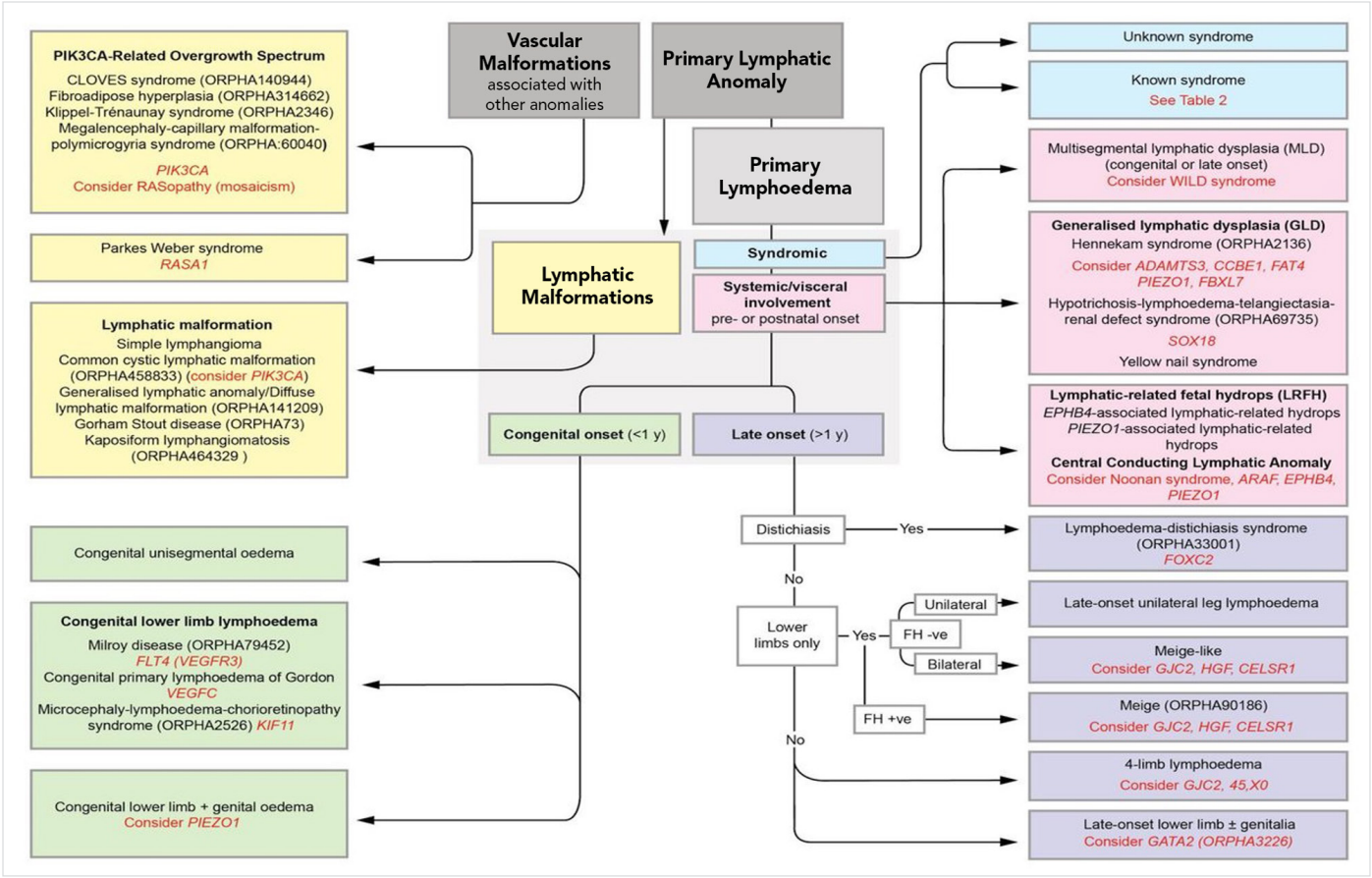

Figure 5. Differential Diagnosis in Lymphatic Disorders: The St George's Algorithm

and fungal infections. Most of these skin conditions cause a breach in the epidermis and, therefore, predispose patients to an increased risk of cellulitis/erysipelas, which often worsens lymphedema.

Most cases of primary lymphedema solely affect the extremities, but some patients may present systemic involvement that gives rise to symptoms from the abdomen[50]. In these cases, patients must be referred for relevant clinical investigations.

Since primary lymphedema is a genetic disease, it is important to screen patients for associated problems, such as segmental hypertrophy, venous insufficiency, intellectual disability, and dysmorphic features, during the diagnostic work-up.

Laboratory Tests

It is important to differentiate between isolated peripheral lymphedema and systemic forms. Systemic involvement of lymphatic impairment may be supported with blood tests. We advise in restricted cases to perform a full blood count (e.g., lymphopenia in intestinal lymphangiectasia, monocytopenia in Emberger syndrome due to GATA2 deficiency), CD4/CD8 ratio (e.g., reduced in WILD syndrome), immunoglobulins (e.g., reduced in intestinal lymphangiectasia) and albumin levels (e.g., reduced in intestinal lymphangiectasia). Furthermore, the presence of alpha 1-antitrypsin in a stool sample confirms a protein-losing enteropathy related to lymph leak into the gastrointestinal tract (e.g., in intestinal lymphangiectasia).

Imaging Techniques

Lymphoscintigraphy can be particularly useful in the diagnosis of primary lymphedema to help define the phenotype. For example, what can seem to be a unilateral lymphatic dysfunction clinically with unilateral leg swelling may prove to be bilateral on lymphoscintigraphy. Furthermore, different patterns of abnormal flow can be seen in different types of primary lymphedema e.g., lymphatic valvular incompetence in lymphedema distichiasis and functional hypoplasia (impaired uptake into the initial lymphatics) in Milroy lymphedema. Venous duplex ultrasound scans can be helpful in diagnosing venous valvular incompetence e.g., in lymphedema distichiasis. The imaging of complex lymphatic and vascular malformations and overgrowth syndromes is described elsewhere in this document.

Genetics

Primary lymphatic anomalies are a highly heterogeneous group of conditions. The classification of

these conditions has been published via the *St. George's Classification Algorithm of Primary Lymphatic Anomalies*, with its latest update in 2020. Genetic causes and testing can be structured around this classification. Genetic testing is appropriate and helpful in the diagnosis and management of children and adults with primary lymphatic disorders, so the patient may need to be referred to a genetic specialist. This field is developing rapidly, and a growing number of genetic causes are being identified each year[47].

A specific genetic diagnosis can inform about the natural history and prognosis of the condition, surveillance for associated complications, and recurrence risk for offspring or siblings of the proband. The availability of genetic testing varies from one center/country to another, although this is rapidly improving. Genetic testing is not usually indicated in those with secondary lymphedema with clear causes. However, some cases of primary lymphedema may present after minor trauma e.g., a sprained ankle, which leads to persistent swelling, where the degree of trauma would not usually be expected to cause chronic swelling. Similarly, persistent swelling after an episode of cellulitis may indicate an underlying primary lymphatic dysplasia[51].

Many of the primary lymphedema cases are single-gene disorders. These can be diagnosed on DNA extracted from blood lymphocytes from an affected individual. Testing can either be for single genes (targeted) or a panel of genes, including many or all the genes currently known to be associated with lymphedema. This is usually done by next-generation sequencing, also known as massive parallel sequencing.

The most frequent causes of primary lymphedema are listed below:

i) The FLT4 gene encodes for the Vascular Endothelial Growth Factor Receptor 3 (VEGFR3). Pathogenic variants in this gene are responsible for Milroy Disease. This presents as congenital lymphedema, particularly of the dorsum of the feet—usually bilateral but may be asymmetrical. Males have an increased risk of hydroceles (at any age) and minor urethral abnormalities (e.g., hypospadias). There is rarely swelling of any other extremity. This condition is autosomal dominant.

ii) Pathogenic variants in the FOXC2 gene cause lymphedema distichiasis syndrome (LDS). This presents with lymphedema of the lower limbs in late childhood or adulthood, varicose veins at a young age of onset, distichiasis from birth (extra eyelashes arising from the inner aspect of the eyelids), and an increased incidence of congenital heart disease, renal abnormalities, cleft palate, and spinal cysts. This condition is also autosomal dominant.

iii) One condition caused by pathogenic variants in GATA2 may present with childhood-onset of lymphedema, often in one leg and the genital area (GATA2 deficiency or Emberger syndrome). This condition is particularly important to diagnose, as it can be complicated by immunodeficiency, myelodysplasia, and leukemia. Surveillance for these complications is indicated.

iv) There are several genes resulting in a generalized lymphatic dysplasia (swelling of all four limbs, genitals, and face) with internal (systemic) lymphatic problems (intestinal lymphangiectasia, pleural or pericardial effusions or may present antenatally with fetal hydrops. These genes are usually inherited in an autosomal recessive manner. These genes include CCBE1, FAT4, ADAMTS3, FBXL7 and PIEZO1.

A child (or adult) may present with lymphedema of the extremities but also with intellectual disability, autism, structural malformations, and or dysmorphic features (unusual facial features). These patients should be carefully evaluated for the underlying cause. It is possibly due to a chromosome abnormality—which would be detected by a test called an array CGH (comparative genomic hybridization). However, some other single-gene disorders may present in this way (e.g., Noonan syndrome). In some centers, the genes for these syndromic conditions may be included in the 'lymphedema gene panel'.

Finally, some patients may have a localized genetic disorder presenting with swelling, segmental overgrowth and vascular malformations (e.g., Klippel-Trenaunay syndrome (KTS)). Testing the DNA extracted from blood lymphocytes rarely identifies the underlying genetic cause. In this group, DNA extracted from a skin biopsy from the affected limb is much more likely to identify the cause, e.g., gain of function pathogenic variants in PIK3CA.

Differential Diagnoses: Primary versus Secondary Lymphedema

In adults, causes of secondary lymphedema need to be considered. However, primary lymphedema is not simply a diagnosis of exclusion. The age of onset, family history, and clinical features as described in the algorithm *(Figure 5)* should be sought and may aid the diagnosis.

The onset of primary lymphedema beyond the age of 35 years is rare (previously known as lymphedema tarda), and consideration of secondary causes in this age group is important in making an accurate diagnosis.

Primary lymphedema in infants is sometimes difficult to diagnose when the foot and lower leg are chubby; the diagnosis becomes clearer over the following

months or years. Hamartomatous or vascular anomalies, especially cystic lymphatic malformation on the dorsal side of the foot, may mimic lymphedema. Ultrasound or magnetic resonance imaging (MRI) are required to confirm the diagnosis.

In children, the main differential diagnoses are limb hypertrophy, especially those entities attributable to the segmental overgrowth syndromes caused by somatic/mosaic phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-gene mutations and called PIK3CA-related overgrowth spectrum (PROS)52. For the differential diagnosis with primary lymphedema, PROS includes CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Skeletal and spinal anomalies), and Klippel–Trenaunay syndrome (KTS). In this context, complementary investigations (e.g., MRI, cutaneous biopsy with genetic analyses) are required[53]. Germline pathogenic variants of the RASA1 (rat sarcoma protein 21 (RAS P21) protein activator-1) gene and EPHB4 (ephrin type-B receptor 4) may present with arterio-venous malformations with an increased size of the affected limb and capillary malformations (Parkes Weber syndrome)[54,55]. More recently, somatic/mosaic variants of RASA1 and KRAS (Kirsten rat-sarcoma viral oncogene) genes have also been shown to be implicated in Parkes Weber syndrome[56,57].

Current Locations within the United States to Obtain Clinical Genetic Testing:

1. The Seattle Children's Hospital: *VANseq Vascular Anomalies Sequencing Panel* https://seattlechildrenslab.testcatalog.org/show/LAB1920-1
2. Lymphoedema–St George's University Hospitals NHS Foundation Trust (stgeorges.nhs.uk)

DIAGNOSIS OF SECONDARY LYMPHEDEMA

Author: *Rebecca Prusinski, PT, DPT, WCS, CLT-LANA (Rebecca Everetts)*

To date, there is no singular, well-defined, or generally accepted form of diagnosis for this population. The current "gold standard" diagnostic criteria for secondary lymphedema relies mostly on findings during a physical exam. The objective measures utilized in the diagnosis of secondary lymphedema include volumetric measurements, bioimpedance spectroscopy (BIS), and subjective questionnaires to assess symptom severity and impact.

- Circumferential measurements are utilized to assess the severity of swelling. These measurements can be calculated to total limb volume and differential volume between affected and unaffected limbs. Generally, a 5% limb volume difference has a 91% sensitivity rate[58].
- Bioimpedance spectroscopy (BIS) is a device used to measure the extracellular fluid volume and is marketed to be able to detect sub-clinical or Stage 0 to 1 lymphedema sooner.

Visual examination is a critical part of diagnosis. Observation of the visibility of veins, tendons, and bony landmarks can indicate the presence of edema.

Palpation of the tissue may reveal signs of edema, including thickening of the tissue, firm, fibrotic, or pitting texture.

> *Stemmer's sign is assessed on the dorsum of the hand or foot. A positive test result occurs when the skin is unable to be lifted between the index and thumb.*

Reported symptoms of secondary lymphedema include heaviness, tightness, achiness, and numbness or tingling[2].

B. TREATMENT OPTIONS FOR LYMPHEDEMA

Lymphedema can be managed through a variety of different strategies and treatment modalities. The treatment options discussed will range from conservative management to increasingly more invasive procedures, and touch on the effectiveness of additional specialty consultations. See *Figure 6* for a treatment framework which will be discussed in further detail in this section.

CONSERVATIVE MANAGEMENT: PRIMARY LYMPHEDEMA

Author: *Rebecca Prusinski, PT, DPT, WCS, CLT-LANA (Rebecca Everetts)*

Treatment of lymphedema is accomplished with the use of the gold standard approach, complete decongestive therapy (CDT). CDT should only be completed by a certified lymphedema therapist, who may be a doctor, nurse, nurse practitioner, physical therapist, occupational therapist, or massage therapist. The first component of CDT is appropriate skin care through daily washing, thorough drying, and application of emollient-based moisturizers. This step is paramount to ensuring good skin health and maintenance of an intact barrier. Depending on the patients' needs, a decongestion phase may be required to properly reduce limb volume to a more normal size with the use of short stretch bandages. Multilayer compression bandaging uses a series of protective cotton, foam, and in-elastic bandaging to

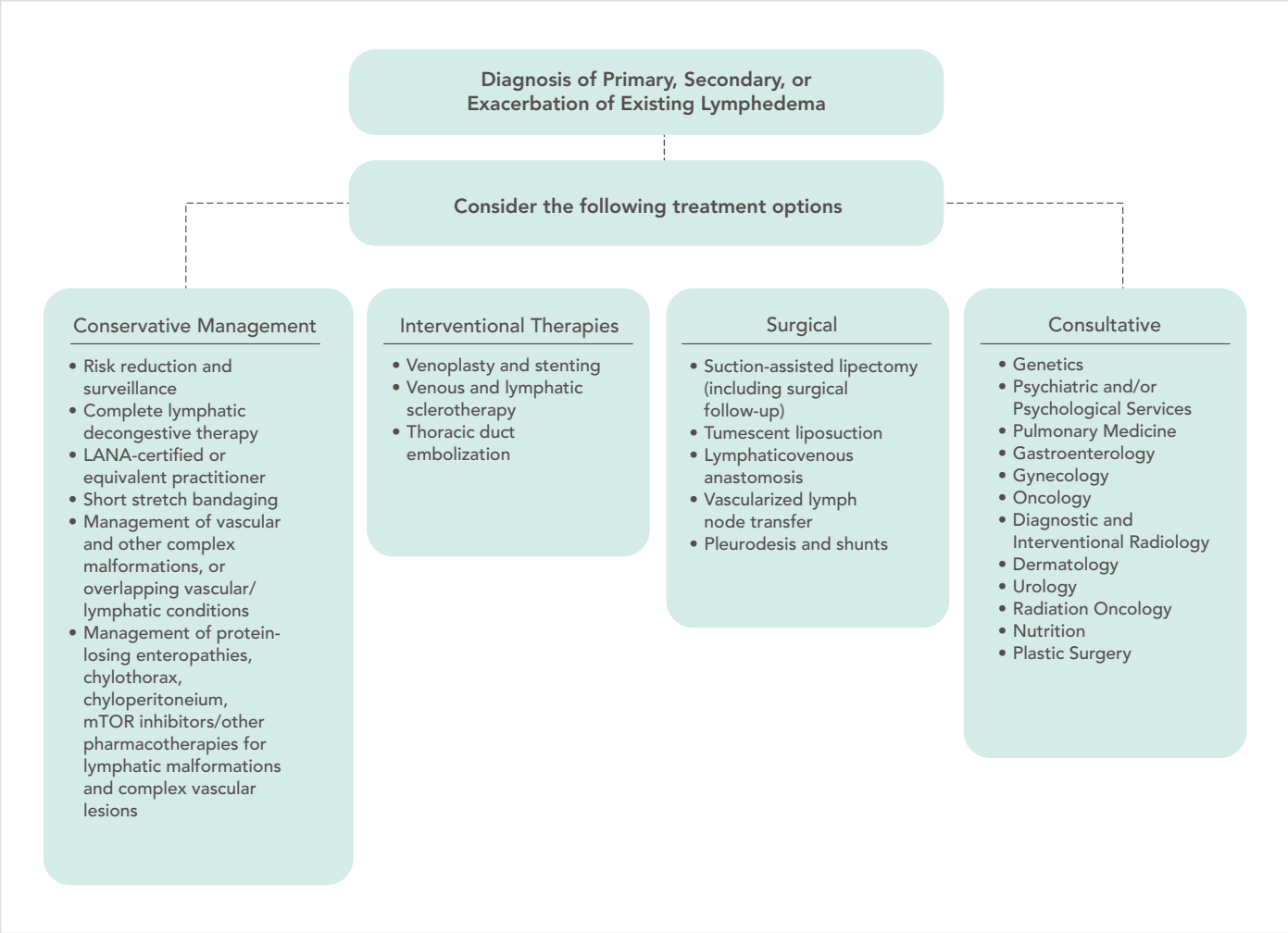

Figure 6. Algorithm with Options in the Treatment of Lymphedema

reduce edema via a compression gradient. Bandaging is applied in a specific pattern to maximize mobilization of edema.

In conjunction with multilayer compression bandaging, manual lymphatic drainage (MLD) should be utilized to increase uptake of lymph into lymph vessels, increase lymph production, and to increase venous return. MLD has an analgesic effect and can help to alleviate symptomatic swelling. Exercise that incorporates the affected limb while wearing compression is another crucial component of CDT. The muscle pump achieved inside of the limb in addition to compression on the outer surface assists the lymphatic drainage and venous return.

Finally, all individuals affected by lymphedema should be fitted with appropriate compression garments. These garments are intended to maintain the progress achieved in the decongestion phase of therapy and to prevent the progression of lymphedema. Compression needs may vary from over-the-counter, circular knit garments to custom, flat knit garments. Individuals should be measured by an experienced lymphedema therapist. Daytime compression garments (circular or flat knit) should be utilized during all waking hours of the day and certain nighttime devices may be utilized for overnight maintenance. Nighttime garments range from VELCRO® bandage alternative devices to foam-based custom pieces. Compression garments should be replaced every six months to achieve quality containment of the affected region. Some individuals with primary lymphedema may even be skilled in self-bandaging; this can be performed at nighttime in place of a foam-based or VELCRO® garment.

In the maintenance phase, individuals should maintain consistent daily use of compression, skin care, self-manual lymphatic drainage, exercise, as well as healthy eating and lifestyle habits. They should continue regular follow up with their physician and lymphedema therapist[59].

CONSERVATIVE MANAGEMENT: LYMPHEDEMA RISK REDUCTION AND SURVEILLANCE FOR HIGH-RISK PATIENTS

Author: *Robin Kauffman, PT, CLT-LANA*

Recognizing those susceptible to developing lymphedema is an important component of reducing the risk of lymphedema. Early intervention can take many forms, such as appropriate patient education and professional surveillance for high-risk individuals. Written materials, such as those available on LE&RN's website, should be offered to the patient to promote continued learning throughout the treatment process. At-risk patients should also be informed about their local lymphedema services. For the physician tasked with monitoring for the early detection of lymphedema, the following assessments should take place during office appointments:

1. A history detailing the patient's symptoms, emphasizing any changes in appearance, size, or sensation of the affected area.
2. A thorough physical examination of the affected limb.
3. Volume measurements of both limbs using any of the previously mentioned methods. Recommend that these measurements, if possible, be taken prior to treatments (e.g., surgery, radiation, chemotherapy) to document a baseline and then track changes from baseline.

COMPLETE DECONGESTIVE THERAPY (CDT)

Author: *Robin Kauffman, PT, CLT-LANA*

Current evidence suggests that complete decongestive therapy (CDT) is associated with a significant reduction in lymphedema volume60. CDT occurs in two phases (Intensive and Maintenance Phases) and consists of four components:

1. Meticulous skincare
2. Compression therapy (e.g., short stretch, multi-layer compression bandaging)
3. Manual lymphatic drainage (MLD)
4. Remedial exercise (e.g., range of motion exercises, and deep breathing).

During the first phase of treatment (Intensive Phase), skin and nail hygiene, MLD, exercise, and limb compression (utilizing compression bandaging), are repetitively utilized. This regimen is carried out four to five times per week in 60– to 90–minute sessions for a duration of two to four weeks depending on numerous factors, which include the number of limbs involved, presence and severity of wounds, tissue condition (texture of the tissue), etc.

In the second phase (Maintenance Phase), the aim is to maintain the benefits achieved in the first phase of treatment. Patients continue proper skin care, exercise, using compression garments, and, when necessary, MLD while monitoring for changes in symptomatology.

For patients undergoing CDT, a certified lymphedema therapist (CLT), Lymphology Association of North America (LANA)-certified therapist, or an equivalent practitioner can provide education and support in applying all four components necessary to complete treatment.

> *Proper measurement and fitting for bandages and compression garments is essential, as is patient compliance with wear guidelines.*

Maintenance treatment can also be supplemented with short stretch bandages, pneumatic compression, and other medical goods.

MANAGEMENT AND SURVEILLANCE OF HEAD AND NECK LYMPHEDEMA (LE)

Author: *Roman Skoracki, MD, FRCSC, FACS*

Swelling in the head and neck due to lymphedema can manifest as external swelling (present in up to 46% of patients suffering from head and neck lymphedema), internal swelling (present in 68%), or a combination of the above (present in up to 38% of patients)[61]. External swelling will manifest as pitting edema, usually in the upper neck and/or the submental region, which in more advanced cases will also affect the lower third of the face, resulting in fullness of the lower cheek(s). In more severe cases the periorbita may be involved and may even include loss of vision due to excessive upper and lower lid swelling. Patients will struggle with tightness and discomfort, as well as the aesthetic stigma of visible volume excess. However, it is the internal swelling that has a more profound impact on the patient's function, as minimal volume changes will significantly affect speech and swallow function.

