

Focused Review: Postmastectomy Lymphedema

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• Upper extremity lymphedema is a relatively frequent complication following the management of breast cancer. This focused review of the pathophysiology, complications, and various treatment options now available for its management will allow physiatrists and other practitioners to better understand this condition and thereby serve as a resource for patients and other physicians.

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Lymphedema is defined as an abnormal accumulation of tissue proteins, edema, and chronic inflammation within an extremity.¹ Persons with this condition may have significant problems, including discomfort, impaired extremity function, and unsatisfactory cosmesis. The early recognition of postmastectomy lymphedema may spare patients unnecessary neglect, lack of information, and delayed implementation of a comprehensive treatment program. The term "postmastectomy lymphedema" is inaccurate in that lymphedema affecting the arm is also found in women treated with axillary node dissection or radiation therapy, as well as in those treated with radical and modified radical mastectomy.

Lymphedema may be classified as either primary or secondary.² Primary lymphedema is typically seen in young females. It is characterized by diffuse swelling of the lower extremities. Primary lymphedema results from defects in the lymphatic system and is often recognized at birth. Conditions of lymphatic aplasia, hypoplasia, and hyperplasia have been identified. The terms "lymphedema praecox" and "lymphedema tarda" have been applied to persons who manifest these symptoms during their second and third decades of life.²

Secondary or acquired lymphedema can be associated with cancer, infection, inflammation, radiation, surgery, or trauma.² The World Health Organization has identified filariasis as the leading cause of secondary lymphedema. In the industrialized countries, the most common cause is cancer and cancer treatments.

INCIDENCE

The overall reported incidence of postmastectomy lymphedema ranges from a low of 5.5% to a high of 80%.³ Most patients appear to have some degree of swelling following radical mastectomy, especially in the early postoperative period, when a 2cm discrepancy between extremities may be inevitable.⁴ The late development of postmastectomy lymphedema, up to 30 years after radical mastectomy, has been reported.⁵ Patients who receive postoperative radiation therapy appear to have a higher incidence of lymphedema than do nonradiated mastectomy patients.⁴

PATHOPHYSIOLOGY

Normal Fluid Dynamics

Interstitial fluid within a limb is maintained in balance by several interacting mechanisms^{6,7} (fig 1). The capillary wall, for example, is selectively permeable and prevents larger plasma colloids from freely exiting into the interstitial space; thus, intravascular oncotic pressure is created which tends to maintain fluid within the capillary. Countering this is the osmotic pressure created by substances within the interstitial space. Likewise, there is hydrostatic pressure within the capillary which encourages filtration across the capillary wall. Hydrostatic pressure may be increased or reduced, depending on the position of the limb relative to the heart. This is affected further by the shear number of capillaries and the total extracellular volume. Finally, the lymphatic system additionally assists in maintaining the balance of interstitial fluid.

Normal Lymphatic System

The lymphatic system consists of a large network of vessels and glands. The vessels are found in almost every body organ containing blood vessels. Though the number of lymphatic vessels in any organ exceeds the number of veins, their size is much smaller and they are considered almost "delicate."⁸ There is both a superficial and a deep system of lymphatic vessels within the arm. Smaller, superficial lymphatic vessels accompany the superficial veins, and larger lymphatics accompany the deep blood vessels.

Lymphatic vessels pass through numerous lymph nodes before the majority of them empty into the thoracic duct. Lymph is then returned to the circulation by being emptied into the left subclavian vein. The lymphatic vessels of the right arm terminate in the right lymphatic duct, which empties into the right subclavian vein.

The lymphatic glands of the upper extremity are divided into a superficial set that is located at the elbow and between the deltoid and pectoralis major muscles. The other set is

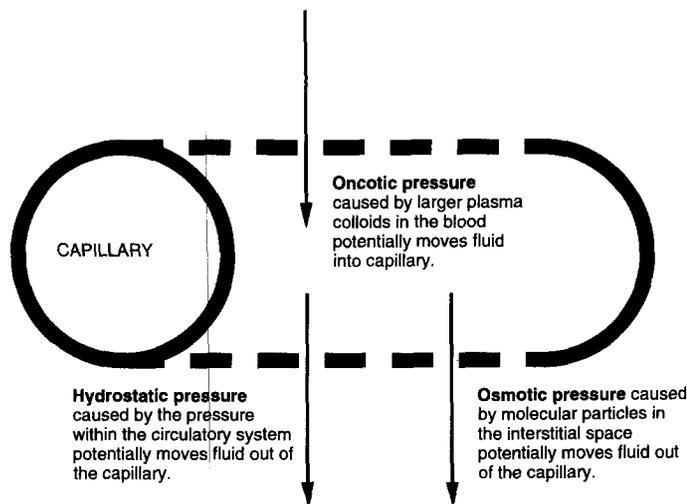


Fig 1. Interacting mechanisms affecting interstitial fluid balance within the arm.

the deep lymphatic glands, which are in the axilla, forearm, and arm.