As such, patients with internal head and neck lymphedema (HNL) may experience symptoms such as dysphonia, dysphagia, difficulty breathing, and restricted range of motion. These may be exacerbated and difficult to diagnostically separate from the other head and neck cancer treatment changes that result from surgery, chemotherapy, and radiation. Supraglottic, laryngeal and hypopharyngeal strictures, denervation and fibrosis will all worsen speech, swallow, and respiratory function, which will be further exacerbated by soft tissue swelling in a physically restricted space. Like other forms of lymphedema, early detection and treatment of HNL often leads to improved outcomes regarding the prevention of swelling and chronic soft tissue changes. Head and neck lymphedema is unique in that early intervention

with manual lymphatic drainage and compression will lead to complete resolution, without the need for ongoing therapy, in the majority of patients after treatment for head and neck malignancies, which is not seen in the extremities. For this reason, early diagnosis and intervention are imperative for head and neck lymphedema, where life-threatening swelling can be treated effectively. The standard of care for head and neck lymphedema[62,63], shares many of the techniques used for the treatment of lymphedema throughout the body and includes patient education, early detection, CDT, and can include pneumatic compression therapy. Studies suggest that overall edema improvement can be achieved with either home-based or hybrid-based (a combination of home and in-clinic sessions) lymphedema therapy. However, overall adherence has been shown to be a better predictor of outcome than treatment strategy. As with all other stages of treatment, it is important for patients to have the opportunity to clarify treatment techniques with their clinician, and for therapists to monitor and maintain adherence throughout the treatment process[64].

There currently exists no reproducible tool for the measurement of head and neck lymphedema as the tape measure method as described by Smith et al[62] has been shown to be invalid. 3D imaging shows great promise with great intra- and inter-rater reliability for external volume measurements. Laryngoscopy and swallow studies must be an integral part of the assessment of head and neck lymphedema patients. While no specific head and neck lymphedema patient self-reported outcome tool exists, the FACT-H&N and EAT-10 as completed by patients and the clinician-administered tools PSS-HN and FOIS will provide a good overview of the patient's functional disability as well as overall quality of life, specifically related to head and neck symptoms. We also feel that a week of intensive CDT with accurate record keeping of speech and dietary histories by the patient throughout that period will give an insight as to the contribution of the reversible swelling due to lymphedema vis a vis other non-reversible treatment effects such as fibrosis, stenosis, and denervation. The rapidity of return of speech and swallow dysfunction after a dilation will also help to differentiate. A return of dysfunction within a few days of dilation points toward internal soft tissue swelling as the primary cause of the patient's symptoms, whereas a slow return on the order of weeks to months points more toward recurrent stenosis and fibrosis. For the longer-term return of dysfunction, lymphedema cannot be ruled out as a contributing factor, and the above outlined week of intensive CDT with record keeping may help to differentiate.

ICG lymphography of the head and neck is very useful to assess a patient's candidacy for surgical intervention as well as to stage the disease. Injection sites commonly include the bilateral temples, the central glabella, the right and left forehead at the level of the hairline, in line with the lateral canthi, as well as the central lower lip in the mental crease. 0.1 cc of ICG injected intradermally in each of these sites will provide a clear image of many of the lymphatic pathways throughout the head and neck as well as areas of dermal reflux.

Surgical treatments of head and neck lymphedema include lymphovenous bypass (LVB), vascularized lymph node transplants (this may be in combination with tissue transfers that address esophageal stenosis and fibrosis at the same time), and suction-assisted lipectomy (generally used for debulking of the submental region only). Details of these techniques will be outlined in the sections below.

GENITAL LYMPHEDEMA

Author: *Shelley DiCecco, PT, PhD, CLT-LANA*

Genital Lymphedema (GLE) can occur with primary and secondary lymphedema for both biological sexes and at any age. Unfortunately, GLE is underrepresented in research and often neglected in evaluating and treating lower extremity and trunk lymphedema. The diagnosis of GLE is usually missed due to the lack of comfort in discussing or looking at one's genitalia by patients and healthcare practitioners (HCPs). The estimated prevalence is between 1~25% typically and up to 80% in some studies for biological males (BM) and biological females (BF) post-cancer treatments in the pelvis[206–213]. Filariasis is the most common cause of GLE worldwide, and according to pharmaceutical company Eisai Global, almost half of the BMs with filariasis have some form of genital dysfunction, and nearly 30% have some form of lymphedema[214]. Currently, there are no prevalence numbers for GLE with primary lymphedema. Young BMs with primary lymphedema are reported to be more likely to have GLE, up to 7x more than BFs in one study[215]. Are BMs more likely to be diagnosed due to the ease of seeing the enlarged external genitalia versus BFs, where the edema may start internally before progressing to the vulvas? One study reports the average age of onset of primary GL is 10.17 years[216], and frequently, GLE is associated with inflammatory bowel diseases (IBD), such as Crohn's disease[217–222]. The prevalence of IBD has increased over the last several years worldwide, with a change from 0.01% to 0.81% in the United States[223]. Frequently, the first symptom of IBD in children is GLE, and symptoms associated with GLE, such as edema, pain or discomfort, itching, skin changes or breakdown, and leakage of lymphorrhea or chyle in the genital region[217–222].

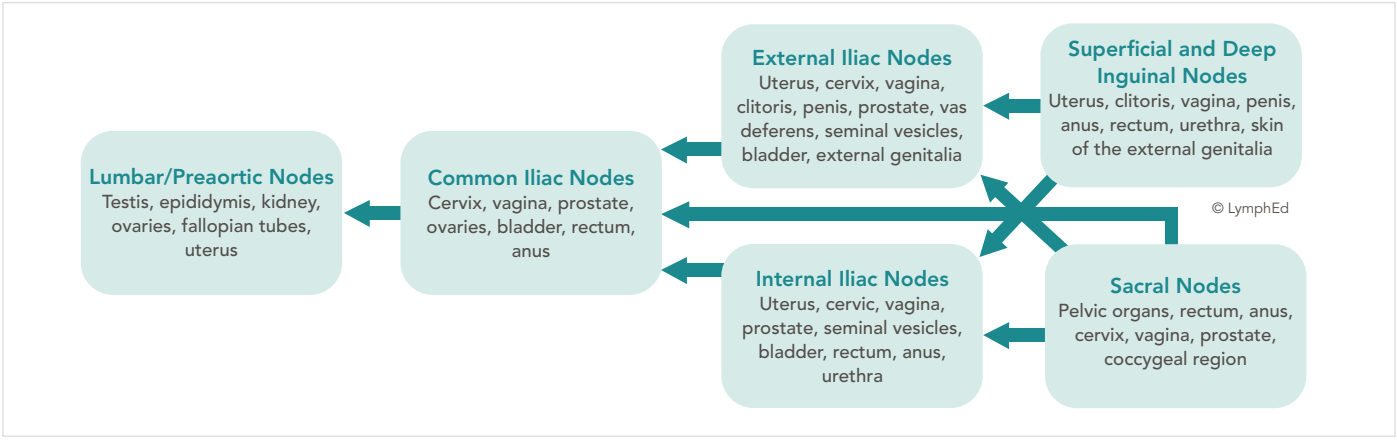

Figure 7. Drainage Routes of the Pelvic Lymph Nodes

The pelvic cavity and genitalia consist of several redundant lymphatic drainage pathways, such as two separate ones to drain the scrotum's internal and external portions, to limit edema damage to the organs or systems, and to protect the ability for procreation[208,224,225]. This redundancy can be seen in *Figure 7*. When there is a dysfunction in the pathway, through excision, trauma, overload, or other means to the lymphatic system, lymphedema will typically result in the regions directly drained by the areas of involvement and those distal to the damage. Edema with GLE can be seen unilaterally or bilaterally in the external genitalia, the mons pubis, inner thighs, and buttocks of both sexes and the vagina. The penis can be engorged by the scrotum or, as previously described, buried by the scrotum[226]. The layers of the body's skin and tissues are altered in design to meet the needs of an area, and the genitalia are no exception. The skin of the external genitalia is highly elastic to allow for fluctuations in size with intimacy and traumas, such as childbirth. This, with the assistance of gravity, allows for quick and extensive enlargement of the labias, scrotum, and penis[227–229]. The genital region is also prone to infections and skin breakdown due to the warmth and moisture in the area and the presence of microbes, urine, sweat, and feces[227–229]. The risk of infections, skin breakdown, and a quick stretch, or fill, of the skin are all reasons early intervention is crucial with GLE. The signs and symptoms associated with GLE are listed in *Figure 8*.

Individuals with lower extremity or lower trunk lymphedema, along with anyone who has undergone trauma or cancer treatments in the pelvic region, should be evaluated for GLE. Individual HCPs must check with their state's practice acts for guidelines or rules involving evaluating and treating the genital region. Individuals not formally trained in internal vaginal or rectal evaluations should refer to the appropriate providers, such as physicians, physician assistants, nurse practitioners, or PT/OT pelvic health specialists. The evaluation contains all the components previously mentioned in the Standardized Approach for the Diagnosis and Management of Lymphedema and Lymphatic Diseases, *Section 1: Primary and Secondary Lymphedema and Lipedema*, and a few additional pieces. Please refer to *Figure 9* for the additional subjective components when evaluating GLE. The key to this portion is that a medical practitioner cannot show uneasiness when asking these questions, which will increase the likelihood of less-

Signs and Symptoms of Genital Lymphedema

Directly Related to the Genitals
- Edema
- Pain
- Heaviness
- Pressure
- Discomfort
- Itching
- Incontinence (bowel and bladder)
- Constipation
- Sexual dysfunctions (dyspareunia, impotency, libido)
- Leakage of chyle
- Lymphorrhea

As a Result of Genital Lymphedema
- Body image concerns
- Limitations in activities of daily living
- Gait/ambulation deviations
- Transfer deviations
- Difficulty sitting
- Difficulty wearing clothing items
- Mental health concerns
- Intimacy difficulties

Figure 8. Signs and Symptoms Associated with Genital Lymphedema

Key Subjective Components for Genital Lymphedema Evaluations

Involvement: Penis, scrotum, labias, mons pubis, internal vagina?

Urinary History: Incontinence, difficulty voiding, pain, number of urinations during the day, number of urinations at night?

Bowel History: Incontinance, constipation, straining, number of bowel movements a day, shape, color?

Infection History: Urinary tract infections, yeast infections, prostate infectioins, cellulitis, or other bacterial or viral infections in the genital region?

Surgical/Treatment History: For any conditions involving gynecological, urological, or colorectal diagnoses?

History/Current Sexual Dysfunctions: Impotency, pain with erections (BMs) or with penetration (BFs), decreased libido, discomfort post intimacy, STDs?

Sexual Activity: Are they currently active? If not, why and would they like to be?

Prolapse: For BFs, any heaviness or pressure sensations in the vagina?

Figure 9. Key Subjective Components for Genital Lymphedema Evaluations

than-truthful responses due to a perceived shame by the patient. The Lower Limb and Genital Lymphedema Questionnaires for Men (LLGLQm) and Women (LLGLQw) were developed to assist in diagnosing GLE and with communication between patients and HCPs. Noble-Jones et al. reported that having specific questions on GLE on a typed intake document showed patients that others experienced some of the same symptoms and improved the patient's willingness to discuss GLE involvement[230–233].

To help ease the HCP and the patient into the objective portion of the evaluation, one should start with evaluating the trunk and lower extremities. Completing every other portion first allows for trust to be developed between the patient and the HCP. After gaining consent, the HCP can begin a thorough evaluation of the genitalia. True truncated cone volumetrics, like those used for the extremities, cannot be applied to the genitalia, so one must complete multiple measurements to show the full involvement

Key Objective Components for Genital Lymphedema Evaluations

Visual Inspection:

1. Location of edema/skin concerns; low back, buttocks, thighs, abdomen, lateral hip/pelvis, external genitals, vestibule and perineum
2. Tissue: any warts, signs of herpes, sores/wounds, hemorrhoids, papillomas, skin breakdown or flaking, discoloration, hair loss, or scars?
3. Any discharge from the penis, vagina, or rectum? Any leakage of chyle?
4. For BMs, is the penis being engorged by the scrotum? What is the shape of the penis?
5. For BFs, can you see any prolapse?

External Palpation:

1. Pitting or fibrosis—abdomen, low back, buttocks, thighs, scrotum, penis, labias, perineum, and vestibule.
2. Mobility of the penis foreskin?
3. Stemmer's Sign on the labias or scrotum?

Internal Palpation:

1. Any pitting/fibrosis noted in the vagina?
2. Any pitting/fibrosis noted in the rectum?
3. Any tone or pain with palpation of the pelvic floor muscles or obturator internus?

Girth Measurements:

1. For both biological sexes
   - Anterior Superior Iliac Spine (SIS) to ASIS
   - Umbilicus to ASIS or public bone
   - Trunk circumference, like umbilicus, ASIS
2. For the biological males:
   - Circumference of the penis and scrotum
   - Length of the penis
   - Anterior to posterior scrotal attachments
3. For the biological females:
   - Length of the labias
   - Width of the labias

Additional Objective Tests:

1. Girth/volune of lower extremeties
2. Gait/transfer/balance deviations
3. Strength or length of the muscles of the abdomen, pelvis, thighs, and pelvic floor.
4. Range of motion of the back, hips, and knees.
5. Can also use calipers, tissue dielectric constant instruments, and ultrasound imaging to provide more objective.

Additional Medical Testing:

1. Blood or urine tests for infection
2. Filariasis testing
3. Sexually transmitted disease testing
4. CT, MRI, ICG, or lymphoscintigraphy

Figure 10. Key Objective Components for Genital Lymphedema Evaluations

of the area. When possible, one should use the bony landmarks of the pelvis to designate repeatable measurements. The tissue in the different areas of the genitalia also needs to be assessed. Is there pitting or fibrosis? Does the tissue move, or is it adhered, especially the foreskin, if present? Stemmer Sign testing can be performed on the scrotum and labias[224,234–236]. A scrotal Stemmer Sign can distinguish lymphatic dysfunction of the scrotum's different internal (hydrocele, - Stemmers) and external (+ Stemmer's) lymphatic systems. However, both systems can be involved with significant dysfunctions. Additional objective evaluation components that are key during GLE evaluations are listed in *Figure 10*.

As mentioned in *Section 1: Primary and Secondary Lymphedema and Lipedema*, complete decongestive therapy (CDT) is the standard treatment for all types of lymphedema, including GLE. A retrospective study of 90 males from an andrology center in London, UK, with GLE showed that 62% could effectively manage their GLE with early conservative CDT and prophylactic antibiotics[237]. The true goals of CDT with GLE are to improve quality of life, reduce the signs and symptoms of GLE, and, most importantly, reduce the risk of cellulitis and the need for debulking surgical intervention. One study of 93 patients with GLE found that 85% of the males and females had at least one infection annually, and almost one-fourth had six or more infections yearly[238]. Several studies have reported that patients who underwent debulking surgeries of the involved genitalia require additional debulking procedures in the future, some as often as every 5–8 years, because these surgeries do not address the underlying lymphatic dysfunction[209,238–241]. The use of microsurgeries, lymphaticovenular anastomosis (LVA) and the new lymph node-to-vein anastomosis (LNVA), as an option for the early stages of GLE has increased and can address the actual lymphatic drainage dysfunction[208,225,240,242–246]. With either surgical approach, the patient will need to continue compliance for life with the components of CDT, especially compression, to maintain improvements and reduce the risk of cellulitis or worsening of the GLE[225,240,242,246,247].

Applying the components of CDT to the genital region can be daunting to HCPs due to the shape of the involved structures, the daily requirements of the involved systems (urinating, defecation, menstruation, intimacy), and the required mobility of the patient (sitting, standing, transfers, and gait). With some patience and creativity, all components can be successfully applied to patients with GLE. Critical points for the different components of CDT are listed in *Figure 11*. Education would encompass explaining to the patient the importance of the other components, signs and symptoms of infections, and how one can participate safely in intimate activities with GLE. Intimacy and sexuality are the two that are most often overlooked by HCPs. Sexuality is considered a basic need for individuals, and intimacy is how one connects to others in a meaningful way. The loss of these two can negatively impact one's overall quality of life. Other adjuncts to CDT can also be used with GLE. The most controversial is the pneumatic compression pump. To use safely, one must thoroughly clear the trunk with self-MLD before and after, ensure the pump

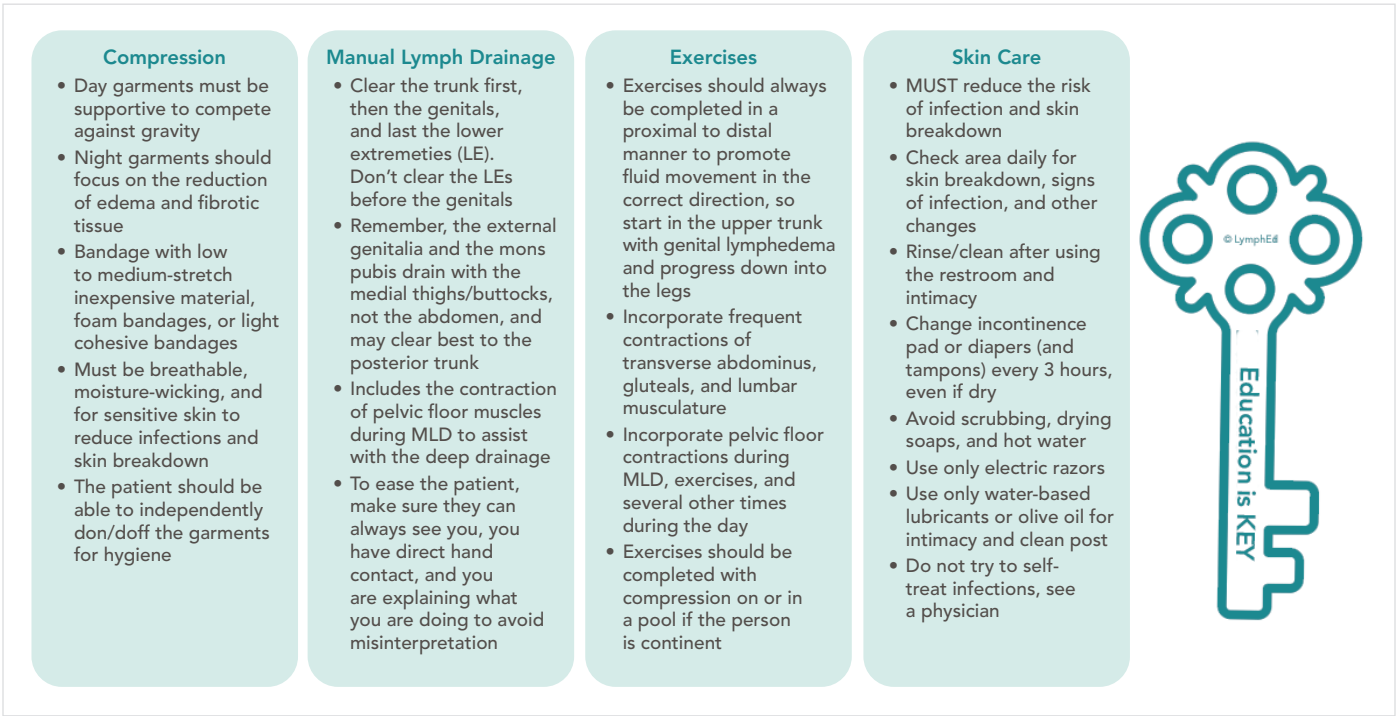

Figure 11. Complete Decongestive Therapy for Genital Lymphedema

reaches the rib area, and closely monitor the genitalia for signs of worsening. If adverse signs do appear, the pump should be discontinued. One reason the pump does not work for all is that the pump is trying to bring the fluid up from the genitals into the lower abdomen anteriorly, and this is often the least efficient way to move fluid. Gravity may assist in returning the fluid to the genitals. Elastic tape can be used on the trunk but should never be used on the skin of the genitals, for it could lead to irritations or sores on the skin. HCPs treating GLE may also need to address or refer out for other conditions related to GLE, such as incontinence, pelvic pain, prolapse, and hormone imbalances.

The ingrained belief that one should not discuss genitalia needs to be suppressed for HCPs to treat patients with GLE successfully. From clinical experience, the genitals will respond favorably with early appropriate intervention from HCPs and compliance with a robust home program. Including GLE in more studies, courses, and books or educational materials will assist in reducing the stigma around GLE and support HCPs in delivering the most appropriate evidence-based interventions to QOL of patients with GLE.

SURGICAL MANAGEMENT OF LYMPHATIC DISEASE

A. SURGICAL METHODS ADDRESSING THE TREATMENT OF PRIMARY LYMPHEDEMA

Author: *Min-Jeong Cho, MD*

Historically, surgical treatment of primary lymphedema was limited to debulking procedures such as liposuction or direct excision due to an abnormal lymphatic system in these patients. However, there has been increased evidence on the efficacy of physiological surgeries such as lympho-venous bypass and lymph node transfer in these patients. It is critical, however, to note that primary lymphedema is an umbrella term that represents a wide variety of conditions caused by several different pathological mechanisms responsible for lymphatic dysfunction. As such surgical interventions may not be successful in all cases (e.g., in cases where venous incompetence such as lymphedema distichiasis or poor uptake by the initial lymphatics in Milroy's lymphedema (see primary lymphedema section) but may be appropriate in others.

Lymphovenous Bypass (LVB)

Previously, surgical treatment for lymphedema was limited to non-physiological surgeries such as liposuction or excisional procedures. With the emergence of super microsurgical instruments and technological advances in microscopes, surgical treatment of lymphedema has evolved to include physiological surgery, which re-establishes the disrupted lymphatic system with microsurgery. Koshima *et al* described and popularized the concept of performing microsurgical lymphovenous bypass (LVB) or lymphovenous anastomosis (LVA) between a functional lymphatic vessel and a recipient vein with a diameter <0.8mm[65]. Since then, LVB/LVA has become the gold standard of treatment for patients with early-stage secondary lymphedema.

Traditionally, lymphovenous bypass is indicated in patients with MDACC (M.D. Anderson Cancer Center) ICG (Indocyanine Green) lymphedema stage 1 or 2. On the ICG lymphography, these patients demonstrate patent lymphatic vessels with patchy (stage 1) or dermal backflow segmental (stage 2), which are ideal targets for LVB. The ICG lymphangiography is performed for mapping of lymphatic channels, and LVBs are typically performed at the areas distal to the region of dermal reflux using incisions 2-cm in length. Subdermal lymphatics and venules are anastomosed in the end-to-end or side-to-end manner using an 11-0 or 12-0 nylon suture. The patency of the lymphovenous bypass is confirmed using the blue dye and ICG dye. Koshima *et al* have demonstrated that patients who underwent LVB have an average decrease in arm circumference by more than 4 cm. In addition, Chang *et al* have shown that patients who underwent LVBs had a 96% subjective improvement with a 42% volume reduction at 1 year postoperative[66].

While the efficacy of lymphovenous bypass in secondary lymphedema has been widely studied and accepted, there are limited studies on its efficacy in primary lymphedema. In a systematic review by Fallahian et al, they found a total of ten studies (254 patients with primary lymphedema) who underwent physiological surgeries67. 88% of these patients underwent lymphovenous bypass, and they had a statistically significant improvement in lymphedema. Yoshida et al found that LVB was more effective in older patients with early-stage bilateral lymphedema than younger patients with late-stage unilateral lymphedema[68]. These findings agree with current findings on the efficacy of lymphovenous bypass on secondary lymphedema. In addition, Demirtas et al found that reduction of edema was similar between primary and secondary lymphedema[69].

Vascularized Lymph Node Transplant (VLNT)

Vascularized lymph node transplant (VLNT) was first described in the 1960s, and it has become the treatment of choice for patients with moderate and advanced stages of lymphedema[70,71]. VLNT procedure involves harvesting lymph nodes from one location and transferring them to the affected area using microsurgical anastomosis. Currently, there are diverse indications and timing of VLNT amongst

reconstructive surgeons due to a varying degree of severity in patients with advanced lymphedema. Some surgeons advocate the use of VLNT in patients with early stages to prevent the progression of the disease, while other surgeons reserve VLNT for patients with a disease that is nonresponsive to physiotherapy. While there's variability, there's a consensus to offer VLNT to patients with ISL Stage 2 or patients with MDACC ICG Stage 3 or 4.

Currently, there are multiple donor sites available for VLNT: supraclavicular, submental, lateral thoracic, inguinal, omental, and jejunal lymph nodes[70,72,73]. The decision on the type of VLNT requires several considerations: the risk of iatrogenic lymphedema, donor site morbidities, and visibility of the scar. As there are different donor sites with comparable outcomes, the decision on the donor site selection depends on both patient and surgeon's preferences and needs. Despite the difference in the location of lymph nodes, studies have shown that VLNT provides comparable outcomes and improves the quality of life in patients with primary lymphedema. In the VLNT procedure, lymph nodes are harvested and transferred to the areas with lymphedema using a microsurgical procedure. Microanastomosis is performed between donor vessels of lymph node flaps and recipient vessels using a microscope. Postoperatively, patients are admitted for postoperative flap monitoring protocol.

Like the current findings on the efficacy of lymphovenous bypass on primary lymphedema patients, there are limited studies on the efficacy of VLNT on patients with primary lymphedema. In a systematic review by Fallahian *et al.*, they found that vascularized lymph node transfer was performed in 12% of patients[67]. All the studies in this systematic review showed an improvement in postoperative measurements and a decrease in the frequency of cellulitis. Cheng et al. showed that patients who underwent VLNT had a greater reduction of cellulitis than patients who underwent LVB only[74].

Liposuction

Traditionally, treatments for primary lymphedema were limited to conservative therapy, such as compression garments, decongestive therapy, and manual lymphatic drainage to prevent the progression of the disease. Similarly, surgical methods were limited to debulking procedures such as liposuction or direct excision to decrease the size of limb volume for cosmesis and functional improvement as it was believed that patients with primary lymphedema would have limited benefit from physiologic surgery due to abnormal lymphatic anatomy[75–78]. The liposuction procedure involves aspirating subcutaneous fat using a liposuction cannula attached to vacuum suction. Several studies have shown that liposuction can achieve 20–118% limb volume reduction, which can be maintained for 4 years with compression therapy. For the long-term results, Brorson showed that liposuction can achieve a mean reduction of 100% during 21 years of follow-up, which confirmed the long-term success of this technique[79]. In addition, this technique has low complication rates and leads to minor complications such as paresthesia of the skin and contour deformity.

B. SURGICAL METHODS ADDRESSING THE TREATMENT OF SECONDARY LYMPHEDEMA

Author: *Mark Schaverien, MD*

Lymphovenous Bypass (LVB)

A technique whereby obstructed yet still functioning lymphatic vessels visualized on lymphatic imaging are anastomosed to adjacent venules using microsurgical techniques, allowing diversion of lymphatic fluid from regions of stasis[80–83]. Intraoperatively, intradermal injection of indocyanine green (ICG) into the web spaces of the affected extremity allows the lymphatic vessels to be visualized using a fluorescent lymphography imaging system, with supplemental use of ultra-high frequency ultrasound (UHFUS) when available. Via short 1 cm–2 cm length incisions, anastomoses are performed between the lymphatic vessels distally adjacent to the areas of dermal backflow visualized on lymphography, using specialist super microsurgical instruments, sutures (11/0 or 12/0 caliber), and surgical techniques, under high-powered specialist microscope visualization. Systematic reviews and prospective studies reporting outcomes of upper or lower extremity lymphedema have consistently demonstrated reductions in limb volume, symptomatology, and in cellulitis incidence, as well as improvement in patient-reported quality-of-life (QoL) measures[84–88]. In these studies, around 55–85% of patients were able to decrease or discontinue their compression garment usage.

Vascularized Lymph Node Transplant (VLNT)

Vascularized lymph node transplant (VLNT) is a surgical technique that involves the microsurgical transfer of lymph nodes with their intrinsic vascular supply into areas affected by lymphedema to provide new physiological function via lymphangiogenic mechanisms[80,81,89,90]. The presence of significant dermal backflow with few or no lymphatic vessels visualized on imaging is an indication for VLNT. Reverse lymphatic mapping using preoperative lymphoscintigraphy is necessary prior to the harvest of peripheral lymph nodes (groin, lateral thoracic) within regional lymphatic basins to minimize the risk of donor-site lymphedema. Other VLN flap options include *omentum* (Latin for "apron"), a medical term referring to layers of peritoneum that surround abdominal organs[91], which may be harvested using

minimally invasive laparoscopic or robotic techniques, or cervical VLN flaps (submental, supraclavicular). Proximal (orthotopic) transfer to the axilla provides an opportunity for lysis of scar bands that result from axillary lymphadenectomy/radiation therapy which may be impeding arm range of motion or contributing[92] to the lymphedema by compression of the axillary venous outflow, and the surgery may be combined with microvascular postmastectomy breast reconstruction using an abdominal flap. There is evidence that performing LVB and VLNT synchronously may provide a synergistic benefit due to their different mechanisms of action[93,94]. A randomized-controlled trial (RCT), systematic reviews and a meta-analysis, as well as prospective and retrospective cohort and comparative studies, support the efficacy of VLNT for the treatment of lymphedema in reduction of limb volume as well as in episodes of cellulitis, functional improvement, and improved QoL, in patients with upper or lower extremity lymphedema[84,85,92,95]. Around half to three-quarters of patients in studies where this outcome was reported were able to discontinue compression therapy postoperatively, and subjective improvement was reported in around 85–100% of patients. An RCT found that outcomes following VLNT were superior to conservative management alone[92].

Suction-assisted Lipectomy

In patients with severe fibroadipose soft-tissue hypertrophy, tumescent suction-assisted lipectomy (SAL) has been shown to be effective at reducing both the limb volume and incidence of postoperative cellulitis in upper or lower extremity lymphedema in systematic reviews and meta-analyses, as well as in prospective cohort and comparative studies[28,84,96,97]. This procedure results in minimal scarring and the complication rate is low; if patients wear compression garments lifelong, the recurrence rate is low over long-term follow-up. Patients who are compliant with wearing compression garments continuously and have lymphedema with minimal or no pitting edema are candidates for surgery. Selected patients may be candidates for staged LVB and/or VLNT surgeries to improve long-term outcomes.

Direct Excisional Procedures

Excisional techniques are indicated for patients with large volume advanced fibrotic disease. These include staged direct excision (including the modified Homan's procedure), or, rarely, excision and skin grafting (Charles procedure). Studies demonstrate improved patient-reported QoL and function, however skin-grafting techniques are associated with high complication rates[84].

Risk-Reducing Surgery: Immediate Lymphatic Reconstruction

Immediate lymphatic repair (ILR) involves anastomosis of lymphatic vessels divided during axillary (or inguinal) lymphadenectomy and that are visualized by axillary reverse lymphatic mapping (ARM) to adjacent veins within the surgical field. The technique has been used predominantly in breast cancer and has demonstrated reduced incidence of lymphedema development in several retrospective and prospective studies when compared with control patients or historical cohorts that did not undergo the intervention[98]. ARM is performed prior to the lymphadenectomy using lymphazurin (isosulfan blue), ICG, or fluorescein isothiocyanate (FITC), and lymphatic vessels visualized can be spared when oncologically safe. Techniques include lymphovenous anastomosis using super microsurgical techniques, and implantation of multiple lymphatic vessels (lymphatic microsurgical preventing healing approach, LYMPHA) or intima-to-intima coaptation technique[99,100].

Venoplasty and Stenting for Venous Lesions Presenting as Lymphedema (Including Ovarian Vein ablation)

Venous obstruction due to vessel occlusion or narrowing can present as lymphedema in the affected area. Venoplasty and stenting may be considered in patients with any symptomatic venous narrowing of accepted anatomic areas such as the superior vena cava (SVC), inferior vena cava (IVC), subclavian vein, innominate vein, iliac veins, and ovarian veins. Relative contraindications include venous thoracic outlet syndrome, bacteremia, and impaired renal function in the setting of contrast agent use. Results have shown primary patency of 75%, primary-assisted patency of 92%, and secondary patency of 93% in iliac vein stenting at 3 years post-procedure. Insertion of an SVC stent has a long-term patency rate of 92%. In summary, venoplasty and stenting are low-risk procedures with high patency rates for up to 3 years and may provide symptomatic improvement in patients with lymphedema[101].

Pleurodesis Shunts

In patients with chylothorax that are unresponsive to conservative management, one of the most used second-line treatments is pleurodesis. Pleurodesis is a procedure that induces intrapleural inflammation and fibrosis through a chemical irritant or mechanical abrasion to eliminate the pleural space. Povidone-iodine has been used in a handful of case reports and case series to treat persistent chylothorax in neonates. In reports with a defined protocol, povidone-iodine was effective in up to 80% of selected cases of refractory neonatal chylothorax. Notable side effects

were rarely observed but included transient acute respiratory distress and transitory lobar atelectasis. Although current literature suggests that pleurodesis may be a viable second-line treatment for chylothorax, the lack of controlled trials does not allow for a definitive conclusion to be reached[102].

C. TREATMENT OF CELLULITIS

Author: *Vaughan Keeley, MD*

Background

The information shared in this section was approved and provided by the British Lymphology Society and taken directly from the most up-to-date *Guidelines on the Management of Cellulitis in Lymphoedema* last published in October 2022 by the British Lymphology Society (BLS) and the Lymphoedema Support Network in the United Kingdom[103].

https://www.thebls.com/documents-library/guidelines-on-the-management-of-cellulitis-in-lymphoedema

What is Cellulitis?

Cellulitis is an acute spreading inflammation of the skin and subcutaneous tissues characterized by pain, warmth, swelling, and erythema. Cellulitis is sometimes called erysipelas or lymphangitis. It is a common complication of lymphedema, with one study of its prevalence in those attending a specialist lymphedema center reporting that 37.6% had experienced at least one episode and 23.3% had recurrent cellulitis[104]. However, in lymphedema, attacks are variable in presentation and may differ from cellulitis occurring in other clinical situations. Most episodes are believed to be caused by group A streptococci[105]. However, microbiologists consider Staphylococcus aureus to be the cause in some patients, for example, Chira and Miller 2010[106].

Some episodes are accompanied by severe systemic upset, with high fever, rigors and even sepsis; others are milder, with minimal or no fever. Increased swelling of the affected area may occur. Inflammatory markers (CRP, ESR) may be raised. Cellulitis can be difficult to diagnose and to distinguish from other causes of inflammation, particularly in the legs, e.g. lipodermato-sclerosis (British Lymphology Society Red Legs Pathway: https://www.thebls.com/public/uploads/documents/document-40881639738634.pdf)

Cellulitis most commonly affects one leg only, whereas lipodermatosclerosis more commonly affects both legs.

Although cellulitis in lymphoedema is most common in the limbs, it can occur in other areas of lymphoedema, e.g. genital. Treatment may need to be different depending on the site of lymphoedema. This is addressed in these guidelines.

A Cochrane review and subsequent partial update concluded that it was not possible to define the best treatment for cellulitis in general based on existing evidence[107,108]. Furthermore, the appropriate treatment of cellulitis in lymphoedema may differ from cellulitis in other clinical situations.

Prompt treatment is essential to reduce the risk of worsening symptoms and the development of life-threatening conditions such as sepsis and to avoid further damage to the lymphatics of the affected part, which in turn may predispose to repeated attacks.

Decision to Manage Cellulitis at Home Versus the Hospital

A decision on whether hospital admission is indicated should be based on the level of system upset (i.e., signs of sepsis and continuing deterioration despite treatment).

Absolute indications for hospitalization to manage cellulitis include the following:

1. **Sepsis—**Signs of sepsis including hypotension, tachycardia, severe pyrexia, delirium, tachypnea, or vomiting).
2. **Continuing or deteriorating systemic signs,** with or without deteriorating local signs, after 48 hours of antibiotics.
3. **Unresolving or deteriorating local signs,** with or without systemic signs, despite trials with first- and second-line antibiotics.

Management of Cellulitis at Home

It is essential as the provider to monitor the patient's response to initial treatment. Your patient should be educated and advised to seek further medical attention immediately should symptoms worsen or are not responding to a 48-hour course of antibiotics and treatment.

To establish a baseline and to monitor the progress of the management of cellulitis, the following should be considered:

1. Extent and severity of rash/erythema—if possible, mark and date the edge of the erythema (may be difficult in lymphedema as the rash is often blotchy)
2. Level of systemic upset (record any system symptoms)
3. Laboratory markers–measure C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR) and complete blood cell count (CBC) with differential as these may be helpful in diagnosis and monitoring of treatment.
4. Always consider sending microbiology swabs of any cuts or breaks in the skin. This should be completed prior to the initiation of antibiotics.

Medical Management of Cellulitis: Use of Antibiotics

Cephalexin 1 gram taken twice daily by mouth (Note in the UK and Australia, the equivalent used is oral flucloxacillin 500 mg—1g 6-hourly is recommended) as the treatment of choice (NICE 2019). (NB Current microbiology guidance favors the use of the upper dose (EUCAST 2022), but gastrointestinal side effects may be more pronounced with this dose, and 1g 6-hourly is an 'off-label' dosing schedule).

Although the likely causative organisms of cellulitis in lymphedema are beta-hemolytic streptococci, microbiologists suggest the use of single-agent flucloxacillin for all cellulitis, as this covers both streptococcal and staphylococcal infections. However, from clinical experience, amoxicillin (500 mg 8-hourly) can be an effective alternative, e.g., in those who develop side effects with flucloxacillin.

In unusual circumstances, e.g., an animal bite or lick preceding an attack, should be discussed with a local infectious disease specialist.

Alternatives to Penicillin

—Patients who are allergic to penicillin should be prescribed **clarithromycin 500 mg twice daily**.

—**Erythromycin 500 mg four times daily** is preferred if a macrolide is needed in pregnancy, for example, if there is a true penicillin allergy and the benefits of antibiotic treatment outweigh the harms (NICE 2019).

For those allergic to penicillin and unable to take macrolides, e.g., because they are taking statins, **doxycycline 100 mg 12-hourly** is recommended.

No Response After 48 hours of Treatment with First Line or Second Line Antibiotics

—If there is no response or a poor response (unresolving systemic symptoms or worsening inflammation) to oral cephalexin (or amoxicillin / clarithromycin) after 48 hours, then **clindamycin 300mg four times daily** should be substituted as second line oral treatment. If signs or symptoms deteriorate despite oral flucloxacillin (at any time) consider hospital admission/IV antibiotics.

Anogenital Cellulitis

—For those with cellulitis associated with lympho-edema of the the anogenital region, flucloxacillin, or amoxicillin should be used as first-line treatment as the causative organism may be streptococcal. If penicillin-allergic, clarithromycin should be used.

—If not responding to this regimen, then the causative organism may not be streptococcal, and Amoxicllin/ Clavulinic Acid (Augmentin) 500/125 mg three times daily is recommended. For those allergic to penicillin, Bactrim DS (sulfamethoxazole 800 mg/ trimethoprim 160 mg) twice daily and metronidazole 400 mg three times daily in combination should be used.

—If these treatments are unsuccessful, advice from an infectious disease specialist or lymphedema service should be sought.

Complications from Antibiotic Treatment: Clostridium difficile

Clostridium difficile (C. *diff*) infection is a rare but serious complication of treatment with a variety of antibiotics. If your patient presents with diarrhea following a course of antibiotic(s), consider the possibility of C. *diff* If positive for C. *diff*, then the antibiotics should be stopped **immediately**, and treatment for C. *diff* be initiated immediately. Further, consultation with an infectious disease specialist is warranted to guide treatment for both the C. *diff* treatment and continued treatment for the cellulitis.

Duration of Antibiotic Treatment in the Management of Cellulitis

Antibiotics should be given for **14 days**. Experience in lymphedema clinics suggests a significant rate of early recurrence of cellulitis with shorter courses, implying incomplete resolution of the infection. Local community/hospital or NICE guidance may recommend 5–7 days of treatment but these may not be specifically aimed at treating cellulitis in lymphedema.

If recurrence/deterioration occurs soon after completion of a 14-day course, advice should be sought from an infectious disease specialist and/or lymphedema service. Longer courses are occasionally needed.

Skin changes e.g. discolouration/staining may persist for months or longer following severe cellulitis and do not require ongoing antibiotics.

Conservative and Symptomatic Management of Cellulitis

—Patients report that rest and elevation are important to help resolve the symptoms of cellulitis.

—If wearing the usual compression garment causes pain, then it should be removed but replaced as soon as the affected area is comfortable enough to tolerate it. This should reduce the risk of worsening the swelling if the garment is left off for a prolonged period, e.g., one week. The fit of the compression garment may need to be checked as the area may become more swollen after an episode of cellulitis.

—The recommended analgesia is acetaminophen (taken as directed and not to exceed 4 grams in 24 hours).

—Ibuprofen is an alternative (*Note:* It has been suggested previously that non-steroidal anti-

inflammatory drugs (NSAIDs) taken at the time of cellulitis may increase the risk of necrotizing fasciitis, but a causative link has not been proven.) One small RCT (n=48) has demonstrated no benefit of the addition of ibuprofen to IV antibiotics in accelerating the resolution of cellulitis, but no patients developed necrotizing fasciitis in this study[109].

—When the patient is feeling better, a return to normal levels of activity is encouraged.

Management of Cellulitis in Hospital Setting

Choice of antibiotics in hospital is usually made according to local hospital guidelines. Hospital guidelines commonly recommend single agent IV such as cefazolin 1 to 2 g IV every eight hours, nafcillin 1 to 2 g IV every four hours, oxacillin 1 to 2 g IV every four hours and flucloxacillin 2 g every six hours, as these choices are felt to cover both Staph. and Strep. infections. When there is evidence of clinical improvement parental antibiotics should be transitioned to an oral agent[110].

Local hospital guidelines will also recommend alternative IV antibiotics for patients allergic to penicillin.

Provided below is *The Johns Hopkins University School of Medicine Antibiotic Guidelines for the Hospitalized Patient:*

https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540106/all/Cellulitis

It is important that those with lymphedema have a total of at least 2 weeks of antibiotics (IV followed by oral) to treat an acute episode of cellulitis.

Antibiotics "In Case" ("Rescue Pack")

The risk of further recurrent cellulitis in lymphedema is high. It is recommended that patients who have a history of recurrent cellulitis carry a two-week supply of antibiotics with them, particularly when away from home for any length of time, e.g., on holiday.

The following oral antibiotics are recommended: dicloxacillin 500 mg orally every six hours, flucloxacillin 500 to 1000 mg orally every six hours (not available in the United States), cephalexin 500 mg orally every six hours or cefadroxil 500 mg orally every twelve hours or 1 g orally once daily (see 1.2.2) or, for those allergic to penicillin, clarithromycin 500mg 12-hourly or doxycycline 100 mg 12-hourly if taking statins.

An antibiotic "in case" ("rescue pack") should be started immediately when familiar symptoms of cellulitis develop, but a medical opinion should be sought as soon as possible to confirm the diagnosis and response to treatment.

Those being treated by specialist lymphedema services, especially those taking antibiotic prophylaxis, are recommended to inform their service when they have needed to use the "in case" course so that appropriate review can be planned.

Preventing or Reducing the Frequency of Episodes of Cellulitis

—There is evidence that decongestive lymphoedema therapy (DLT) reduces the frequency of attacks[111], and that compression reduces the risk of recurrence[112]. Control of the swelling is, therefore, important. Patients undergoing intensive DLT who are known to have suffered cellulitis in the past during intensive DLT may benefit from antibiotic coverage in case cellulitis is provoked. This is an uncommon occurrence, but in this group, it is suggested that a therapeutic course of antibiotics is considered for the duration of the intensive treatment.

—Other risk factors for recurrent cellulitis, including cracked and/or macerated inter-digital skin, dermatitis, open wounds including leg ulcers, and weeping lymphangiectasia (leaking lymph blisters on the skin surface), should be treated.

—Skin care, including the use of emollients as part of routine maintenance DLT, is recommended to optimize the skin's natural barrier function.

—Treatment of inter-digital fungus should be with the application of an antifungal topical such as terbinafine cream daily for two weeks. This may be followed by maintenance treatment, providing the skin is unbroken, with alcohol wipes daily.

There is evidence that surgery carried out by experienced lymphedema surgeons in combination with optimized conservative treatment in carefully selected patients may reduce the frequency of cellulitis. There is also evidence that obesity is a risk factor for the development of cellulitis (Burian 2021) and recurrent episodes. Obesity is known to reduce lymph drainage.

Weight management—in addition to the treatment of lymphedema and cellulitis—is essential in those suffering with obesity.

Prophylactic Antibiotics

If, as a primary care provider, you are considering prophylactic antibiotics, it is recommended that the use and duration of prophylactic antibiotics be made together with the local specialist lymphedema service or the infectious disease specialist if there is no local lymphedema service to consult.

When considering prophylactic antibiotics in patients with lymphedema, factor in all risk factors for cellulitis, including DLT-provoked cellulitis, history of cracked

and/or macerated inter-digital skin, dermatitis, open wounds including leg ulcers, and weeping lymphaniectasia (leaking lymph blisters on the skin surface) and history of obesity.

In addition, antibiotic prophylaxis should be considered in patients who have had two or more attacks of cellulitis per year.

The following should be considered in this decision:

1. Were the episodes all bacterial cellulitis?
2. Could they have been due to conditions such as acute venous hypertension/ lipodermatosclerosis, which are not bacterial and should be managed with compression etc. See the British Lymphology Society Red Legs Pathway: https://www.thebls.com/public/uploads/documents/document-40881639738634.pdf
3. Were the episodes bacterial cellulitis which was incompletely treated, e.g., by multiple short (5–7 days) courses of antibiotics? In this situation, the symptoms of cellulitis may resolve in a few days but recur after 2–3 weeks. This may reflect an incompletely treated single episode of cellulitis which should be treated with a longer course of antibiotics (at least 2 weeks) and counted as one episode.
4. Was there a clear, easily reversible cause e.g., athlete's foot/other skin problem? If so, treating this may reduce the risk of further cellulitis and remove the need for antibiotic prophylaxis.