Edema and Lymphedema

Edema is “the accumulation of interstitial fluid in abnormally large amounts.”⁶ There are many possible causes for edema, and table 1 lists the potential factors that could increase interstitial volume and create edema.

The cause of arm swelling after mastectomy and axillary

Table 1: Factors Associated With Increased Edema Formation

| | |
|--|--|
| I. Increased Capillary Pressure | |
| A. | Excessive kidney retention of salt and water |
| B. | High venous pressure |
| 1. | Heart failure |
| 2. | Local venous block |
| 3. | Failure of venous pumps |
| (a) | Paralysis of muscles |
| (b) | Immobilized parts of body |
| (c) | Failure of venous valves |
| II. Decreased Plasma Proteins | |
| A. | Loss of proteins in urine (nephrosis) |
| B. | Loss of proteins from denuded skin areas |
| 1. | Burns |
| 2. | Wounds |
| C. | Failure to produce proteins |
| 1. | Liver disease |
| 2. | Serious protein or caloric malnutrition |
| III. Increased Capillary Permeability | |
| A. | Immune reactions that cause release of histamine and other immune products |
| B. | Toxins |
| C. | Bacterial infections |
| IV. Blockage of Lymph Return | |
| A. | Blockage of lymph nodes by cancer |
| B. | Blockage of lymph nodes by infection, especially with filaria nematodes |

Adapted from: Guyton AC. Human physiology and mechanisms of disease. 5th ed. Philadelphia: Saunders, 1992:201-2.

node dissection has been discussed at length by several authors. Földi et al⁹ have stated that “chronic postmastectomy swelling of the arm is always due to a disease of the lymphatic and never to that of the venous system.” Postmastectomy lymphedema is considered to be a secondary form of lymphedema. The edema may arise from either direct tumor effects on the lymphatics or the indirect impact of antineoplastic therapies.¹⁰ Treatment of the tumor through resection may injure the lymphatic vessels and nodes. Radiation therapy may cause fibrosis around these structures, interfering with their function. Finally, metastasis to the axillary area can block and disrupt lymphatic function.

In the acute, early phase of postaxillary dissection lymphedema, the swelling is characterized by pitting, which occurs because the extra fluid is relatively free in an easily distensible and large subcutaneous tissue space. At this stage, response to physical measures for edema management is very good. However, as time passes, the fluid becomes more enmeshed in the subcutaneous connective tissue structure and is less free to move. Therefore, as the edema becomes chronic, it is less likely to pit and it becomes brawny. Though physical measures may still be effective at this point, the magnitude of improvement will likely be less and more treatments will be required to obtain significant benefit from therapy.^{1,9,10}

Complications

Full joint range of motion about the elbow, wrist, and hand requires distensible subcutaneous tissue about the joint. With increasing lymphedema, this capacity of the subcutaneous tissue to distend is lost and movements of the joints in the involved area become stiff and their overall range decreases. Joint range of motion is also negatively affected by the shear increase in mass. This lost range, coupled with the increased fluid tension in the subcutaneous tissue, can cause symptoms ranging from discomfort to outright pain in the lymphedematous arm. The decreased range and the pain can affect arm use in functional activities of self-care and work. Although no data are available that assess the effect of lymphedema on range of motion or function, one series reported pain in approximately 30% of patients being treated for lymphedema.¹¹

In addition to loss of range and the potential for pain, the edematous arm can be difficult to clothe and become cosmetically displeasing. These problems can create added emotional distresses and social barriers.¹² A prospective survey of lymphedema patients found increased levels of emotional distress in patients with pain or edema in the dominant hand, those with avoidance coping styles, and those with low social support.¹³

The edema also compromises the health of the cutaneous and subcutaneous tissue and thereby increases the risk of infection with injury and decreases the healing capacity of the tissue. Recurrent cellulitis may further aggravate the edema formation by creating the potential for more scarring of the subcutaneous tissue and fibrin deposition. Lymphangiosarcoma has been associated with chronic lymphedema; it is extremely rare but is aggressively malignant. Annual follow-up should include thorough skin assessment.