Choice of Prophylactic Antibiotics to Prevent Cellulitis

—If antibiotic prophylaxis is indicated, Pencillin V K (phenoxymethylpenicillin) 250mg two times daily of if BMI33, use 500 mg two times daily should be the first choice[114].

—For those allergic to penicillin, clarithromycin 250mg daily is recommended.

—For those with penicllin allergy and taking statins, doxycycline 100mg daily is recommended.

It is recommended that patients requiring antibiotic prophylaxis for anogenital cellulitis should receive Penicillin V (phenoxymethylpenicillin) or an alternative as above if penicillin-allergic, but if this is not effective, trimethoprim 100 mg daily taken at night, should be used instead.

Following one year of successful prophylaxis, discontinuation should be considered, particularly if the risk factors described above, including DLT-provoked cellulitis, history of cracked and/or macerated inter-digital skin, dermatitis, open wounds including leg ulcers, and weeping lymphaniectasia (leaking lymph blisters on the skin surface) and history of obesity have been successfully addressed.

However, if there are ongoing significant risk factors continuing prophylaxis for a further year should be considered. If there have been no further episodes of cellulitis during this period, antibiotic prophylaxis should be stopped.

Prophylaxis may need to be life-long if relapse occurs after prophylactic antibiotics have been discontinued and there are persistent risk factors. However, ongoing regular review (at least annually, ideally by local specialist lymphedema services) is still recommended for those on long-term prophylaxis. Discontinuation again should be considered if risk factors have improved at any stage.

It may not be possible to fully prevent further episodes of cellulitis even with prophylactic antibiotics. However, there may be a reduction in the frequency of cellulitis and/or the severity of episodes.

If the response to first-line prophylactic antibiotics is inadequate, then alternative strategies, including trials of other prophylactic antibiotics, e.g., cefalexin 125 mg daily or clindamycin 150 mg daily, may need to be considered. In these circumstances, review by local specialist lymphoedema services and advice from microbiologists is recommended.

There is a need to balance the use of certain antibiotics (e.g. clindamycin, cefalexin) as prophylaxis against the risks of predisposing to Clostridium difficile infections and promoting antibiotic resistance. If at any stage with prophylactic antibiotics Clostridium difficile occurs, then those antibiotics should be stopped immediately.

It is usual practice to discontinue antibiotic prophylaxis while antibiotics are taken to treat acute cellulitis.

Antibiotic Prophylaxis to Prevent Cellulitis in Patients with Lymphedema Undergoing Surgical Procedures

Patients undergoing surgical procedures such as knee replacement or carpal tunnel surgery in the lymphoedematous region should receive a therapeutic course of antibiotics commenced before surgery (oral or IV as appropriate) as described previously or as indicated by the procedure. This would also include surgery to treat lymphedema, such as lymphaticovenular anastomosis or lymphoedema liposuction. ***The antibiotics should begin just before surgery and are usually continued for five to seven days after surgery.***

The risk of cellulitis after minor skin surgery, e.g., mole removal, is believed to be small. For minor skin procedures in people who have previously had cellulitis a single prophylactic dose of antibiotics may be considered by the operating surgeon.

Type of Operation	Previous History	Recommendation
Minor skin surgery	No cellulitis	No anbitiotics
	One attack of cellulitis	Single dose of antibiotics
	Recurrent cellulitis	Treatment course of antibiotics
More invasive surgery	No cellulitis	Treatment course of antibiotics
	One attack of cellulitis	Treatment course of antibiotics
	Recurrent cellulitis	Treatment course of antibiotics

Drug Interactions

—It is recommended that the prescriber checks individual drug interactions, particularly when prescribing macrolides, e.g., clarithromycin and erythromycin. The most common interactions are outlined below (see 4.2-4.4).

—For patients receiving a statin, e.g., simvastatin or atorvastatin, who are penicillin allergic, the recommended first-line antibiotic to treat acute cellulitis is doxycycline 100 mg twice daily.

—If these patients require prophylactic antibiotics, they should be offered doxycycline 100 mg daily.

—It is known that many of the different groups of antibiotics alter the anticoagulant effect of coumarins, e.g., warfarin. It is advised that interactions are checked before prescribing antibiotics for patients receiving coumarins.

—**Note as per** The British National Formulary (BNF), there is a possible increased risk of convulsions when NSAIDs are given with quinolones, e.g., ciprofloxacin, moxifloxacin.

Recommendations for the Treatment of Cellulitis in Children with Lymphedema

As in adults, cellulitis in children may present with local symptoms of pain, discomfort, redness, or swelling with or without general ill health and malaise (systemic symptoms). It is important to treat early and recognize that those children who present with systemic symptoms of infection or have deteriorating local signs should be seen in the hospital and treated with intravenous antibiotics. The management of cellulitis in children with lymphedema should follow the previous sections above with reference to appropriate documents (e.g. NICE 2019) to determine the required antibiotic dosing.

Provided below is *The Johns Hopkins University School of Medicine Antibiotic Guidelines for the Management of Cellulitis in Children:*

https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540106/all/Cellulitis?q=cellulitis

D. TREATMENT OF LIPEDEMA

Author: *Russell Ashinoff, MD, FACS*

Introduction

Lipedema is a painful, progressive syndrome characterized by symmetrical enlargement of the lower extremities, sometimes involving the upper extremities as well. The feet and hands are spared, and the trunk is unaffected, leading to a disproportionate deposition of subcutaneous fat on the hips, buttocks, and legs. This condition is known to affect women and is often misdiagnosed as lymphedema or obesity[115–117] almost exclusively. Furthermore, the condition has been shown to have an inherited component and run in families[118]. Symptoms often start at the onset of puberty or at other drastic hormonal or body changes such as pregnancy, childbirth, or menopause. It can also occur after an event that alters tissue structure, such as surgery or trauma[21].

The clinical features of lipedema include a "cuff sign" above the ankle, column-shaped legs, minimal pitting edema, pain, tenderness, and easy bruising. Over time, the edema progresses and becomes non-pitting[119]. The main complaint of patients diagnosed with lipedema is pain and easy bruising[120]. The pain in lipedema is mainly described to be pressing, dull, heavy, pulling, torturing, enervating, violent, unbearable, exhausting, and stabbing[121]. Many patients complain of symptoms and pain worsening towards the end of the day[119].

Lipedema Diagnosis

Lipedema is classified in stages by observational characteristics in the extremities[122]:

Stage 1: Smooth skin; homogenous increase in subcutaneous tissue

Stage 2: Irregular skin surface, nodular changes of the subcutaneous tissue

Stage 3: Pronounced increase in circumference with loose skin/tissue

Imaging of Lipedema

Lipedema is underdiagnosed due to its similarity to obesity and lymphedema. Diagnostic metrics for both ultrasound and magnetic resonance imaging (MRI) have been developed and studied to alleviate the ambiguity when considering lipedema as a diagnosis.

The following subsections will elaborate on how ultrasound, MRI, and ICG lymphography imaging techniques are being utilized to better diagnose and characterize lipedema,

Ultrasound

Ultrasound was first studied by Marshall et al in 2011 for assessing the severity of lipedema[123]. They measured thickness of the dermal and cutaneous tissue in 38 patients with lipedema 6-8 cm above the medial malleolus. They classified combined cutaneous and subcutaneous thickness of 12–15 mm as mild lipedema, 15–20 mm as moderate lipedema, and greater than 30 mm as severe lipedema. A group of 38 health controls had a combined thickness of 11.2 mm. Furthermore, ultrasound has also been studied by Amato et al as a diagnostic imaging method for lipedema[124]. In their study of 62 lipedema patients and 27 healthy controls, they found that measurements of dermal and subcutaneous thickness at three lower extremity anatomical regions were significantly larger than controls. The area of measurement at the anterior thigh region was defined as the midpoint between the iliac crest and the lower patellar border. The area of measurement of the pre-tibial region was defined as the midpoint between the anterior tibial tuberosity and the medial malleolus. The lateral leg region was defined as the midpoint between the lateral malleolus and the fibular head. Upon receiver operating curve (ROC) analysis, the best-performing area of measurement, based on the area under the curve, was found to be the pre-tibial region with an optimal cutoff value of 11.6 mm on the right (with a sensitivity of 79% and a specificity of 96%) and 11.8 mm on the left (with a sensitivity of 77% and a specificity of 92%). The authors recommend that measurements from the pre-tibial region are to be considered first followed by measurements of the thigh and the lateral leg regions.

Magnetic Resonance Imaging (MRI)

Crescenzi et al established an elevated level of sodium content and higher fat/water volume ratio as biomarkers of lipedema in a study of 10 lipedema patients and 11 healthy controls[125]. Using MRI, biomarkers were measured in both cutaneous tissue and subcutaneous adipose tissue (SAT) using the Dixon post-processing technique. Both sodium content and fat/water volume ratio were significantly greater in lipedema patients when compared to controls. The authors suggested that their findings of significantly increased intramuscular sodium and adipose content explains the symptoms of myopathy commonly reported amongst lipedema patients.

ICG Lymphography

Mackie et al used indocyanine green lymphography to study the presence of lymphedema in 40 patients clinically diagnosed with lipedema[126]. 85% of the patients did not have any evidence of any dermal backflow, and 2 patients were diagnosed with lymphedema based on the results of the lymphography. The authors suggest that ICG lymphography can be used to differentiate lipedema from lymphedema as well as help guide therapeutic management in patients who are found to have both lipedema and lymphedema.

TREATMENT OF LIPEDEMA

Conservative Management

Conservative therapy, also called complex decongestive physiotherapy (CDP), for lipedema consists of compression garments and bandages, manual lymph drainage (MLD), physical exercise, and skin care. However, because of the painful nature of lipedema, some patients cannot tolerate compression stockings[127]. In some cases, this therapy can also be combined with intermittent pneumatic compression (IPC)[116,128]. In a study of 38 women with bilateral leg lipedema, CDP, along with specialized skin care, has been shown to decrease limb volume and capillary fragility and is the most successful conservative therapy[128]. However, conservative therapy does not address fat accumulation and only treats the edema and does not have reliable long-term success[129]. Because the conservative therapy used for lipedema was designed for lymphedema patients, the best effects that are documented for lipedema patients are temporary reduction of leg volume, and CDP shows better results when patients also have secondary lymphedema as a complication[127].

SURGICAL MANAGEMENT OF LIPEDEMA

Liposuction as a Treatment for Lipedema

Liposuction using the tumescent anesthesia technique has been shown to be a safe and successful therapy for people with lipedema. A study done in 2003 by Hoffmann studied the dry liposuction technique with the tumescent liposuction technique in 9 cadavers and 18 legs to determine whether the tumescent liposuction technique is safer and causes less damage to the lymph vessels. They found that tumescent liposuction caused significantly fewer lymph vessel lesions than the dry technique and is much safer overall[130]. Furthermore, Schmeller reported that in 21 patients who followed up after having received between 1 and 4 liposuction treatments, "all experienced a satisfactory, often dramatic, improvement in body proportions". Out of 18 patients who reported spontaneous pain before surgery, 6 patients reported a complete disappearance of spontaneous pain, and 10 reported an improvement. 2 patients reported no change. Out of all the patients who reported pressure sensitivity, 13 reported

improvement, 8 reported disappearance, and 2 reported no change in this symptom. All patients reported a significant increase in their quality of life[131]. Few adverse effects seem to be present even after multiple tumescent liposuction procedures. A study done by Wollina et al. demonstrated that out of 18 patients who had multiple microcannula tumescent liposuction (MTL) procedures done, liposuction was tolerated well by all of them, and even after the first liposuction procedure, pain scores decreased, and eight women had no spontaneous or pressure-induced pain 2 weeks after completing their treatment. Mobility also increased in 16 out of 17 patients. Later in the study, laser-assisted tumescent liposuction (LATL) was added. Of the 6 patients who had both MTL and LATL, 5 reported preferring LATL because it was "less invasive, "less bruising," and patients healed faster, although there was no difference between the two procedures in the reduction of pain scores[127].

Long term studies of tumescent liposuction being used to treat lipedema have also been conducted and show promising results. Rapprich et al. studied 25 patients who received liposuction treatment and followed up 6 months after their final liposuction treatment. Leg volume was measured by 3D imaging pre- and 6 months post-op in all patients, and there was a relative volume reduction of 19.8%. In self-reported quality of life surveys conducted pre- and 6 months post-op, there was significant improvement in pain, sensitivity to pressure, and bruising. The study found an average of 58% improvement in overall quality of life[129]. In addition, Schmeller et al. conducted a long-term study of 112 patients who were evaluated at a mean of 3 years and 8 months after their initial surgery and a mean of 2 years and 11 months after their last surgery. There was a significant reduction of subcutaneous fatty tissue, and it helped in creating a more proportionate body post-surgery. Using a 7-question questionnaire they created for lipedema-related complaints, there were significant improvements in scores of spontaneous pain, pain attributable to pressure, amount of edema, bruising, reduction of movement, cosmetic impairment, and overall reduction of quality of life. Patients with stage II and III lipedema had a larger improvement than patients with stage I lipedema.

In addition to improvement in quality of life, 80.6% of patients had some sort of reduction in the need for conservative management, with 22.4% no longer needing any sort of conservative therapy[132]. Finally, in a longitudinal study, Dadras studied 25 patients who underwent multiple liposuction procedures and completed a standardized questionnaire. They followed up with each patient twice, with mean follow-up times of 16 months and 37 months, respectively. In the questionnaire, they were asked about spontaneous pain, pain upon pressure, feeling of tension, bruising, cosmetic impairment, and general impairment of quality of life pre-and post-operatively. These symptoms were significantly reduced in all but one patient in the first post-operative follow up and between the first and second postoperative follow-up, only the severity of cosmetic impairment significantly increased and there was significant improvement in all symptoms between the preoperative questionnaire and the second postoperative follow-up[133].

SECTION 2: LYMPHATIC AND VASCULAR ANOMALIES

A. CLINICAL FEATURES & DIAGNOSIS

Author: *Ionela Iacobas, MD*

Lymphatic anomalies cover a large spectrum of diseases responsible for causing lymphatic dysfunction. If the lymphatic fluid (a clear yellowish fluid) is not draining well via the lymphatic system and its vessels (either because they don't exist, are interrupted, or simply leak), then it can accumulate either diffusely between tissues (causing lymphedema) or in abnormal cystic spaces defined by their size as microcystic (small) or macrocystic (large) cysts; and classified as lymphatic malformations in the International Society for the Study of Vascular Anomalies (ISSVA) classification system[134].

If the lymphatic fluid accumulates inside the pleural space, pericardial space, or abdominal cavity, then it is called an "effusion": pleural effusion, pericardial effusion, or ascites. And, when the lymphatic fluid has already collected the lipid-rich nutrients from the gastrointestinal tract, as it passes through the mesentery, then it is no longer a clear, yellowish fluid, but instead appears as a thicker, white fluid (milky in color) and is called "chyle": chylous effusion, or chylous ascites.

Using the correct terminology to describe a complex lymphatic and/or vascular anomaly helps both diagnosis and management purposes.

Clinical example: In pediatrics, multiple complex vascular syndromes are described by the genetic mutation(s) responsible for the syndrome.

Somatic genetic alteration (not inherited from parents) causes multiple forms of lymphatic anomalies in the same patient. For example, PIK3CA-related overgrowth syndrome (PROS) results in over-proliferation of the affected tissues resulting in structure and functional anomalies. In the same patient, one can identify overgrowth of muscle or

lipomatous (adipose) tissue, cystic lymphatic malformations, areas of lymphedema, and areas with venous malformations predisposing and placing the patient at risk for developing thrombosis.

Teachable Fact:

Using lymphatic massage or lymphatic pump in an area mistaken for lymphedema but is a lipomatous overgrowth or cystic lymphatic malformations does not have any effect, while recognizing and addressing the lymphedema component in a patient with multiple elements of lymphatic dysfunction can significantly improve quality of life.

History and Physical Examination

Section A above reviews the history and physical examination key components that may help in differentiating lymphedema versus lipedema. We will now emphasize the key elements that are important to be included when considering lymphatic and vascular anomalies in the differential diagnosis.

History Elements:

As the provider, consider these "fact-finding" questions as essential in making an accurate diagnosis.

1. When was the anomaly first noted, and in what circumstances? (i.e., Did the lesion or symptoms present at birth versus in adulthood? This small detail has a high influence and impacts on management and quality of life, etc.)
2. Did it seem to increase in size after the initial presentation? (i.e., an isolated lesion versus diffuse involvement. Some clinical entities are progressive while others seem to be static/not extending outside of the original region identified).
3. What symptoms does the anomaly cause? (i.e., pain, bruising, bleeding, limitation of range of motion, recurrent infections, oozing from skin lesions, shortness of breath, fatigue, decreased appetite, other functional impairment, etc.).
4. Is there a family history of similar findings? (i.e., lymphedema may have autosomal dominant inheritance in some cases).
5. What interventions have been tried? (i.e., scarring following prior endovascular or surgical interventions may change the original characteristics of the malformation).
6. Has the anomaly affected appetite? (Consider obtaining a nutritional history (i.e., while weight gain and a history of obesity may adversely affect lymphedema and lipedema, complex lymphatic anomalies present in early childhood and may predispose the child to malnutrition. An example that we see in these cases is protein-losing enteropathy (PLE)).

Physical Examination Elements:

1. A whole-body skin evaluation may identify areas of capillary malformations or epidermal nevi that can change the initial assessment of simple lymphatic malformation or lymphedema.
2. Respiratory and cardiac evaluation is critical. One of the classic missed presentations is a child/adult who shows up in the emergency room or their primary care provider with shortness of breath and/or wheezing (often being misdiagnosed with asthma or pneumonia).

   Clinical Pearl:

   Decreased air entry or muffled cardiac sounds may represent the presence of chylothorax or pericardial effusion (because these are rare conditions, it is something we don't generally consider in our differential).

3. Head and neck evaluation (i.e., A child presenting with presence of macrocephaly which is defined as the head circumference of an infant that is > 2 standard deviations or above the 97th percentile[135] —consider raising the suspicion of PIK3CA-related overgrowth syndrome or PTEN hamartoma tumor syndrome)[136]
4. Musculoskeletal evaluation of the enlarged body part.

   Clinical Pearl:

   - *A malformation that increases in volume in a dependent position is most probably a venous malformation, not lymphatic.*
   - *Translucency exams may identify macrocystic lymphatic malformations.*
   - *Leg length discrepancy is noted in asymmetric overgrowth syndromes associated with vascular anomalies.*

The evaluating medical team should complete a comprehensive history and physical evaluation of the patient and avoid focusing on only the current complaint.

B. MANAGEMENT OF VASCULAR AND OTHER COMPLEX MALFORMATIONS, FOR OVERLAPPING VASCULAR/LYMPHATIC CONDITIONS

Patients with vascular and other complex malformations may present with heterogeneous signs and symptoms, oftentimes requiring treatment by interdisciplinary teams. Consultations with experts such as hematologists, dermatologists, interventional radiologists, vascular surgery, genetics, etc. are necessary when making decisions on laboratory testing, diagnostic imaging, and care planning.

Most interdisciplinary teams function as vascular anomaly clinics and are well equipped to treat patients with a wide spectrum of vascular disorders[137]. Treatment approaches typically include medical management and minimally invasive and interventional radiologic techniques, with operative intervention reserved for only the most severe cases.

Diagnosis will trigger management. Therefore, the correct diagnosis is essential for timely and appropriate treatment.

Clinical Example:

—Using the term "hemangioma" for a venous or lymphatic malformation will automatically result in the initiation of propranolol, which not only has no efficacy on malformations but may cause significant side effects.

—Also, not recognizing a PIK3CA-related overgrowth syndrome or generalized lymphatic anomaly delays the initiation of the appropriate targeted medical therapy that the patient needs to stabilize the disease and, therefore, improve outcomes.

C. MANAGEMENT OF PROTEIN-LOSING ENTEROPATHIES, CHYLOTHORAX, AND CHYLOPERITONEUM

In patients with protein-losing enteropathies, chylothorax, and/or chyloperitoneum, symptom severity reflects the amount of accumulated fluid and the location of the lymphatic leakage. Congenital/gestational disease, where lymph leaks into the pleural, pericardial and/or peritoneal spaces, can cause lung compression, impaired cardiovascular function, or abdominal compartment issues for the fetus. In neonatal disease, similar features may be present, and if left untreated, result in respiratory failure requiring ventilatory support or cardiac tamponade. Conservative management can take many forms, with several therapeutic measures implemented simultaneously or sequentially.

In some cases, support and observation may be the appropriate approach to allow the development of collateral lymphatic circulation and the possibility of spontaneous closure.

In cases where chyle leakage is not self-limited, replenishment of necessary fluid losses in the form of enteral or total parenteral nutrition (TPN) is essential.

Enteral nutrition, which contains a low-fat formula of medium-chain triglycerides (MCT), may promote decreased chyle production and spontaneous closure of the leak.

TPN, which must contain lipid emulsions, can be used in patients with massive chyle leakage to provide the patient with caloric support.

In all these cases, it is recommended that a highly trained nutritionist be an active member of the multidisciplinary team.

D. MEDICAL MANAGEMENT: USE OF MTOR INHIBITORS AND OR OTHER PHARMACOTHERAPIES FOR LYMPHATIC MALFORMATIONS AND COMPLEX VASCULAR LESIONS

To date, medical therapy is institution-dependent and, unfortunately, not yet standardized. We have found that sirolimus[138] and sometimes everolimus, both mTOR inhibitors, are safe and effective for lymphatic and vascular anomalies even in infants with multiple comorbidities[139]. Other agents used include trametinib, octreotide, propranolol, etc.

In recent years, lymphatic malformations were found to be caused by somatic activating mutations of PIK3CA, and targeted therapy with PIK3CA inhibitor, alpelisib, received FDA approval in 2022, marketed as VIJOICE®.

Supportive care for a patient with lymphatic effusions includes close monitoring and management of hypoalbuminemia and hypogammaglobulinemia that may predispose to recurrent and difficult-to-treat infections.

Deep lymphatic imaging, such as MRL with contrast, may be utilized to localize the source of the leakage, and more aggressive interventions may be indicated in cases that fail to respond to conservative medical management[140].

CAUTION when using mTOR Inhibitors—may be responsible for causing lymphedema.

Another consideration in treating lymphatic malformations and complex vascular lesions involves careful management of mTOR inhibitors, such as sirolimus and everolimus. mTOR inhibitors are narrow therapeutic drugs meaning that small differences in dose or blood concentrations may be a cause of serious therapeutic failures and/or adverse drug reactions that can be life-threatening or result in persistent or significant disability or interfere with activities of daily living.

Education of the patient and their families on proper medication dosing and monitoring of these drugs is essential.

It is known in the transplant and oncology literature that the use of mTOR inhibitors can carry undesirable side effects, such as unilateral or bilateral upper and/or lower extremity edema or facial/eyelid edema.

The mean interval between symptom onset and mTOR inhibitor initiation is approximately 12 months.

Additionally, patients typically exhibit lymphedema in stages II or III according to ISL staging criteria. Patients exhibiting lymphedema secondary to mTOR inhibitor use may benefit from dose reduction or if necessary careful consideration of the discontinuation of the offending agent.

Furthermore, earlier detection of lymphedema and cessation of mTOR inhibitors is more likely to prevent permanent limb changes.

E. INTERVENTIONAL THERAPIES IN THE TREATMENT OF LYMPHATIC AND VASCULAR ANOMALIES

Venous and Lymphatic Sclerotherapy

For focal venous and lymphatic malformations, sclerotherapy is considered first-line therapy. Sclerotherapy involves injecting the lesion with sclerosing agents to induce damage to the endothelium, causing a cascade of inflammation, vascular occlusion, and sclerosis. The most common sclerosing agents used today include doxycycline, sodium tetradecyl sulfate (STS), absolute ethanol, and bleomycin[141].

All sclerosing agents are considered effective, with a mean overall response rate from 71% to 100%. Complications such as cellulitis and skin necrosis have been seen following sclerotherapy, with a higher frequency of 18% occurring after ethanol sclerotherapy compared to the other sclerosing agents of 0–6%. Less common complications include facial nerve paralysis after OK-432 and ethanol use[142].

Larger or syndromic vascular malformations may benefit from a combined approach, including medical therapy, endovascular, laser, and surgical interventions[143].

Thoracic Duct Embolization for Plastic Bronchitis, Chylothorax, and Chyloperitoneum

Thoracic duct embolization (TDE) is a historic minimally invasive procedure, infrequently used now for the percutaneous treatment of plastic bronchitis, chylothorax, and chyloperitoneum. The procedure involves a diagnostic pedal lymphangiography to identify the location of the chyle leak along with anatomical variations, followed by transabdominal catheterization and embolization of the thoracic duct. Although identifying the cause of chyle leak has proven to be difficult, with one study reporting a success rate of 65%, TDE was clinically successful in 73% of patients with nontraumatic chylothoraces with thoracic duct occlusion. However, in cases of nontraumatic chylothorax with a normal thoracic duct, TDE was largely unsuccessful, emphasizing the importance of identifying the cause of the lymphatic leak to achieve better procedural outcomes[144].

At the time, the belief was that a TDE would close the lymphatic feeders responsible for the accumulation of chylothorax. However, unfortunately, while TDE resulted in immediate, short-term benefits, surgeons and interventional radiologists soon learned that these procedures can sometimes cause disruption of the normal lymphatic drainage into the main circulation, leading to significant long-term complications and morbidity.

SECTION 3: CONSULTATIVE SERVICES FOR LYMPHATIC DISEASES

A. GENETICS (SCREENING FOR KNOWN GENES AND MUTATIONS, GENETIC COUNSELING TO PATIENTS AND FAMILIES)

Author: *Salma Adham, MD*

Primary lymphedema (LE) is thought to be caused by defects in genes involved in the development of lymphatic vessels. The Lymphatic Education & Research Network (LE&RN) endorses the utilization of St. George's University Hospital's Classification Algorithm of Primary Lymphatic Anomalies, described previously[145], for the diagnosis of primary lymphedema and guide for genetic testing and management. The St. George's classification is meant to help physicians better categorize their patients and offer the possibility of molecular diagnosis. The St. George's lymphedema team performed careful phenotyping and identified five subgroups of primary lymphedema.

1. Lymphedema associated with other genetic syndromes (where lymphedema is not the predominant feature of the syndrome)
2. Lymphedema with systemic, or internal, lymphatic problems (i.e., pleural effusions, pericardial effusions, ascites, chylous reflux, protein-losing enteropathy/intestinal lymphangiectasia, or fetal hydrops)
3. Congenital lymphedema (present at birth or within the first few months of life but with no systemic involvement)
4. Lymphedema that occurs later in life (after 1 year of age, but with no systemic involvement)
5. Lymphedema may be associated with lymphatic malformations, vascular malformations, or segmental overgrowth problems.

Within these subgroups, genetic mutations common to the cohort were successfully identified. A molecular

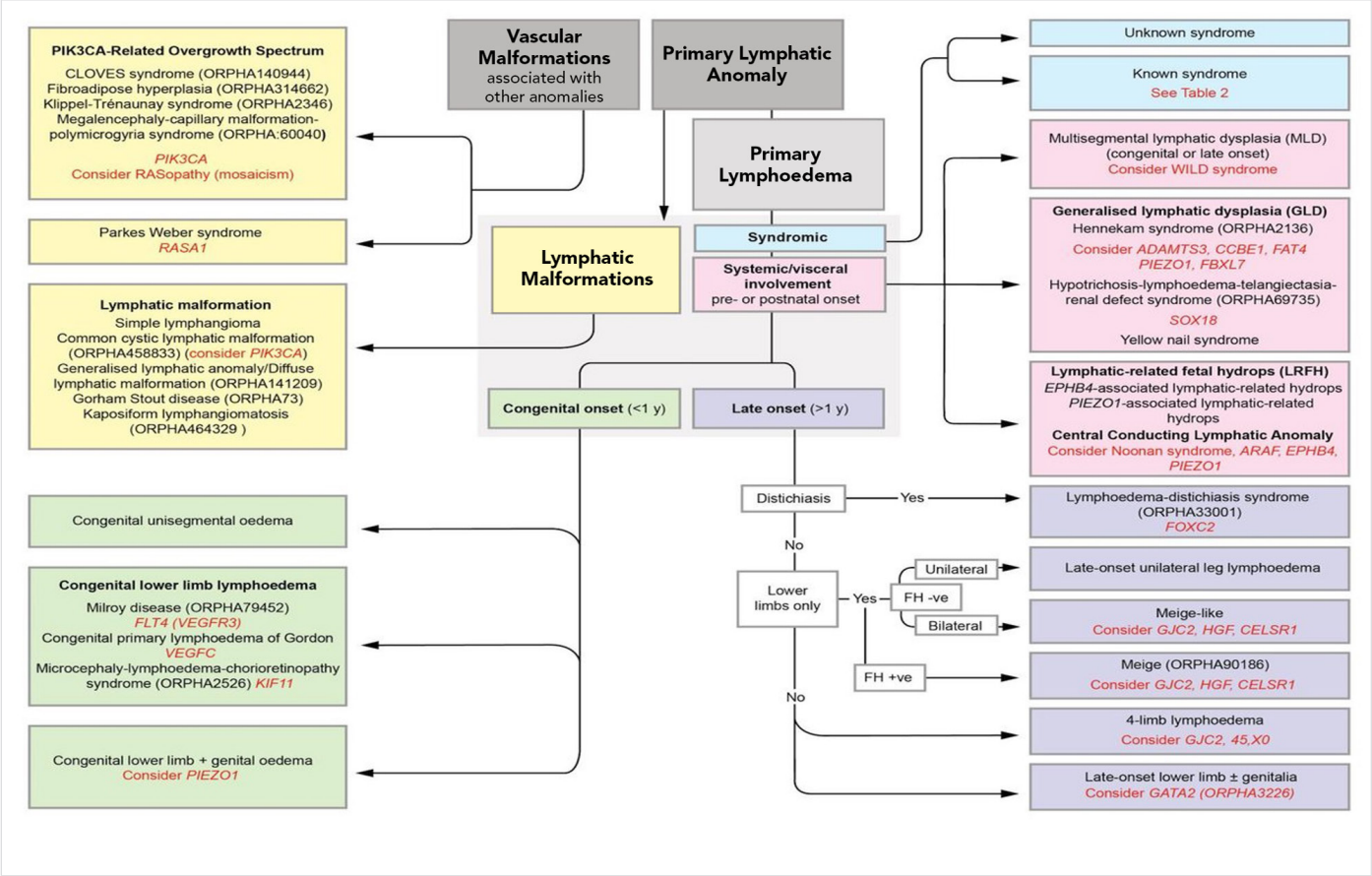

Figure 12. St George's Classification Algorithm of Primary Lymphatic Anomalies

diagnosis can be used to inform the patient and family members of inheritance patterns, likely prognosis, and screening of diseases the patient or relatives may be at risk of developing. The St. George's classification has been updated in 2020 and aligns with the 2018 ISSVA classification of vascular anomalies.

As an example, for using the algorithm, follow the steps detailed below (and see *Figure 12*).

1. Start in the dark gray box titled "Primary Lymphatic Anomaly" and move through the pathway by identifying which subgroup to which your patient belongs.
2. Determine if your patient is "syndromic" (blue box), meaning that the patient exhibits a constellation of characteristics likely, including dysmorphic features.
3. If your patient does not have a genetic syndrome, determine if there are associated internal/systemic lymphatic problems (pink section).
4. If syndromes or systemic involvement have been excluded, move to the green section for congenital swelling or the purple section for swelling that comes on after the first year of life.
5. If your patient has pedal lymphedema present at birth with no syndromic or systemic features, Milroy disease is likely, and the patient should be tested for mutations in *VEGFR3*. If Milroy disease can be confirmed, advice pertaining to natural history, prognosis, and risks should be given to the patient and their family.
6. If your patient has late-onset lymphedema, three diagnoses remain on the differential.
   a. Lymphedema distichiasis syndrome (LDS) due to mutations in the *FOXC2* gene with associated varicose veins, congenital heart disease, cleft palate, spinal cysts, and renal problems
   b. Emberger syndrome due to mutations in the *GATA2* gene with associated warts, monocytopenia/pancytopenia, and predisposition to myelodysplasia and acute myeloid leukemia
   c. Meige disease for which no causal gene has been identified.

With new genes associated with the development of lymphedema continuously being studied, the algorithm is likely to be revised as new developments occur in the field of lymphedema research. Nonetheless, the latest version of the algorithm remains a good working model for the present genetic screening and counseling needs of patients and families affected by lymphedema[47].

Early examples in the genetics of primary lymphedema involve genes such as FLT4 and FOXC2, identified in Nonne-Milroy disease and lymphedema-distichiasis syndrome, respectively. These genes were discovered through classical human genetic approaches using linkage studies in large families with a history of lymphedema. Later findings in mice (*PROX1, ANGPT1, ANGPT2*) and zebrafish allowed us to enlarge the number of genes possibly involved in primary lymphedema.

The core of the lymphatic pathway is the *VEGF-C/VEGFR3* axis. However, other ligand-receptor signaling pathways are progressively identified. These new pathways include ANGPT2-TIE1 or TIE2, HGF-MET. There are also phenotypes that carry a pathogenic variant in one of the RAS/MAPK pathway proteins. As many as 31 loci and genes have nowadays been confirmed as involved in primary lymphedema. Eighteen other genes have been suggested as lymphedema genes and need to be confirmed either in additional patients or through a functional validation of the variants. These genes are involved in the initiation of lymphatics, lymphatic valve formation, expansion, and proliferation of lymphatics. Chromosomal disorders are also associated with lymphedema, such as Turner syndrome, Prader-Willi syndrome, and more rare diseases such as Phelan-McDermid syndrome. There are also overgrowth syndromes that involve lymphatics, such as *PIK3CA* or *AKT1* mutations[146].

Molecular diagnosis is nowadays a routine exam in referral centers taking care of patients with primary lymphedema. In most cases, gene panels are performed; however, with the increasing number of new genes discovered in primary lymphedema, whole exome sequencing might become a most interesting option.

Being able to precisely describe the phenotype of our patients is the core of genotype-phenotype correlations, as genetic testing will increase our experience and our knowledge both in variable expressivity and incomplete penetrance. Genetic counseling will, therefore, be improved by the better stratification of the lymphatic subtypes of the patients. As the use of genetic testing as a diagnostic tool continues to rise, enabling more precise molecular diagnosis and family screening, it will be important to set up personalized support for family members to prevent lymphedema if it is still infraclinical and to treat it if already diagnosed.

Others

The visible accumulation of fluid seen in lymphedema patients may negatively impact psychosocial well-being due to diminished quality of life and the development of psychological problems such as anxiety and depression. Major contributing factors to the psychosocial effects of lymphedema may include physical symptoms, lack of social and emotional support, time-consuming medical care, lack of sensitivity and awareness amongst the public, inadequate health insurance, and associated financial burdens[147]. Additionally, body image-related concerns may manifest as problems with sexual well-being, including sexual pain and dysfunction[148]. Specialist services may be of use in terms of effectively addressing such concerns. Consultative services may include but are not limited to:

- psychiatry and psychology for mental-emotional disorders and relational counseling services for the development of effective coping strategies,
- gynecology for problems with sexual pain and dysfunction,
- oncology for cancer-related pain,
- dermatology or wound care for skin-related changes and infections,
- Occupational therapy when LD affects the ability to work, and
- other referrals for the improvement of quality of life.

B. MENTAL HEALTH

Authors: *Kay T. Pham, MD, Alexander M. Kaplan, MD, MPH*

Introduction

Lymphedema, lipedema, and vascular and lymphatic anomalies are chronic conditions that impact a person's physical, psychological, and social functioning. A comprehensive understanding of biopsychosocial factors in lymphatic disease and their impact on mental health will help providers address patients' unmet psychosocial needs and empower patients to better manage their condition to experience a higher quality of life (QoL). **Here, we review the physical, psychological, and social effects of lymphatic disease as it pertains to mental health.** We discuss psychotherapeutic approaches as they relate to the aforementioned factors. In closing, we discuss psychotropic medications and potential adverse effects relevant to patients with lymphatic disease.

Physical Effects

The physical effects of lymphedema and other lymphatic diseases vary, given a wide range of manifestations and severity. Symptoms may include pain, upper or lower extremity disability, progressive dyspnea, shortness of breath, and abdominal distention due to pericardial effusions, pleural effusions or ascites, and impediments in speech and swallowing, to name a few. These effects can

negatively impact activities of daily living (ADLs), general functionality, and mobilization. Patients may describe their symptoms as "swelling, soreness, tenderness, aching, burning, stabbing, numbness, heaviness, tightness, rigidity, fatigue, and tiredness."[149] Associated physical difficulties present in daily tasks such as cleaning, cooking, dressing, shopping, and self-care activities[150]. Patients are also prone to recurrent episodes of cellulitis or erysipelas. Lymphatic system-associated structural changes and impaired antigen-presentation mechanisms may lead to a reduction in the skin's ability to prevent pathogen entry, resulting in chronic or recurrent soft tissue infections [151].

Psychological Effects

Lymphedema and lymphatic diseases negatively impact psychosocial well-being due to diminished QoL, stigmatization, disruption of interpersonal relationships, and the development of psychological problems such as anxiety and depression. Major contributing factors to the psychosocial effects of these chronic diseases include physical symptoms, lack of social and emotional support, time-consuming medical care, lack of sensitivity and awareness amongst the public, inadequate health insurance, and associated financial burdens[147]. Body image and sexuality-related concerns may manifest with depression, anxiety, and stress. In breast cancer patients, psychosocial sequelae of breast cancer have been associated with oncological treatments, including surgery, radiation, chemotherapy, and hormone therapy. Body image and self-confidence may be marred by dissatisfactory cosmetic outcomes from surgery, body (notably breast) asymmetry following radiation, and ovarian failure with menopausal symptoms and infertility secondary to chemotherapy and hormonal therapy[152].

Notably, increased risk for depressive symptoms during the menopause transition has been observed in large, longitudinal studies such as the Harvard Study of Mid-life Mood and Cycles[153], the Australian Longitudinal Study of Women's Health[154], and the Seattle Midlife Women's Health Study[155]. In patients with lipedema, many have experienced psychological distress due to "weight-shaming," given the increased prevalence of comorbid obesity or a misconception of lipedema as obesity. Research has shown a prevalence of depression among patients with lipedema between 31 and 59% and eating disorders at 18%[156]. In patients with oral maxillofacial vascular malformations, increased anxiety and depressive symptoms were associated with facial vascular malformations and decreased utility of social support with poor emotional illness perception[157]. These findings underline the necessity of providing patients with lymphedema and lymphatic diseases with appropriate psychological consultation.

Social Effects

The social impact of lymphedema and lymphatic disease encompasses struggles in multiple domains, including condition-related self-disclosure to social networks, social stigma (i.e., related to wearing compression garments), occupational and educational limitations and restrictions, and sexual dysfunction. Cultural factors and related distress may be found within the familial unit. For example, the patient's social role within the family may be challenged or exacerbated by unsupportive or unhelpful responses to limitations in ADLs or role expectations. Unfavorable prognoses or diagnoses (i.e. previous cancer diagnosis) may influence whether patients choose to disclose a diagnosis of lymphedema[158].

Compression garments exacerbate distress as patients may be considered by themselves or others as unsightly; additionally, such garments serve as a constant reminder of the cancer experience in BCRL. Lymphedema and the use of compression garments are further associated with adverse occupation functionality and outcomes, including reduced work productivity, delay in return to work, unemployment, decreased income, and diminished work capacity[159]. Unsurprisingly, detrimental effects are also frequently described in patients' familial and romantic relationships. Patients with lymphedema and sexual challenges may struggle with feeling misunderstood by their partners, shame, poor self-esteem, and sexual pain and dysfunction[148].

Social impairment has also been reported in patients with lipedema and those with facial vascular and/or lymphatic malformations. A higher prevalence of social impairment (fearfulness, loneliness, isolation) in the later stages of lipedema is linked to increased exposure to weight stigma[156]. Patients with facial vascular and/or lymphatic malformations, particularly teenagers, experience difficulties with public appearances and making new friends. Parents of these patients have also reported experiences of loss, accusations of child abuse[160], negative stares, and avoidance of public places, including that of enrolling their child in daycare[161].

Psychotherapeutic Considerations

Patients at all stages of lymphedema treatment should be routinely screened for anxiety, depression, and concerns regarding sexual well-being. The *Patient Health Questionnaire-9*[162] and the *Generalized Anxiety Disorder* 7-item scale[163] are reliable and valid measures of depression and anxiety severity, respectively. Psychotherapy should be offered and may be helpful in addressing loss, anticipatory grief, self-worth, and normalization of the experience. It is imperative that providers within the care team assess how patients feel about lifestyle modifications, changes in family roles,

fears of dependency, and social support networks. Currently, there is a lack of literature examining the impact of evidence-based psychotherapeutic modalities in patients with lymphedema; however, the current state of evidence supports their utilization in cancer patients as well as those with chronic conditions (e.g., chronic obstructive pulmonary disease). Specifically, cognitive behavioral therapy (CBT) is an established treatment that guides the patient in challenging and changing cognitive distortions and their connected behaviors, resulting in an improved emotional state and mood regulation. One meta-analysis concluded that CBT is effective in improving QoL in cancer patients and reducing anxiety, depression, and stress symptoms[164]. Other studies have shown that brief CBT improved illness intrusiveness in veterans[165] and health outcomes (anxiety, depression, breathlessness, QoL, and exercise capacity) in patients with COPD[166]. The improvement in psychological health is partially possible through the reduction of rumination about past events and persistent worries about the future[164]. Mindfulness-based cognitive therapy (MBCT) incorporates cognitive behavioral methods like psychoeducation and cognitive restructuring; MBCT research has shown promising results in the reduction of anxiety and depressive symptoms, fear of recurrence, and fatigue in patients with nonmetastatic breast cancer[167], and other chronic conditions such as chronic migraine and medication overuse headache[168]. Other studies are ongoing in the study of MBCT in patients with inflammatory bowel disease[169]. Acceptance and commitment therapy (ACT) is a robust therapeutic approach that focuses on increasing resilience to discomforting emotions; important aspects of ACT include acceptance, cognitive diffusion, contact with the present moment, self-as-context values, and committed action. ACT has been effective in the short-term reduction of depressive symptoms and demonstrated positive effects on pain acceptance and psychological flexibility in women with breast cancer; however, effect sizes were small, and statistically significant effects that lasted up to 12 months were only found for anxiety symptoms[170]. Reduced levels of fatigue were also seen in a meta-analysis of patients with chronic conditions inclusive of fibromyalgia[171]. Improvements in depression and anxiety were reported in patients with inflammatory bowel disease treated with ACT[172].

Patients with lymphedema and lymphatic diseases frequently seek out complementary, integrative therapies to address disease or treatment-related physical impacts, enhance physical and mental wellness, and improve QoL. The Society for Integrative Oncology has published clinical practice guidelines with information on the use of such integrative therapies and their respective strength of available evidence for patients undergoing breast cancer treatment[173]. The methods of graded recommendations for specific therapeutic modalities were adapted from the U.S. Preventative Services Task Force. Given the reportedly high incidence of secondary lymphedema following breast cancer treatment, these guidelines may be suitably applied to patients with other lymphatic diseases. Meditation received a Grade A recommendation indicating evidence for substantial benefit in the reduction of anxiety, stress, depression, and mood disturbances. Relaxation techniques also received a Grade A recommendation for improving mood disturbances and depressive symptoms. The National Cancer Institute (NCI) recognizes relaxation techniques as progressive muscle relaxation, guided imagery, autogenic training, biofeedback, self-hypnosis, and deep breathing exercises[173]. Relaxation methods may be tailored to reduce stress surrounding the rehabilitation process; for example, relaxation techniques can improve pumping device tolerability by teaching patients to visualize themselves in a relaxing environment while using their pumping device[174]. Additionally, yoga, massage, music therapy, and stress management received Grade B recommendations for mood-related outcomes. Studies of yoga have demonstrated effectiveness in improving QoL in patients with BCRL[175,176], COPD[177], and chronic pain conditions[178].

Social impairment may be reduced by encouraging patients to find creative ways to feature positive physical attributes in their manner of dressing. Therapeutic role-playing of social situations (i.e., individuals practice answering anxiety-provoking questions about their condition) may help in the development of relevant vocabulary and emotional regulation in response to perceived negative reactions[174]. Breast cancer survivors and those experiencing BCRL-related symptoms who feel unable or hesitant to disclose health-related information to those in their social circle may benefit considerably from support programs in survivorship care planning[158]. Interventions may address return-to-work issues in lymphedema, including assessments of functional impairments through low-cost job accommodations like changes in job responsibilities, schedules, or the use of adaptive equipment. Rehearsal of responses to interpersonal stressors associated with work (i.e., discussing necessary workplace accommodations) may serve to alleviate anxiety surrounding return to work[159]. Relational counseling services may be employed in the development of effective coping strategies and the exploration of strategies for emotional support from spouses and family members. Sex therapy may also be beneficial in teaching intimate partners new or creative methods to express intimacy and navigate patterns of sexual behavior in the context of their chronic condition[174].

Psychopharmacologic Considerations

Chronic medical illness has been consistently associated with depressive symptoms and disorders. Comorbid depression and medical illness are further associated with increased disease-related morbidity and mortality[179]. Randomized controlled trials have proven efficacy in both pharmacologic and psychosocial treatments of mood symptoms and disorders in numerous chronic medical conditions such as ischemic heart disease, chronic obstructive pulmonary disease, and diabetes[180–182]. Treatment of comorbid anxiety and depression is integral in improving adaptability in patients with chronic disease symptoms[183]. A Cochrane review has shown that antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are more effective in the treatment of depression in physical illness compared to placebo[184]. Currently, there is a dearth of high-quality efficacy and safety data on the use of specific psychotropics in lymphatic disease. Therefore, psychotropic decision-making should include patient-centered education on the benefits and potential adverse effects in the context of comorbid conditions.