Table 2: Tracy Classification: Absolute Volume

| | |
|---------------|------------------------------------|
| Insignificant | 0-150ml > normal extremity |
| Slight | 150-400ml > normal extremity |
| Moderate | 400-700ml > normal extremity |
| Severe | More than 750ml > normal extremity |

Therefore, although postmastectomy lymphedema may not be a medical emergency, timely and adequate treatment is medically justified, given that delayed intervention increases the potential for complications and for difficulty in achieving improvement.

ASSESSMENT

Symptoms and physical findings become clinically detectable as subcutaneous fluid pressure increases. Various systems for measuring and classifying postmastectomy lymphedema have been proposed. Tracy et al¹⁴ have classified postmastectomy lymphedema by the absolute increase in volume of the affected extremity in comparison with the normal limb (table 2). Segerstrom et al¹⁵ noted that patients with brachial edema did not notice any symptoms until the volume difference between the two arms was 200ml or more. Stillwell¹⁶ has suggested a classification based on the percentage increase in volume of the involved limb rather than the absolute volume (table 3).

Three stages of lymphedema have been described. Stage one, in which the edema is pitting, is purportedly reversible with elevation of the arm. Stage two, which is not considered to be "spontaneously reversible," constitutes protein-rich edema and a proliferation of connective tissues. This causes progressive hardening of the extremity, and elevation does not reduce edema. Stage three is lymphostatic elephantiasis, which may have cartilage-like hardening and papillomatous outgrowth of the skin.

Laboratory tests to evaluate lymphedema include sodium-24 studies, lymphoscintigraphy, lymphangiography, computed tomography, and optoelectronic volumetry. Lymphoscintigraphy is an effective test for assessment of the lymphatic system, but its routine use in evaluating postmastectomy arm edema is controversial.¹⁷ Lymphangiography should be reserved for surgical candidates and is not recommended for routine evaluation of patients with acquired lymphedema. Computed tomography can demonstrate a shift in fluid volume in the various tissue compartments as well as reveal structural changes in the soft tissue. By measuring the relative disappearance of isotope from affected patients, sodium-24 studies allow measurement of local circulation and determination of the extent of edematous fluids. Optoelectronic volumetry allows the practitioner to obtain precise measurements and detect minor volume changes in the affected arm. Its clinical relevance is unclear at this time.

TREATMENT

Treatment of acquired lymphedema remains frustrating for patient and physician alike. Since a cure is not yet available, therapies are directed toward reduction of limb size in

order to preserve or restore function and cosmesis. Much of the data supporting various treatment approaches to lymphedema have been obtained by means of uncontrolled, non-randomized trials, and most therapies currently prescribed are based on anecdotal experience. Despite this, a rational assessment of treatment options permits the prescription of safe and potentially effective interventions.

Therapy is difficult, multidisciplinary in nature, and, even in the best outcomes, costly and time consuming.^{1,10,18,19} Lymphedema management begins with a comprehensive evaluation of the extremity. Treatment plans addressing infections, limitations in range of motion, and impairment of activities of daily living should be instituted either before or concomitantly with reduction therapies. Psychosocial issues should also be addressed by appropriate referral for supportive care.

The treatments available for edema reduction may be divided into two general categories: external compression and surgery. Regimens of intensive specialized massage and bandaging techniques, the so-called complex decongestive therapies, are utilized in Australia and Europe and are becoming more available in this country. Drug therapies have also been suggested. However, the most promising class of agents, the benzo-pyrones, are not as yet available in the United States. Other interventions have been recommended, including superficial heating and various diathermy techniques, but little evidence exists to support their use at this time.²⁰⁻²³

The goal of therapy is to ease the amount of swelling experienced by the patient in order to retain or restore function and cosmesis to the affected limb. It is important to communicate with the patient that multiple modalities and an interdisciplinary approach are needed, and that a protracted course of therapy may be required in order to provide satisfactory control of swelling.

External Compression

Compression is defined for purposes of this review as application of any external pressure to the limb. Table 4 lists the various ways increased pressure may be applied to an edematous extremity.

The rationale for external compression in the management of edema is twofold. The compression may limit the amount of lymph formed, and it may reduce the extant swelling within the limb.