In patients with lymphedema and lymphatic diseases, certain psychiatric medications have the potential to exacerbate lymphatic disease. Pregabalin and gabapentin are two anticonvulsant medications that are often prescribed off-label for the treatment of anxiety and neuropathic pain. Both medications are prescribed with increasing frequency for chronic pain and surgery-induced neuropathic pain. However, providers should exercise caution with their use, given the potential for worsening lymphedema. The incidence of peripheral edema in adult patients using pregabalin is up to 16%[185], and 7% with gabapentin[186]. According to the FDA, 3% of patients taking pregabalin experienced potentially clinically significant thrombocytopenia[187].

Gabapentin has a 1.1% rate of adverse effects on the hematologic and lymphatic systems, which include anemia, thrombocytopenia, and lymphadenopathy[188]. Among the psychotropics targeting depressive symptoms, trazodone has been reported to cause fluid retention with a frequency of less than 10%[51]. A review of ten case studies found that, in patients with a predisposition to edematous states, trazodone administration with gradual titration of dose may decrease further fluid retention[189]. Edema has also been reported in treatment with mirtazapine and phenelzine[190,191]. Several dopamine-blocking psychotropics, especially atypical antipsychotics, have been associated with peripheral edema. One case report specifically mentions that risperidone and olanzapine are likely to be associated with edema[192].

Limitations in the State of Evidence

The current literature robustly supports the negative mental health and psychosocial impacts of lymphatic diseases. Unfortunately, there has been little consistency in the literature in quantifying the incidence and prevalence of mental illness and associated symptoms in patients with lymphatic diseases. In addition, there is a significant lack of evidence-based research into the application of psychotherapeutic and psychotropic interventions for this patient population.

The National Institutes of Health (NIH) established the National Commission on Lymphatic Diseases in 2022, subsequently establishing an NIH research category for lymphedema. The Congressionally Directed Medical Research Program (CDMRP) also recently included lymphedema within its top 50 research areas requiring further funding for the fiscal year of 2023. With these promising developments, it is our recommendation and hope that targeted research may improve our ability to assess, recommend, and apply evidence-based psychotherapeutic and psychiatric interventions to patients with lymphatic diseases.

Other Consult Services to Consider

In addition to services offered by genetics, psychiatry, and psychology, as previously detailed, other consultative services may include but are not limited to:

- gynecology for problems with sexual pain and dysfunction,
- oncology for cancer-related pain,
- dermatology or wound care for skin-related changes and infections,
- occupational therapy when LD affects the ability to work, and
- other referrals deemed necessary for the improvement of QoL.

SECTION 4: GUIDELINES FOR COMMUNICATION IN LYMPHEDEMA AND LYMPHATIC DISEASES

Authors: *Bryan Anthony Sisk, MD, MSCI, Anna Michelle Kerr, PhD, and Shelbie Blake Fishman, BS*

A. INTRODUCTION

High-quality communication is essential to providing safe and effective medical care, especially for patients with rare lymphatic diseases (LD). Prior work has identified eight core functions that communication fulfills for patients and families affected by lymphatic and vascular disorders: exchanging information, building relationships, enabling self-management, managing uncertainty, responding to emotions, making decisions, providing validation, and supporting hope[193]. Providing reliable information is also associated with better mental health, physical health, and the ability to navigate the healthcare system for patients with rare vascular anomalies. (Manuscripts under review) In other serious illnesses, communication and care are interrelated, with better communication supporting better care. For example, patients and parents who report better communication also report better physical and psychosocial health, functional ability, and emotional well-being[194,195.] Furthermore, effective clinician-family communication is essential to support informed decision-making and engagement and involvement of the family in care[196–198].

Many patients and families affected by lymphatic diseases, however, experience communication challenges. Parents of children with vascular anomalies, for example, report persistent uncertainties related to the limited information available about a rare disease, unknowns about the child's future well-being and ability to lead a 'normal' life, and worries about future social stigma[199–201]. This uncertainty can affect the fulfillment of all communication functions, leading to frustration, confusion, and diminished trust in clinicians[193]. Patients and parents can respond to communication failures with confrontational advocacy, which can lead to further tensions in the clinical relationship[202,203]. These communication challenges are likely exacerbated for families affected by congenital lymphedema syndromes and lymphatic anomalies due to a lack of knowledgeable clinicians, limited treatment options, limited interest in the scientific community, and long diagnostic odysseys.

Clinicians caring for patients with lymphedema (LE) and lymphatic anomalies should strive to fulfill their patients' and families' multiple communication needs. Such efforts could help families to navigate care, support better health, and foster a trusting clinical relationship. Without effective communication, families can feel alone and unsupported by the healthcare system. Below, we highlight the eight core functions of communication and suggest ways that clinicians can strive to fulfill these functions for their patients and families.

B. COMMUNICATION FUNCTIONS

Managing Uncertainty

Patients with rare diseases experience myriad uncertainties, some of which can be mitigated or are time-limited (e.g., "What will this MRI show?") while others will persist (e.g., "How will this disease affect me in the future?"). Furthermore, clinicians, at times, increase patient uncertainty by providing information about unknowns. As such, clinicians should strive to understand and acknowledge the patient's uncertainty, minimize uncertainties that are scientific or factual, and help patients tolerate uncertainties that will persist. To overcome communication barriers, some communication researchers have suggested a framework using "what if" questions to acknowledge and address the patient's uncertainties[204]. Additionally, clinicians must remain aware of their own uncertainty tolerance and how it might affect their decision-making and communication with patients.

Exchanging Information

Patients with rare diseases struggle to find high-quality information about their disease, which leads them to search the internet and social media. Many families struggle to determine which online information is trustworthy. As a result, these families often rely on clinicians to provide reliable and understandable information and help clarify information found through external sources, but most clinicians have limited knowledge about these diseases. As such, it is imperative that clinicians with expertise in lymphedema and lymphatic diseases provide honest, accurate, and understandable information about the disease and its management. Given the complexity of these diseases, clinicians should strive to use text, pictures, and videos to improve the patient's understanding. Ideally, these informational resources can be incorporated into standard clinical workflows to ensure all patients have access to understandable and trustworthy information. Moreover, patients with rare diseases often become experts on their condition. Clinicians should ask patients questions to encourage patients to provide or clarify information.

Making Decisions

Engaging in shared decision-making is a standard expectation for all clinicians. However, patients can differ in what type of role they desire in decision-making. Some might prefer to defer decisions to the

clinician, others might prefer a deliberative process and shared decision, and still others might prefer to drive the decision-making process after receiving information from the clinician. These preferred roles can change based on the clinical situation and type of decision. For example, a patient might prefer to make decisions about when to time imaging or laboratory tests, but they might defer to the clinician on which tests to perform. Patients with lymphedema and lymphatic diseases often lack high-quality data to inform decisions. Often, the only evidence comes from preclinical animal models, case reports, and case series. In these situations, it is imperative that clinicians provide information about what is known, what is unknown, and how to measure the success of the treatment. For example, clinicians might help patients make a list of three things they hope a treatment might change, such as swelling, mobility, pain, or leakage. Then the clinician can discuss the likelihood that a proposed treatment would affect these important outcomes. As a field, we need more evidence to guide diagnosis, treatment, and management. In the absence of this evidence, patients require detailed and transparent communication to inform decision-making. Clinicians should also be transparent about their uncertainty related to decision making and their rationale for suggesting certain treatments over others.

Building Relationships

Patients with rare lymphatic diseases who face long diagnostic odysseys are often referred from provider to provider before they reach an accurate diagnosis. In the process, the rarity of their presentations may lead providers to dismiss or diminish these patients' concerns, which can engender mistrust in the healthcare system and disbelief that any provider will be able to help them. Therefore, providers caring for patients with these conditions can benefit patients affected by these rare diseases by striving to build strong, trusting relationships and demonstrating compassion and humility. To foster a therapeutic alliance with these patients, providers should strive to demonstrate kindness, concern for the patient, and reliability. Many patients struggle to find clinicians who will commit to their care, and clinicians can strengthen these relationships by demonstrating that they will 'be there' for the patient, whether they have effective treatments or not. Providing a consistent, reliable voice of support and understanding to patients with rare diseases is key to building meaningful relationships that can support the patient's health and well-being.

Enabling Self-Management

Patients with lymphedema and lymphatic diseases will often be affected by their disease for the duration of their lives. As such, enabling patients and families to self-manage their medical difficulties is essential to supporting these patients' well-being and reducing the risk of serious complications. Clinicians play an integral role in educating patients and their caregivers on how to prevent, recognize, and manage complications of their lymphatic disease. To enable self-management, providers should strive to learn from patients how their diseases most commonly affect their health and quality of life. In doing so, clinicians can tailor guidance and recommendations to the most pertinent medical challenges for that unique patient. Patients with lymphedema and lymphatic diseases often require multidisciplinary care, and clinicians can also support self-management by helping patients navigate consultation and referrals to other specialists.

Responding to Emotions

Patients with lymphedema and lymphatic diseases experience emotional distress because of their disease as well as the reactions of others in society to their disease. Patients can experience grief, anger, helplessness, and stigma[201]. Additionally, these patients can experience anxiety and depression that are exacerbated by their clinical experiences. Clinicians can acknowledge these emotions by staying alert for overt expressions of emotional distress, as well as subtle cues. When addressing these emotional concerns, clinicians can use open-ended questions that provide space for the patient to elaborate on their emotional distress. However, not every patient will want to discuss their emotions, and some patients prefer to focus on scientific advances and updates on new treatments. Clinicians should follow the lead of their patients so they feel supported but not pressured to talk about their emotions. Clinicians should also rely on other psychosocial professionals to provide additional support for these patients. Clinicians might support these services by normalizing the emotional struggles inherent to chronic disease and destigmatizing the role of mental health professionals.

Supporting Hope

Lymphedema and lymphatic diseases are lifelong chronic conditions with limited treatment options. Many patients have heard from multiple clinicians, "There is nothing I can do for you." As such, patients might lose hope that they will ever have improvement in their symptoms. While clinicians should be open and transparent with their patients about realistic outcomes, clinicians can still support their patients' hopes. First, clinicians should recognize that patients can hold hopes for multiple different outcomes, rather than only being "hopeful" in a vague, general sense. Clinicians can address this "breadth of hopes" by directly asking what the patient is hoping for, or what their goals are[205]. Clinicians might then be honest about hopes that are unachievable while directing

efforts toward fulfilling those that are achievable. Clinicians can also support these patients' hopes by offering achievable and realistic hopes, maintaining optimism, and demonstrating a commitment to finding answers and committing to helping the patient in the future[193].

Providing Validation

Patients and families affected by lymphedema and lymphatic diseases have rich knowledge about the manifestations of their disease. Additionally, these families and patients have often developed knowledge about their disease after years of networking and research. As such, they have helpful information and knowledge that can inform their care. Furthermore, many patients and families have experienced dismissive clinicians in the past. By creating space for their patients to share their experiences and knowledge, clinicians can empower patients to advocate for themselves. Additionally, clinicians can gain important insights from listening to and valuing these experiences. In rare diseases, patients might have unique insights about their disease that have not yet been published in the scientific literature. To provide validation, clinicians might communicate to patients that their thoughts and concerns matter and that they are integral members of the care team.

C. CONCLUSION

Communication is essential to providing high-quality care for patients with lymphedema and lymphatic disease. Clinicians should be aware of the functions they are striving to fulfill for patients through their communication. Additionally, clinicians should remain open to actively listening and learning from the patient's experience and knowledge. This field needs additional research to develop tools to enable clinicians to better support the needs of patients with lymphedema and lymphatic disease.

SECTION 5: FINAL REMARKS:

Author: *William J. Repicci*

Since its founding in 1998, the Lymphatic Education & Research Network (LE&RN) has promoted education, training, and collaboration among healthcare providers dedicated to those with lymphatic diseases (LD) such as lymphedema (LE), lipedema, and vascular and lymphatic anomalies. Recognizing that optimal management of these diseases involves early identification, informed diagnosis, and evidence-based treatment, we thank the many experts who contributed to this document to help guide healthcare professionals to improve patient outcomes.

Lymphatic medicine is beginning to receive unprecedented attention. Healthcare bureaucracies that previously paid little or no attention to lymphatic health are now focused on these diseases. Established by a United States Senate Resolution authored by LE&RN, World Lymphedema Day is now celebrated across the globe, and the number of LE&RN Centers of Excellence in the Diagnosis and Treatment of Lymphatic Diseases has grown exponentially worldwide.

We look forward to regularly updating this document as new diagnostic tools, treatments, and cures become standards of care. I would like to acknowledge all the lymphatic heroes who have brought the field to this crossroads by dedicating themselves to reducing suffering in the world through their advocacy.

REFERENCES

1. Bittar S, Simman R, Lurie F. Lymphedema: a practical approach and clinical update. *Wounds 2020;32*(3):86-92. (In eng).
2. Rockson SG. Lymphedema. *Vasc Med 2016;21*(1):77-81. (In eng). DOI: 10.1177/1358863x15620852.
3. Greene AK, Goss JA. Diagnosis and staging of lymphedema. *Seminars in Plastic Surgery 2018;32*(1):12-16. (In eng). DOI: 10.1055/s-0038-1635117.
4. Center for Disease Control and Prevention NCfHA. Estimated HIV incidence and prevalence in the United States, 2015–2019. *HIV Surveillance Supplemental Report 2021*. CDC, May 2021 2021. (http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html).
5. Willis AW, Roberts E, Beck JC, et al. Incidence of Parkinson disease in North America. *NPJ Parkinsons Dis 2022;8*(1):170. (In eng). DOI: 10.1038/s41531-022-00410-y.
6. Wallin MT, Culpepper WJ, Campbell JD, et al. *The prevalence of MS in the United States.* A population-based estimate using health claims data 2019;92(10):e1029-e1040. DOI: 10.1212/wnl.0000000000007035.
7. Zhang Y, Mann JR, James KA, et al. Duchenne and Becker Muscular Dystrophies' Prevalence in MD STARnet Surveillance Sites: An Examination of Racial and Ethnic Differences. *Neuroepidemiology 2021;55*(1):47-55. (In eng). DOI: 10.1159/000512647.
8. Mehta P, Raymond J, Punjani R, et al. Prevalence of amyotrophic lateral sclerosis in the United States using established and novel methodologies, 2017. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2023;24*(1-2):108-116. DOI: 10.1080/21678421.2022.2059380.
9. Gallagher JR, Martini J, Carroll S, Small A, Teng J. Annual prevalence estimation of lymphatic malformation with a cutaneous component: observational study of a national representative sample of physicians. *Orphanet Journal of Rare Diseases 2022;17*(1):192. (In eng). DOI: 10.1186/s13023-022-02336-3.
10. Introduction. *Skandinavisches Archiv Für Physiologie 1940;83*(S16):7-10. DOI: 10.1111/j.1748-1716.1940.tb01347.x.
11. Clinckaert A, Callens K, Cooreman A, et al. The Prevalence of Lower Limb and Genital Lymphedema after Prostate Cancer Treatment: A Systematic Review. *Cancers (Basel) 2022;14*(22) (In eng). DOI: 10.3390/cancers14225667.
12. Hayes SC, Janda M, Ward LC, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. *Gynecol Oncol 2017;146*(3):623-629. (In eng). DOI: 10.1016/j.ygyno.2017.06.004.
13. Fadhil M, Singh R, Havas T, Jacobson I. Systematic review of head and neck lymphedema assessment. *Head Neck 2022;44*(10):2301-2315. (In eng). DOI: 10.1002/hed.27136.
14. Arié A, Yamamoto T. Lymphedema secondary to melanoma treatments: diagnosis, evaluation, and treatments. *Glob Health Med 2020;2*(4):227-234. (In eng). DOI: 10.35772/ghm.2020.01022.
15. Melrose WD, Leggat PA. Acute lymphatic filariasis infection in United States armed forces personnel deployed to the Pacific area of Operations during World War II provides important lessons for today. *Trop Med Infect Dis 2020;5*(2) (In eng). DOI: 10.3390/tropicalmed5020063.
16. Society AC. *Military Burn Pits and Cancer Risk*. In: team ACSmae, ed. CHEMICALS and CANCER. www.cancer.org: American Cancer Society; 2022.
17. Cuijpers I, Simmonds SJ, van Bilsen M, et al. Microvascular and lymphatic dysfunction in HFpEF and its associated comorbidities. *Basic Res Cardiol 2020;115*(4):39. (In eng). DOI: 10.1007/s00395-020-0798-y.
18. D'Alessio S, Tacconi C, Danese S. Targeting lymphatics in inflammatory bowel disease. *Oncotarget 2015;6*(33):34047-8. (In eng). DOI: 10.18632/oncotarget.6026.
19. Shah C, Arthur DW, Wazer D, Khan A, Ridner S, Vicini F. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. *Cancer Med 2016;5*(6):1154-62. (In eng). DOI: 10.1002/cam4.691.
20. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology 2020;53*(1):3-19. (In eng).
21. Herbst KL, Kahn LA, Iker E, et al. Standard of care for lipedema in the United States. *Phlebology 2021;36*(10):779-796. (In eng). DOI: 10.1177/02683555211015887.
22. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther 2006;86*(2):205-14. (In eng).
23. Deltombe T, Jamart J, Recloux S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology 2007;40*(1):26-34. (In eng).
24. Dylke ES, Schembri GP, Bailey DL, et al. Diagnosis of upper limb lymphedema: development of an evidence-based approach. *Acta Oncol 2016;55*(12):1477-1483. (In eng). DOI: 10.1080/0284186x.2016.1191668.
25. Fu MR, Cleland CM, Guth AA, et al. L-dex ratio in detecting breast cancer-related lymphedema: reliability, sensitivity, and specificity. *Lymphology 2013;46*(2):85-96. (In eng).
26. Ward LC. Is BIS ready for prime time as the gold standard treatment. *Journal of Lymphedema 2009;4*(2):5. (Critical review of research, literature review, critical commentary).
27. Iker E, Mayfield CK, Gould DJ, Patel KM. Characterizing lower extremity lymphedema and lipedema with cutaneous ultrasonography and an objective computer-assisted measurement of dermal echogenicity. *Lymphatic Research and Biology 2019;17*(5):525-530. (In eng). DOI: 10.1089/lrb.2017.0090.
28. Forte AJ, Boczar D, Huayllani MT, et al. Use of magnetic resonance imaging lymphangiography for preoperative planning in lymphedema surgery: A systematic review. *Microsurgery 2021;41*(4):384-390. (In eng). DOI: 10.1002/micr.30731.
29. Hassanein AH, Maclellan RA, Grant FD, Greene AK. Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of false-negative tests. *Plast Reconstr Surg Glob Open 2017;5*(7):e1396. (In eng). DOI: 10.1097/gox.0000000000001396.
30. Iimura T, Fukushima Y, Kumita S, Ogawa R, Hyakusoku H. Estimating limphodynamic conditions and lymphovenous anastomosis efficacy using (99m)Tc-phytate lymphoscintigraphy with SPECT-CT in patients with lower-limb lymphedema. *Plast Reconstr Surg Glob Open 2015;3*(5):e404. (In eng). DOI: 10.1097/gox.0000000000000375.
31. Abbaci M, Conversano A, De Leeuw F, Laplace-Builhé C, Mazouni C. Near-infrared fluorescence imaging for the prevention and management of breast cancer-related lymphedema: A systematic review. *Eur J Surg Oncol 2019;45*(10):1778-1786. (In eng). DOI: 10.1016/j.ejso.2019.06.009.

32. Szuba A, Razavi M, Rockson SG. Diagnosis and treatment of concomitant venous obstruction in patients with secondary lymphedema. *Journal of Vascular and Interventional Radiology: JVIR 2002;13*(8):799-803. (In eng). DOI: 10.1016/s1051-0443(07)61988-5.
33. Krishnamurthy R, Hernandez A, Kavuk S, Annam A, Pimpalwar S. Imaging the central conducting lymphatics: initial experience with dynamic MR lymphangiography. *Radiology 2015;274*(3): 871-8. (In eng). DOI: 10.1148/radiol.14131399.
34. Lee H, Kim SJ, Hur S, et al. The feasibility of mesenteric intranodal lymphangiography: Its clinical application for refractory pPostoperative chylous Ascites. *Journal of Vascular and Interventional Radiology: JVIR 2018;29*(9):1290-1292. (In eng). DOI: 10.1016/j.jvir.2018.01.789.
35. Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvascular Research 2009;77*(3):335-9. (In eng). DOI: 10.1016/j.mvr.2009.01.005.
36. Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal lymphangiogram for thoracic duct embolization. *Journal of Vascular and Interventional Radiology: JVIR 2012;23*(5):613-6. (In eng). DOI: 10.1016/j.jvir.2012.01.078.
37. Nowak S, Henkel A, Theis M, et al. Deep learning for standardized, MRI-based quantification of subcutaneous and subfascial tissue volume for patients with lipedema and lymphedema. *Eur Radiol 2023;33*(2):884-892. (In eng). DOI: 10.1007/s00330-022-09047-0.
38. Patel S, Hur S, Khaddash T, Simpson S, Itkin M. Intranodal CT lymphangiography with water-soluble Iodinated contrast medium for imaging of the central lymphatic system. *Radiology 2022;302*(1):228-233. (In eng). DOI: 10.1148/radiol.2021210294.
39. Pieper CC. Nodal and pedal MR lymphangiography of the central lymphatic system: techniques and applications. *Semin Intervent Radiol 2020;37*(3):250-262. (In eng). DOI: 10.1055/s-0040-1713442.
40. Polomska AK, Proulx ST. Imaging technology of the lymphatic system. *Adv Drug Deliv Rev 2021;170*:294-311. (In eng). DOI: 10.1016/j.addr.2020.08.013.
41. Pons G, Clavero JA, Alomar X, Rodríguez-Bauza E, Tom LK, Masia J. Preoperative planning of lymphaticovenous anastomosis: The use of magnetic resonance lymphangio-graphy as a complement to indocyanine green lymphography. *J Plast Reconstr Aesthet Surg 2019;72*(6):884-891. (In eng). DOI: 10.1016/j.bjps.2019.02.024.
42. Rockson SG. Advances in lymphedema. *Circulation Research 2021;128*(12):2003-2016. (In eng). DOI: 10.1161/circresaha.121.318307.
43. Unno N, Inuzuka K, Suzuki M, et al. Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema. *Journal of Vascular Surgery 2007;45*(5):1016-21. (In eng). DOI: 10.1016/j.jvs.2007.01.023.
44. van Heumen S, Riksen JJM, Bramer WM, van Soest G, Vasilic D. Imaging of the lymphatic vessels for surgical planning: a systematic review. *Annals of Surgical Oncology 2023;30*(1): 462-479. (In eng). DOI: 10.1245/s10434-022-12552-7.
45. Connell F, Brice G, Jeffery S, Keeley V, Mortimer P, Mansour S. A new classification system for primary lymphatic dysplasias based on phenotype. *Clin Genet 2010;77*(5):438-52. (In eng). DOI: 10.1111/j.1399-0004.2010.01394.x.
46. Connell FC, Gordon K, Brice G, et al. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. *Clin Genet 2013;84*(4):303-14. (In eng). DOI: 10.1111/cge.12173.
47. Gordon K, Varney R, Keeley V, et al. Update and audit of the St George's classification algorithm of primary lymphatic anomalies: a clinical and molecular approach to diagnosis. *J Med Genet 2020;57*(10):653-659. (In eng). DOI: 10.1136/jmedgenet-2019-106084.
48. Devoogdt N, Van Zanten M, Damstra R, et al. Paediatric lymphoedema: an audit of patients seen by the paediatric and primary lymphoedema group of vascular European Reference Network (VASCERN). *Eur J Med Genet 2022;65*(12):104641. (In eng). DOI: 10.1016/j.ejmg.2022.104641.
49. Greene AK, Goss JA. Vascular anomalies: from a clinico-histologic to a cenetic framework. *Plastic and Reconstructive Surgery 2018;141*(5):709e-717e. (In eng). DOI: 10.1097/PRS.0000000000004294.
50. Vignes S, Bellanger J. [Primary intestinal lymphangiectasia (Waldmann's disease)]. *Rev Med Interne 2018;39*(7):580-585. (In fre). DOI: 10.1016/j.revmed.2017.07.009.
51. Keeley V. Drugs that may exacerbate and those used to treat lymphoedema. *Journal of Lymphoedema 2008;3*(1): 57-65.
52. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. *Am J Med Genet A 2014;164a*(7):1713-33. (In eng). DOI: 10.1002/ajmg.a.36552.
53. Diociaiuti A, Rotunno R, Pisaneschi E, et al. Clinical and molecular spectrum of sporadic vascular malformations: a single-center study. *Biomedicines 2022;10*(6) (In eng). DOI: 10.3390/biomedicines10061460.
54. Amyere M, Revencu N, Helaers R, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation 2017;136*(11):1037-1048. (In eng). DOI: 10.1161/circulationaha.116.026886.
55. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat 2008;29*(7):959-65. (In eng). DOI: 10.1002/humu.20746.
56. Eng W, Sudduth CL, Konczyk DJ, et al. Parkes Weber syndrome with lymphedema caused by a somatic KRAS variant. *Cold Spring Harb Mol Case Stud 2021;7*(6) (In eng). DOI: 10.1101/mcs.a006118.
57. Flores Daboub JA, Grimmer JF, Frigerio A, et al. Parkes Weber syndrome associated with two somatic pathogenic variants in RASA1. *Cold Spring Harb Mol Case Stud 2020;6*(4) (In eng). DOI: 10.1101/mcs.a005256.
58. Network NL. Position Statement of the National Lymphedema Network: Screening and Early Detection of Breast Cancer-Related Lymphedema—The Imperative. National Lymphedema Network Webpage: *NLN, 2011*.
59. Zuther JE, Norton S. *Lymphedema Management: The Comprehensive Guide for Practitioners. 4th Edition.* New York, NY: Thieme Medical Publishers, Inc., 2018.
60. Koul R, Dufan T, Russell C, et al. Efficacy of complete decongestive therapy and manual lymphatic drainage on treatment-related lymphedema in breast cancer. *Int J Radiat Oncol Biol Phys 2007;67*(3):841-6. (In eng). DOI: 10.1016/j.ijrobp.2006.09.024.
61. Deng J, Murphy BA, Dietrich MS, et al. Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. *Head Neck 2013;35*(7):1026-35. (In eng). DOI: 10.1002/hed.23084.

62. Smith BG, Hutcheson KA, Little LG, et al. Lymphedema outcomes in patients with head and neck cancer. *Otolaryngol Head Neck Surg 2015;152*(2):284-291. (In eng). DOI: 10.1177/0194599814558402.
63. Smith BG, Lewin JS. Lymphedema management in head and neck cancer. *Current Opinion in Otolaryngology & Head and Neck Surgery 2010;18*(3):153-8. (In eng). DOI: 10.1097/MOO.0b013e32833aac21.
64. Dawson C, Roe J, Starmer H, et al. Patient advocacy in head and neck cancer: Realities, challenges and the role of the multi-disciplinary team. *Clin Otolaryngol 2020;45*(4):437-444. (In eng). DOI: 10.1111/coa.13508.
65. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg 2000;16*(6):437-42. (In eng). DOI: 10.1055/s-2006-947150.
66. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plastic and Reconstructive Surgery 2013;132*(5):1305-1314. (In eng). DOI: 10.1097/PRS.0b013e3182a4d626.
67. Fallahian F, Tadisina KK, Xu KY. Efficacy of microsurgical treatment of primary lymphedema: a systematic review. *Ann Plast Surg 2022;88*(2):195-199. (In eng). DOI: 10.1097/sap.0000000000002862.
68. Yoshida S, Koshima I, Imai H, et al. Characteristics and outcomes of lymphaticovenular anastomosis in older patients with bilateral involvement versus younger patients with unilateral involvement in lower extremity lymphedema. *J Vasc Surg Venous Lymphat Disord 2020;8*(4):646-657. (In eng). DOI: 10.1016/j.jvsv.2019.10.013.
69. Demirtas Y, Ozturk N, Yapici O, Topalan M. Comparison of primary and secondary lower-extremity lymphedema treated with supermicrosurgical lymphaticovenous anastomosis and lymphaticovenous implantation. *J Reconstr Microsurg 2010;26*(2):137-43. (In eng). DOI: 10.1055/s-0029-1243299.
70. Maldonado AA, Chen R, Chang DW. The use of supraclavicular free flap with vascularized lymph node transfer for treatment of lymphedema: A prospective study of 100 consecutive cases. *Journal of Surgical Oncology 2017;115*(1):68-71. (In eng). DOI: 10.1002/jso.24351.
71. Garza RM, Beederman M, Chang DW. Physical and functional outcomes of simultaneous vascularized lymph node transplant and lymphovenous bypass in the treatment of lymphedema. *Plastic and Reconstructive Surgery 2022;150*(1):169-180. (In eng). DOI: 10.1097/prs.0000000000009247.
72. Ciudad P, Manrique OJ, Date S, et al. Double gastroepiploic vascularized lymph node tranfers to middle and distal limb for the treatment of lymphedema. *Microsurgery 2017;37*(7):771-779. (In eng). DOI: 10.1002/micr.30168.
73. Schaverien MV, Badash I, Patel KM, Selber JC, Cheng MH. Vascularized lymph node transfer for lymphedema. *Seminars in Plastic Surgery 2018;32*(1):28-35. (In eng). DOI: 10.1055/s-0038-1632401.
74. Cheng MH, Loh CYY, Lin CY. Outcomes of vascularized lymph node transfer and lymphovenous anastomosis for treatment of primary lymphedema. *Plast Reconstr Surg Glob Open 2018;6*(12):e2056. (In eng). DOI: 10.1097/gox.0000000000002056.
75. Brorson H, Svensson H. Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than controlled compression therapy alone. *Plastic and reconstructive Surgery 1998;102*(4):1058-67; discussion 1068. (In eng).
76. Garza R, 3rd, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. *BMC Cancer 2017;17*(1):468. (In eng). DOI: 10.1186/s12885-017-3444-9.
77. O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphatico-venous anastomoses for the treatment of obstructive lymphedema. *Plastic and Reconstructive Surgery 1990;85*(4):562-72. (In eng). DOI: 10.1097/00006534-199004000-00011.
78. Schaverien MV, Munro KJ, Baker PA, Munnoch DA. Liposuction for chronic lymphoedema of the upper limb: 5 years of experience. *J Plast Reconstr Aesthet Surg 2012;65*(7):935-42. (In eng). DOI: 10.1016/j.bjps.2012.01.021.
79. Brorson H. Complete reduction of arm lymphedema following breast cancer: a prospective twenty-one years' study. *Plastic and Reconstructive Surgery 2015;136*(4S):134-135. DOI: 10.1097/01.prs.0000472450.00980.04.
80. Chang DW, Dayan J, Greene AK, et al. Surgical treatment of lymphedema: a systematic review and meta-analysis of Controlled Trials. Results of a Consensus Conference. *Plastic and Reconstructive Surgery 2021;147*(4):975-993. (In eng). DOI: 10.1097/prs.0000000000007783.
81. Chang DW, Masia J, Garza R, 3rd, Skoracki R, Neligan PC. Lymphedema: surgical and medical therapy. *Plastic and Reconstructive Surgery 2016;138*(3 Suppl):209s-218s. (In eng). DOI: 10.1097/prs.0000000000002683.
82. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. *Plastic and Reconstructive Surgery 2010;126*(3):752-758. (In eng). DOI: 10.1097/PRS.0b013e3181e5f6a9.
83. Yamamoto T, Koshima I. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plastic and Reconstructive S urgery 2014;133*(6):887e-888e. (In eng). DOI: 10.1097/prs.0000000000000189.
84. Carl HM, Walia G, Bello R, et al. Systematic review of the surgical treatment of extremity lymphedema. *J Reconstr Microsurg 2017;33*(6):412-425. (In eng). DOI: 10.1055/s-0037-1599100.
85. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. *Plastic and Reconstructive Surgery 2014;133*(4):905-913. (In eng). DOI: 10.1097/prs.0000000000000010.
86. Sharkey AR, King SW, Ramsden AJ, Furniss D. Do surgical interventions for limb lymphoedema reduce cellulitis attack frequency? *Microsurgery 2017;37*(4):348-353. (In eng). DOI: 10.1002/micr.30115.
87. Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery 2017;37*(8):947-953. (In eng). DOI: 10.1002/micr.30246.
88. Cornelissen AJM, Beugels J, Ewalds L, et al. Effect of lymphatico-venous anastomosis in breast cancer-related lymphedema: a review of the literature. *Lymphatic Research and Biology 2018;16*(5):426-434. (In eng). DOI: 10.1089/lrb.2017.0067.
89. Brown S, Mehrara BJ, Coriddi M, McGrath L, Cavalli M, Dayan JH. A prospective study on the safety and efficacy of vascularized lymph node transplant. *Annals of Surgery 2022;276*(4):635-653. (In eng). DOI: 10.1097/sla.0000000000005591.
90. Schaverien MV, Coroneos CJ. Surgical treatment of lymphedema. *Plastic and reconstructive surgery 2019;144*(3):738-758. (In eng). DOI: 10.1097/prs.0000000000005993.
91. Wikipedia. *Omentum*. Wikipedia. (https://en.wikipedia.org/wiki/Omentum).

92. Dionyssiou D, Demiri E, Tsimponis A, et al. A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer. *Breast Cancer Res Treat 2016;156*(1):73-9. (In eng). DOI: 10.1007/s10549-016-3716-0.
93. Beederman M, Garza RM, Agarwal S, Chang DW. Outcomes for physiologic microsurgical treatment of secondary lymphedema involving the extremity. A*nnals of surgery 2022;276*(4):e255-e263. (In eng). DOI: 10.1097/sla.0000000000004457.
94. Schaverien MV, Asaad M, Selber JC, et al. Outcomes of vascularized lymph node transplantation for treatment of lymphedema. *Journal of the American College of Surgeons 2021;232*(6):982-994. (In eng). DOI: 10.1016/j.jamcollsurg.2021.03.002.
95. Ozturk CN, Ozturk C, Glasgow M, et al. Free vascularized lymph node transfer for treatment of lymphedema: a systematic evidence based review. *J Plast Reconstr Aesthet Surg 2016;69*(9):1234-47. (In eng). DOI: 10.1016/j.bjps.2016.06.022.
96. Lee D, Piller N, Hoffner M, Manjer J, Brorson H. Liposuction of postmastectomy arm lymphedema decreases the incidence of erysipelas. *Lymphology 2016;49*(2):85-92. (In eng).
97. Hoffner M, Ohlin K, Svensson B, et al. Liposuction gives complete reduction of arm lymphedema following breast cancer treatment: a 5-year prospective study in 105 patients without recurrence. *Plast Reconstr Surg Glob Open 2018;6*(8):e1912. (In eng). DOI: 10.1097/gox.0000000000001912.
98. Coriddi M, Mehrara B, Skoracki R, Singhal D, Dayan JH. Immediate lymphatic reconstruction: technical points and literature review. *Plast Reconstr Surg Glob Open 2021;9*(2): e3431. (In eng). DOI: 10.1097/gox.0000000000003431.
99. Boccardo F, Casabona F, De Cian F, et al. Lymphatic microsurgical preventing healing approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: over 4 years follow-up. *Microsurgery 2014;34*(6):421-4. (In eng). DOI: 10.1002/micr.22254.
100. Boccardo F, Valenzano M, Costantini S, et al. LYMPHA technique to prevent secondary lower limb lymphedema. *Annals of Surgical Oncology 2016;23*(11):3558-3563. (In eng). DOI: 10.1245/s10434-016-5282-4.
101. Bjarnason H. *Venoplasty and Stenting*. Springer London, 2009.
102. Scottoni F, Fusaro F, Conforti A, Morini F, Bagolan P. Pleurodesis with povidone-iodine for refractory chylothorax in newborns: personal experience and literature review. *Journal of Pediatric Surgery 2015;50*(10):1722-5. (In eng). DOI: 10.1016/j.jpedsurg.2015.03.069.
103. (BLS) BLS. *Guidelines on the Management of Cellulitis in Lymphoedema 2022*. September 26, 2023 2022. (https://www.thebls.com/documents-library/guidelines-on-the-management-of-cellulitis-in-lymphoedema).
104. Vignes S, Poizeau F, Dupuy A. Cellulitis risk factors for patients with primary or secondary lymphedema. *J Vasc Surg Venous Lymphat Disord 2022;10*(1):179-185.e1. (In eng). DOI: 10.1016/j.jvsv.2021.04.009.
105. Cox N. Chapter 41, Streptococcal cellulitis /erysipelas of the lower leg. In: Williams H BM, Diepan T, Herxheimer A, Naldi L and Rzany B, ed. *Evidence-Based Dermatology, Second Edition.* Oxford, Blackwell Publishing; 2009.
106. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect 2010;138*(3):313-7. (In eng). DOI: 10.1017/s0950268809990483.
107. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *The Cochrane Database of Systematic Reviews 2010;2010*(6): Cd004299. (In eng). DOI: 10.1002/14651858.CD004299.pub2.
108. Brindle R, Williams OM, Barton E, Featherstone P. Assessment of antibiotic treatment of cellulitis and erysipelas: a systematic review and meta-analysis. *JAMA Dermatol 2019;155*(9):1033-1040. (In eng). DOI: 10.1001/jamadermatol.2019.0884.
109. Davis JS, Mackrow C, Binks P, et al. A double-blind randomized controlled trial of ibuprofen compared to placebo for uncomplicated cellulitis of the upper or lower limb. *Clin Microbiol Infect 2017;23*(4):242-246. (In eng). DOI: 10.1016/j.cmi.2017.02.036.
110. Denis Spelman LMB. Acute Cellulitis and erysipelas in adults: treatment. In: Nelson S, ed. *Cellulitis*. UpToDate2023:UpToDate.
111. Ko DS, Lerner R, Klose G, Cosimi AB. Effective treatment of lymphedema of the extremities. *Archives of Surgery (Chicago, Ill : 1960) 199*8;133(4):452-8. (In eng). DOI: 10.1001/archsurg.133.4.452.
112. Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression therapy to prevent recurrent cellulitis of the leg. *The New England Journal of Medicine 2020;383*(7):630-639. (In eng). DOI: 10.1056/NEJMoa1917197.
113. Network TLS. *Skin Care for People Living with Lymphoedema.* (https://www.lymphoedema.org/).
114. Dalal A, Eskin-Schwartz M, Mimouni D, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. *The Cochrane Database of Systematic Reviews 2017;6*(6):Cd009758. (In eng). DOI: 10.1002/14651858.CD009758.pub2.
115. Rudkin GH, Miller TA. Lipedema: a clinical entity distinct from lymphedema. *Plastic and Reconstructive Surgery 1994;94*(6): 841-7; discussion 848-9. (In eng).
116. Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome—systematic review. *Clin Obes 2012;2*(3-4):86-95. (In eng). DOI: 10.1111/j.1758-8111.2012.00045.x.
117. Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. *Int Wound J 2018;15*(6):921-928. (In eng). DOI: 10.1111/iwj.12949.
118. Child AH, Gordon KD, Sharpe P, et al. Lipedema: an inherited condition. *Am J Med Genet A 2010;152a*(4):970-6. (In eng). DOI: 10.1002/ajmg.a.33313.
119. Langendoen SI, Habbema L, Nijsten TE, Neumann HA. Lipoedema: from clinical presentation to therapy: a review of the literature. *The British Journal of Dermatology 2009;161*(5):980-6. (In eng). DOI: 10.1111/j.1365-2133.2009.09413.x.
120. Romeijn JRM, de Rooij MJM, Janssen L, Martens H. Exploration of patient characteristics and quality of life in patients with lipoedema using a survey. *Dermatol Ther (Heidelb) 2018;8*(2):303-311. (In eng). DOI: 10.1007/s13555-018-0241-6.
121. Szolnoky G, Varga E, Varga M, Tuczai M, Dósa-Rácz E, Kemény L. Lymphedema treatment decreases pain intensity in lipedema. *Lymphology 2011;44*(4):178-82. (In eng).
122. Reich-Schupke S, Schmeller W, Brauer WJ, et al. S1 guidelines: Lipedema. *J Dtsch Dermatol Ges 2017;15*(7):758-767. (In eng). DOI: 10.1111/ddg.13036.
123. Marshall M, Schwahn-Schreiber C. Prävalenz des Lipödems bei berufstätigen Frauen in Deutschland. *(Lipödem-3-Studie) 2011;40*(03):127-134. (In De). DOI: 10.1055/s-0037-1621766.
124. Amato ACM, Saucedo DZ, Santos KDS, Benitti DA. Ultrasound criteria for lipedema diagnosis. *Phlebology 2021;36*(8):651-658. (In eng). DOI: 10.1177/02683555211002340.
125. Crescenzi R, Marton A, Donahue PMC, et al. Tissue sodium content is elevated in the skin and subcutaneous adipose tissue in women with lipedema. *Obesity (Silver Spring) 2018; 26*(2):310-317. (In eng). DOI: 10.1002/oby.22090.

126. Mackie H, Thompson BM, Suami H, et al. Differentiation of lipoedema from bilateral lower limb lymphoedema by imaging assessment of indocyanine green lymphography. *Clin Obes 2023;13*(3):e12588. (In eng). DOI: 10.1111/cob.12588.
127. Wollina U, Heinig B. Tumescent icrocannular (laser-assisted) liposuction in painful lipedema. 2012.
128. Szolnoky G, Nagy N, Kovács RK, et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. *Lymphology 2008;41*(4):161-6. (In eng).
129. Rapprich S, Dingler A, Podda M. Liposuction is an effective treatment for lipedema-results of a study with 25 patients. *J Dtsch Dermatol Ges 2011;9*(1):33-40. (In engger). DOI: 10.1111/j.1610-0387.2010.07504.x.
130. Hoffmann JN, Fertmann JP, Baumeister RG, Putz R, Frick A. Tumescent and dry liposuction of lower extremities: differences in lymph vessel injury. *Plastic and Reconstructive Surgery 2004;113*(2):718-24; discussion 725-6. (In eng). DOI: 10.1097/01.Prs.0000101506.84361.C9.
131. Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. *J Cutan Med Surg 2006;10*(1):7-10. (In eng). DOI: 10.1007/7140.2006.00006.
132. Schmeller W, Hueppe M, Meier-Vollrath I. Tumescent liposuction in lipoedema yields good long-term results. *The British Journal of Dermatology 2012;166*(1):161-8. (In eng). DOI: 10.1111/j.1365-2133.2011.10566.x.
133. Dadras M, Mallinger PJ, Corterier CC, Theodosiadi S, Ghods M. Liposuction in the treatment of lipedema: a longitudinal study. *Arch Plast Surg 2017;44*(4):324-331. (In eng). DOI: 10.5999/aps.2017.44.4.324.
134. Wassef M, Blei F, Adams D, et al. Vascular Anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics 2015; 136*(1):e203-14. (In eng). DOI: 10.1542/peds.2014-3673.
135. Jones SG SD. *Macrocephaly*. StatPearls Publishing. (https://www.ncbi.nlm.nih.gov/books/NBK560786/).
136. Perkins JA, Manning SC, Tempero RM, et al. Lymphatic malformations: review of current treatment. *Otolaryngol Head Neck Surg 2010;142*(6):795-803, 803.e1. (In eng). DOI: 10.1016/j.otohns.2010.02.026.
137. Rochon PJ. Importance of multidisciplinary approach to vascular malformation management. *Semin Intervent Radiol 2017;34*(3):301-302. (In eng). DOI: 10.1055/s-0037-1604302.
138. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatric Blood & Cancer 2011;57*(6):1018-24. (In eng). DOI: 10.1002/pbc.23124.
139. Agarwal S, Anderson BK, Mahajan P, Fernandes CJ, Margolin JF, Iacobas I. Sirolimus efficacy in the treatment of critically ill infants with congenital primary chylous effusions. *Pediatric Blood & Cancer 2022;69*(2):e29510. (In eng). DOI: 10.1002/pbc.29510.
140. Lopez-Gutierrez JC, Tovar JA. Chylothorax and chylous ascites: management and pitfalls. *Seminars in Pediatric Surgery 2014;23*(5):298-302. (In eng). DOI: 10.1053/j.sempedsurg.2014.09.011.
141. Caton MT, Baker A, Smith ER, et al. Dual-agent percutaneous sclerotherapy technique for macrocystic lymphatic malformations. J *Neurointerv Surg 2023;15*(9):931. (In eng). DOI: 10.1136/jnis-2022-019255.
142. Horbach SE, Lokhorst MM, Saeed P, de Goüyon Matignon de Pontouraude CM, Rothová A, van der Horst CM. Sclerotherapy for low-flow vascular malformations of the head and neck: A systematic review of sclerosing agents. *J Plast Reconstr Aesthet Surg 2016;69*(3):295-304. (In eng). DOI: 10.1016/j.bjps.2015.10.045.
143. Dorrity J, Mack J, Wong K, Richter GT. Multimodality treatment of vascular anomalies of the head and neck. *J Oral Pathol Med 2022;51*(10):860-871. (In eng). DOI: 10.1111/jop.13322.
144. Nadolski GJ, Itkin M. Thoracic duct embolization for non-traumatic chylous effusion: experience in 34 patients. *Chest 2013;143*(1):158-163. (In eng). DOI: 10.1378/chest.12-0526.
145. Gordon K, Mortimer PS, van Zanten M, Jeffery S, Ostergaard P, Mansour S. The St George's classification algorithm of primary lymphatic anomalies. *Lymphatic Research and Biology 2021;19*(1):25-30. (In eng). DOI: 10.1089/lrb.2020.0104.
146. Brouillard P, Witte MH, Erickson RP, et al. Primary lymphoedema. *Nat Rev Dis Primers 2021;7*(1):77. (In eng). DOI: 10.1038/s41572-021-00309-7.
147. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology 2013;22*(7): 1466-84. DOI: 10.1002/pon.3201.
148. Winch CJ, Sherman KA, Smith KM, Koelmeyer LA, Mackie H, Boyages J. "You're naked, you're vulnerable": Sexual well-being and body image of women with lower limb lymphedema. *Body Image 2016;18:*123-34. DOI: 10.1016/j.bodyim.2016.06.002.
149. Fu MR, Rosedale M. Breast cancer survivors' experiences of lymphedema-related symptoms. *J Pain Symptom Manage 2009;38*(6):849-59. (In eng). DOI: 10.1016/j.jpainsymman.2009.04.030.
150. Arikan Dönmez A, Kuru Alici N, Borman P. Lived experiences for supportive care needs of women with breast cancer-related lymphedema: A phenomenological study. *Clin Nurs Res 2021;30*(6):799-808. (In eng). DOI: 10.1177/1054773820958115.
151. Rockson SG, Keeley V, Kilbreath S, Szuba A, Towers A. Cancer-associated secondary lymphoedema. *Nat Rev Dis Primers 2019;5*(1):22. DOI: 10.1038/s41572-019-0072-5.
152. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2016;34*(6):611-35. (In eng). DOI: 10.1200/jco.2015.64.3809.
153. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry 2006;63*(4):385-90. (In eng). DOI: 10.1001/archpsyc.63.4.385.
154. Hickey M, Schoenaker DA, Joffe H, Mishra GD. Depressive symptoms across the menopause transition: findings from a large population-based cohort study. *Menopause 2016;23*(12): 1287-1293. (In eng). DOI: 10.1097/gme.0000000000000712.
155. Woods NF, Smith-DiJulio K, Percival DB, Tao EY, Mariella A, Mitchell S. Depressed mood during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Menopause 2008;15*(2):223-232. (In eng). DOI: 10.1097/gme.0b013e3181450fc2.
156. Clarke C, Kirby JN, Smidt T, Best T. Stages of lipoedema: experiences of physical and mental health and health care. *Qual Life Res 2023;32*(1):127-137. (In eng). DOI: 10.1007/s11136-022-03216-w.
157. Zhang X, Zhao X, Wu P, Zhao Z, Liu M, Wang YA. Prevalence and associated factors of anxiety and depression among patients with oromaxillofacial venous malformations. *Ann Palliat Med 2021;10*(8):8642-8650. (In eng). DOI: 10.21037/apm-21-608.
158. Tsuchiya M, Horn S, Ingham R. Social disclosure about lymphoedema symptoms: A qualitative study among Japanese breast cancer survivors. *Psychol Health Med 2015;20*(6):680-4. (In eng). DOI: 10.1080/13548506.2014.986140.

159. Sun Y, Shigaki CL, Armer JM. The influence of breast cancer related lymphedema on women's return-to-work. *Womens Health (Lond) 2020;16:*1745506520905720. (In eng). DOI: 10.1177/1745506520905720.
160. Dieterich-Miller CA, Cohen BA, Liggett J. Behavioral adjustment and self-concept of young children with hemangiomas. *Pediatric Dermatology 1992;9*(3):241-5. (In eng). DOI: 10.1111/j.1525-1470.1992.tb00339.x.
161. Espinel AG, Bauman NM. Psychosocial impact of vascular anomalies on children and their families. *Otolaryngol Clin North Am 2018;51*(1):99-110. (In eng). DOI: 10.1016/j.otc.2017.09.018.
162. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine 2001;16*(9):606-13. (In eng). DOI: 10.1046/j.1525-1497.2001.016009606.x.
163. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine 2006;166*(10):1092-7. (In eng). DOI: 10.1001/archinte.166.10.1092.
164. Ye M, Du K, Zhou J, et al. A meta-analysis of the efficacy of cognitive behavior therapy on quality of life and psychological health of breast cancer survivors and patients. *Psycho-Oncology 2018;27*(7):1695-1703. (In eng). DOI: 10.1002/pon.4687.
165. Renn BN, Hundt NE, Sansgiry S, et al. Integrated brief cognitive behavioral therapy improves illness intrusiveness in veterans with chronic obstructive pulmonary disease. *Ann Behav Med 2018;52*(8):686-696. (In eng). DOI: 10.1093/abm/kax045.
166. Williams MT, Johnston KN, Paquet C. Cognitive behavioral therapy for people with chronic Obstructive pulmonary disease: Rapid Review. *Int J Chron Obstruct Pulmon Dis 2020;15:*903-919. (In eng). DOI: 10.2147/copd.S178049.
167. Park S, Sato Y, Takita Y, et al. Mindfulness-based cognitive therapy for psychological distress, fear of cancer recurrence, fatigue, spiritual well-being, and quality of life in patients with breast cancer: a randomized controlled trial. *J Pain Symptom Manage 2020;60*(2):381-389. (In eng). DOI: 10.1016/j.jpainsymman.2020.02.017.
168. Grazzi L, D'Amico D, Guastafierro E, et al. Efficacy of mindfulness added to treatment as usual in patients with chronic migraine and medication overuse headache: a phase-III single-blind randomized-controlled trial (the MIND-CM study). *The Journal of Headache and Pain 2023;24*(1):86. (In eng). DOI: 10.1186/s10194-023-01630-0.
169. Ter Avest MM, van Velthoven ASM, Speckens AEM, et al. Effectiveness of Mindfulness-Based Cognitive Therapy in reducing psychological distress and improving sleep in patients with Inflammatory Bowel Disease: study protocol for a multicentre randomised controlled trial (MindIBD). *BMC Psychol 2023;11*(1):183. (In eng). DOI: 10.1186/s40359-023-01127-0.
170. Ghorbani V, Zanjani Z, Omidi A, Sarvizadeh M. Efficacy of acceptance and commitment therapy (ACT) on depression, pain acceptance, and psychological flexibility in married women with breast cancer: a pre- and post-test clinical trial. *Trends Psychiatry Psychother 2021;43*(2):126-133. (In eng). DOI: 10.47626/2237-6089-2020-0022.
171. Maunick B, Skvarc D, Olive L, Mikocka-Walus A. Effects of acceptance and commitment therapy on fatigue for patients with cancer and other chronic health conditions: a systematic review and meta-analysis. *Journal of Psychosomatic Research 2023;171:*111366. (In eng). DOI: 10.1016/j.jpsychores.2023.111366.
172. Romano D, Chesterman S, Fuller-Tyszkiewicz M, et al. Feasibility, acceptability, and preliminary efficacy of acceptance commitment therapy for adults living with inflammatory bowel disease and distress. *Inflamm Bowel Dis 2023* (In eng). DOI: 10.1093/ibd/izad122.
173. Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin 2017;67*(3):194-232. (In eng). DOI: 10.3322/caac.21397.
174. Passik S, Newman M, Brennan M, Holland J. Psychiatric consultation for women undergoing rehabilitation for upper-extremity lymphedema following breast cancer treatment. *J Pain Symptom Manage 1993;8*(4):226-33. (In eng). DOI: 10.1016/0885-3924(93)90132-f.
175. Loudon A, Barnett T, Piller N, Immink MA, Visentin D, Williams AD. The effect of yoga on women with secondary arm lymphoedema from breast cancer treatment. *BMC Complement Altern Med 2012;12:*66. (In eng). DOI: 10.1186/1472-6882-12-66.
176. Pasyar N, Barshan Tashnizi N, Mansouri P, Tahmasebi S. Effect of yoga exercise on the quality of life and upper extremity volume among women with breast cancer related lymphedema: a pilot study. *Eur J Oncol Nurs 2019;42:*103-109. (In eng). DOI: 10.1016/j.ejon.2019.08.008.
177. Heredia-Rizo AM, Martinez-Calderon J, Piña-Pozo F, González-García P, García-Muñoz C. Effectiveness of mind-body exercises in chronic respiratory diseases: an overview of systematic reviews with meta-analyses. *Disabil Rehabil 2023:*1-16. (In eng). DOI: 10.1080/09638288.2023.2233899.
178. Portz JD, Schmid A, Fruhauf C, et al. Acceptability of online yoga among individuals with chronic conditions and their caregivers: qualitative study. *JMIR Form Res 2023;7:*e39158. (In eng). DOI: 10.2196/39158.
179. Simon GE. Treating depression in patients with chronic disease: recognition and treatment are crucial; depression worsens the course of a chronic illness. *The Western Journal of Medicine 2001;175*(5):292-3. (In eng). DOI: 10.1136/ewjm.175.5.292.
180. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA: The Journal of the American Medical Association 1998;279*(4):287-91. (In eng). DOI: 10.1001/jama.279.4.287.
181. Borson S, McDonald GJ, Gayle T, Deffebach M, Lakshminarayan S, VanTuinen C. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. *Psychosomatics 1992;33*(2):190-201. (In eng). DOI: 10.1016/s0033-3182(92)71995-1.
182. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care 2000;23*(5):618-23. (In eng). DOI: 10.2337/diacare.23.5.618.
183. Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Ann Intern Med 2001;134*(9 Pt 2):917-25. (In eng). DOI: 10.7326/0003-4819-134-9_part_2-200105011-00017.
184. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. *The Cochrane Database of Systematic Reviews 2010*(3):Cd007503. (In eng). DOI: 10.1002/14651858.CD007503.pub2.
185. Gallagher R, Apostle N. Peripheral edema with pregabalin. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne 2013;185*(10):E506. (In eng). DOI: 10.1503/cmaj.121232.
186. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *The Cochrane Database of Systematic Reviews 2017;6*(6):Cd007938. (In eng). DOI: 10.1002/14651858.CD007938.pub4.
187. Parke-Davis. Lyrica Prescribing Information. FDA; 2018.
188. Parke-Davis. Neurontin Final Printed Labeling. FDA; 1999.

189. Barrnett J, Frances A, Kocsis J, Brown R, Mann JJ. Peripheral edema associated with trazodone: a report of ten cases. *J Clin Psychopharmacol 1985;5*(3):161-4. (https://www.ncbi.nlm.nih.gov/pubmed/3998206).
190. Kutscher EC, Lund BC, Hartman BA. Peripheral edema associated with mirtazapine. *The Annals of Pharmacotherapy 2001;35*(11):1494-5. (In eng). DOI: 10.1345/aph.10320.
191. Remick RA, Froese C, Keller FD. Common side effects associated with monoamine oxidase inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry 1989;13*(3-4):497-504. (In eng). DOI: 10.1016/0278-5846(89)90137-1.
192. Chen HJ, Lin ST, Hsu HC, Cheng KD, Tsang HY. Paliperidone-related peripheral edema: a case report and review of the literature. *J Clin Psychopharmacol 2014;34*(2):269-71. (In eng). DOI: 10.1097/jcp.0000000000000046.
193. Sisk BA, Bereitschaft C, Kerr A. Communication with parents and young adult patients affected by complex vascular malformations. *Pediatric Blood & Cancer 2023;70*(3):e30158. DOI: doi: 10.1002/pbc.30158.
194. Street RL, Jr., Makoul G, Arora NK, Epstein RM. How does communication heal? Pathways linking clinician-patient communication to health outcomes. *Patient Educ Couns 2009;74*(3):295-301. (In eng). DOI: 10.1016/j.pec.2008.11.015.
195. Sisk BA, Fasciano K, Block SD, Mack JW. Longitudinal prognostic communication needs of adolescents and young adults with cancer. *Cancer 2020;126*(2):400-407. (In eng). DOI: 10.1002/cncr.32533.
196. Entwistle VA, Watt IS. Patient involvement in treatment decision-making: the case for a broader conceptual framework. *Patient Educ Couns 2006;63*(3):268-78. (In eng). DOI: 10.1016/j.pec.2006.05.002.
197. Strull WM, Lo B, Charles G. Do patients want to participate in medical decision making? *JAMA: The Journal of the American Medical Association 1984;252*(21):2990-4. (In eng).
198. Arora NK, McHorney CA. Patient preferences for medical decision making: who really wants to participate? *Med Care 2000;38*(3):335-41. (In eng). DOI: 10.1097/00005650-200003000-00010.
199. Kerr AM, Harrington NG, Scott AM. Uncertainty management and decision making: parents' experiences during their first visit to a multidisciplinary clinic for their child's vascular anomaly. *J Pediatr Nurs 2020;52*:18-24. (In eng). DOI: 10.1016/j.pedn.2020.02.009.
200. Kerr AM, Sisk BA. Unanswered questions and unmet needs: a call for communication research in vascular anomalies. *Patient Educ Couns 2021;104*(11):2839-2842. (In eng). DOI: 10.1016/j.pec.2021.03.035.
201. Kerr AM, Thompson CM, Rubinsky V. Memorable messages parents of children with vascular birthmarks receive from others: implications for stigma and identity. *Health Communication 2020;35*(6):685-695. (In eng). DOI: 10.1080/10410236.2019.1582314.
202. Sisk BA, Zavadil JA, Blazin LJ, Baker JN, Mack JW, DuBois JM. Assume it will break: parental perspectives on negative communication experiences in pediatric oncology. *JCO Oncol Pract 2021;17*(6):e859-e871. (In eng). DOI: 10.1200/op.20.01038.
203. Mack JW, Ilowite M, Taddei S. Difficult relationships between parents and physicians of children with cancer: a qualitative study of parent and physician perspectives. *Cancer 2017;123*(4):675-681. (In English)
204. Snaman JM, Feraco AM, Wolfe J, Baker JN. "What if?": addressing uncertainty with families. *Pediatric Blood & Cancer 2019;66*(6):e27699. (In eng). DOI: 10.1002/pbc.27699.
205. Feudtner C. The breadth of hopes. *N Engl J Med 2009;361*(24):2306-2307. (In eng). DOI: 10.1056/NEJMp0906516.
206. Bakar Y, Tuğral A. Lower extremity lymphedema management after gynecologic cancer surgery: A review of current management strategies. *Annals of Vascular Surgery.* 2017;44:442. doi: 10.1016/j.avsg.2017.03.197.
207. Beesley V, Janda M, Eakin E, Obermair A, Battistutta D. Lymphedema after gynecological cancer treatment. *Cancer.* 2007;109(12):2607. doi: 10.1002/cncr.22684.
208. Aulia I, Yessica EC. Surgical management of male genital lymphedema: A systematic review. *Arch Plast Surg.* 2020;47(01):3. doi: 10.5999/aps.2019.01123.
209. Lang EM, Munder BI, Andree CE, Foeldi EG, Felmerer GGB, Stark GB. A modified therapeutic option for a long lasting success in the treatment of genital lymphedema. *Eur J Plast Surg.* 2006;29(1):13. doi: 10.1007/s00238-006-0033-6.
210. Nakamura Y, Fujisawa Y, Maruyama H, Furuta J, Kawachi Y, Otsuka F. Intraoperative mapping with isosulfan blue of lymphatic leakage during inguinal lymph node dissection (ILND) for skin cancer for the prevention of postoperative lymphocele. *Journal of Surgical Oncology.* 2011;104(6):657. doi: 10.1002/jso.21989.
211. Finnane A, Hayes SC, Obermair A, Janda M. Quality of life of women with lower-limb lymphedema following gynecological cancer. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2011;11(3):287. doi: 10.1586/erp.11.30.
212. Cohn JC, Geyer H, Lee J, Fisher MI. Oncology section EDGE task force on urogenital cancer outcomes: Clinical measures of Lymphedema—A systematic review. *Rehabilitation Oncology.* 2017;35(3):119. doi: 10.1097/01.reo.0000000000000077.
213. Clinckaert A, Callens K, Cooreman A, et al. The prevalence of lower limb and genital lymphedema after prostate cancer treatment: A systematic review. *Cancers.* 2022;14(22). doi: 10.3390/cancers14225667.
214. Takeuchi T, Endo H. Lymphatic filariasis. Eisai Global Web site. https://www.eisai.com/sustainability/atm/ntds/diseases/lymphaticfilariasis.html. Accessed June 14, 2024.
215. Schook CC, Mulliken JB, Fishman SJ, Grant FD, Zurakowski D, Greene AK. Primary lymphedema: Clinical features and management in 138 pediatric patients. *Plastic and Reconstructive Surgery.* 2011;127(6):2419. doi: 10.1097/prs.0b013e318213a218.
216. Gennaro P, Gabriele G, Aboh IV, Cascino F, Zerini F, Aboud MG. Ultramicrosurgery: A new approach to treat primary male genital lymphedema. *JPRAS Open.* 2019;20:72. doi: 10.1016/j.jpra.2019.01.007.
217. Granese R, Calagna G, Morabito G, et al. Vulvar involvement in pediatric crohn's disease: A systematic review. *Arch Gynecol Obstet.* 2017;297(1):3. doi: 10.1007/s00404-017-4539-x.
218. Pei S, Fischer AS, Yan AC, et al. Lymphedematous verrucous changes of the genital skin: An extraintestinal manifestation of crohn disease. *J Cutan Pathol.* 2021;48(4):465. doi: 10.1111/cup.13723.
219. Barrick BJ, Tollefson MM, Schoch JJ, et al. Penile and scrotal swelling: An underrecognized presentation of crohn's disease. *Pediatric Dermatology.* 2016;33(2):172. doi: 10.1111/pde.12772.
220. Rios Melendez S, Majluta A, Medina A, Restrepo R, Felipez LM. Can vulvar edema be the presenting sign of crohn's disease? A case series. *J Pediatr Gastroenterol Nutr.* 2023;78(2):289. doi: 10.1002/jpn3.12059.

221. Dederichs F, Iesalnieks I, Sladek M, et al. Genital granulomatosis in male and female patients with crohn's disease: Clinical presentation and treatment outcomes. *Journal of Crohn's and Colitis*. 2017;12(2):197. doi: 10.1093/ecco-jcc/jjx131.
222. Shields BE, Richardson C, Arkin L, Kornik R. Vulvar crohn disease: Diagnostic challenges and approach to therapy. *International Journal of Women's Dermatology*. 2020;6(5):390. doi: 10.1016/j.ijwd.2020.09.007.
223. Lewis JD, Parlett LE, Jonsson Funk ML, et al. Incidence, prevalence, and racial and ethnic distribution of inflammatory bowel disease in the united states. *Gastroenterology*. 2023;165(5):1197. doi: 10.1053/j.gastro.2023.07.003.
224. Földi, Michael, Ethel Földi, Cornelia Strößenreuther, and Stefan Kubik. *Földi's Textbook of Lymphology: For Physicians and Lymphedema Therapists. 3rd Ed*. Elsevier Health Sciences; 2012.
225. Guiotto M, Bramhall RJ, Campisi C, Raffoul W, Di Summa PG. A systematic review of outcomes after genital lymphedema surgery. *Ann Plast Surg*. 2019;83(6):e85. doi: 10.1097/sap.0000000000001875.
226. Lee, Byung-Boong, Stanley G. Rockson, and John Bergan. *Lymphedema: A Concise Compendium of Theory and Practice*. 2nd ed. Springer.
227. Mirastschijski U, Jiang D, Rinkevich Y, Karim R, Sorg H. Wound repair and scarring of genital skin. *PAR*. 2020;2020. doi: 10.20517/2347-9264.2020.147.
228. Mirastschijski U, Jiang D, Rinkevich Y. Genital wound repair and scarring. *Medical Sciences*. 2022;10(2). doi: 10.3390/medsci10020023.
229. Téot, Luc, Thomas A. Mustoe, Esther Middelkoop, and Gerd G. Gauglitz. *Textbook On Scar Management: State of the Art Management and Emerging Technologies*. Springer; 2020.
230. Noble-Jones R, Thomas MJ, Bose P. The lymphoedema genitourinary cancer questionnaire in urology follow-up clinics. *Int J of Uro Nursing*. 2018;13(1):5. doi: 10.1111/ijun.12174.
231. Noble-Jones R, Thomas MJ, Davies L, Morgan K. Are you handling genital oedema confidently?
232. Noble-Jones R, Thomas MJ, Gabe-Walters M, et al. The education needs of health professionals conservatively managing genital oedema: UK survey findings.
233. DiCecco S. Genital lymphedema. LymphEd, LLC Web site. https://www.lymphed.com/. Updated 2024.
234. Halperin TJ, Slavin SA, Olumi AF, Borud LJ. Surgical management of scrotal lymphedema using local flaps. . 2007;59(1):67. doi: 10.1097/01.sap.0000258448.17867.20.
235. Theisen KM, Fuller TW, Rusilko P. Surgical management of adult-acquired buried penis: Impact on urinary and sexual quality of life outcomes. *Urology*. 2018;116:180. doi: 10.1016/j.urology.2018.03.031.
236. DiCecco S. Lymphedema: The ins and outs of genital lymphedema. *Today's Wound Clinic*. 2022
237. Garaffa G, Christopher N, Ralph DJ. The management of genital lymphoedema. *BJU International*. 2008;102(4):480. doi: 10.1111/j.1464-410x.2008.07559.x.
238. Zvonik M, Földi E, Felmerer G. The effects of reduction operation with genital lymphedema on the frequency of erysipelas and the quality of life. *Lymphology*. 2011;44(3):121-130.
239. Schook CC, Kulungowski AM, Greene AK, Fishman SJ. Male genital lymphedema: Clinical features and management in 25 pediatric patients. *Journal of Pediatric Surgery*. 2014;49(11):1647. doi: 10.1016/j.jpedsurg.2014.05.031.
240. Torio-Padron N, Björn Stark G, Földi E, Simunovic F. Treatment of male genital lymphedema: An integrated concept. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2015;68(2):262. doi: 10.1016/j.bjps.2014.10.003.
241. Ross JH, Kay R, Yetman RJ, Angermeier K. Primary lymphedema of the genitalia in children and adolescents.
242. DiCecco S. Lymphedema: Practical insights on treating genital lymphedema and its complications. *Today's Wound Clinic*. 2022.
243. Bailey EA, Pandey SK, Chen WF. Advances in surgical lymphedema management: The emergence and refinement of lymph node-to-vein anastomosis (LNVA). *Curr Surg Rep*. 2024;12(5):83. doi: 10.1007/s40137-024-00395-y.
244. Hara H, Mihara M. Lymphaticovenous anastomosis and resection for genital acquired lymphangiectasia (GAL). *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2018;71(11):1625. doi: 10.1016/j.bjps.2018.05.015.
245. Hara H, Mihara M. Genital lymphaticovenous anastomosis (LVA) and leg LVA to prevent the recurrence of genital acquired lymphangiectasia. *Microsurgery*. 2021;41(5):412. doi: 10.1002/micr.30733.
246. Giacalone G, Yamamoto T, Hayashi A, et al. Lymphatic supermicrosurgery for the treatment of recurrent lymphocele and severe lymphorrhea. Microsurgery. 2019;39(4):326. doi: 10.1002/micr.30435.
247. Hara H, Mihara M. Indocyanine green lymphographic and lymphoscintigraphic findings in genital Lymphedema—Genital pathway score. *Lymphatic Research and Biology*. 2017;15(4):356. doi: 10.1089/lrb.2017.0025.

LE&RN's mission is to fight lymphatic diseases through education, research, and advocacy. We seek to accelerate the prevention, treatments and cures for lymphedema, lipedema, lymphatic anomalies, and the continuum of lymphatic diseases.



Lymphatic Education & Research Network

154 West 14th Street, 2nd Floor • New York, NY 10011
Phone: (516) 625-9675 • Fax: (516) 625-9410
E-mail: lern@LymphaticNetwork.org

www.LymphaticNetwork.org