Elevation

Elevation of an extremity reduces intravascular hydrostatic pressure. This in turn helps to reduce the tendency to

Table 3: Stillwell Classification: Percentage-Based Criteria

| | |
|---------------|----------------------------|
| Insignificant | 0%-10% > normal arm |
| Slight | 11%-20% > normal arm |
| Moderate | 21%-40% > normal arm |
| Marked | 41%-80% > normal arm |
| Severe | More than 80% > normal arm |

Table 4: External Pressure Application

| Technique | Mechanism | Effect |
|------------------------------------|--|--|
| Elevation | Reduce intravascular hydrostatic pressure; may facilitate drainage | Reduce tendency to form edema |
| Compression garments and bandaging | Increase interstitial pressure | Reduce tendency to form edema |
| Massage and manual lymph drainage | Increase interstitial pressure; may foster lymph clearance; may increase total body lymph flow | Lessen tendency to form edema; may remove lymph from extremity |
| Pumps | Increase interstitial pressure; may foster lymph clearance | Lessen tendency to form edema; may remove lymph from extremity |

form edema, as described by Starling's forces.⁷ Elevation is among the first interventions recommended by oncologists, surgeons, and physiatrists.^{18,19,24} However, there are no data on the efficacy of elevation in the treatment of lymphedema. Recommended guidelines are also not available, and most clinicians appear to base their continued prescription of elevation on anecdotal experience.

Compression Garments

The use of elastic compression garments is widespread in the management of lymphedema. Garments may be prefabricated or custom made. Additionally, garments may be obtained that provide gradient pressures to the limb, in which the pressure exerted distally is somewhat greater than that applied to the more proximate part of the limb.²⁵ Though not necessarily thought of as garments, bandaging and other wrapping techniques likely work on similar principles.

There are few controlled data concerning the use of compression garments in the management of lymphedema.^{25,26} Compression garments may lessen the amount of edema formed within the involved extremity, and also lend a measure of protection against both intrinsic and extrinsic trauma to the limb. Garments may help reduce the amount of edema formed by increasing the interstitial hydrostatic pressures within the limb. This effect would theoretically impede lymph formation according to Starling's forces.⁷ It is less clear whether compression garments facilitate lymph removal. Therefore, the likely benefit offered by compression garments is in *easing* the burden on the remaining functional lymphatics.

Garments also allow a measure of protection from incidental skin trauma such as minor burns, abrasions, and lacerations. Avoiding such minimal trauma may lessen acute exacerbations of swelling. More importantly, garments may act to protect the arm from *intrinsic* injury, the so-called cycle of edema,¹ by lessening the tendency for skin to stretch.^{9,27,28} Stretching of the skin likely occurs as a result of interstitial pressure being exerted on the skin. Over time, the skin's elastic nature eventually relaxes in response to the relentless

forces being exerted on it. As this occurs, an accompanying reduction in the interstitial hydrostatic pressure permits the formation of additional edema. It is this cycle of increasing interstitial pressure followed by stretching of the skin which likely causes the gradual worsening in limb size experienced by many patients with lymphedema. Use of a garment or other type of wrap such as a bandage relieves the skin from bearing the pressure exerted by the accumulating interstitial edema and may therefore lessen the tendency to stretch.

Selection of garment type and recommended guidelines for use remain unclear. There are no data supporting the value of customized over prefabricated garments. Prefabricated garments are usually less expensive than customized. The use of a glove or gauntlet depends on whether the hand is swollen. If hand swelling becomes problematic or is brought on by the use of an arm sleeve, consideration should be given to either a long wrist piece gauntlet or a one-piece customized sleeve. Other indications for customized garments include patients who are difficult to fit or those in need of either a zipper or some other assistive device to facilitate donning of the garment. Garments typically last no more than 6 months; they should be replaced when they begin to lose their elasticity.

Recommended guidelines for the use of garments are unclear. Pressures ranging from 30 to 60mm Hg may be employed. Use of the garment for up to 20 hours per day and longer has been suggested,¹⁰ but there are no studies supporting or refuting this concept. Bertelli et al²⁶ found statistically significant reduction of edema in patients who wore garments for 6 consecutive hours per day. Multivariate analysis of this group found superior reduction in those women who had not had significant weight gain following treatment for breast cancer. Some authors recommend that compression garments be used with any physical activity.^{28,29} Compliance is difficult for patients, as even the most customized garment is typically uncomfortable, unsightly, and laborious to put on. Patient education may improve compliance with the prescribed garment.

Wrapping techniques have been described as part of a treatment regimen consisting of "complex physiotherapy"^{9,29}; others recommend bandaging as part of a comprehensive treatment program.^{28,30,31} Low-elasticity bandages are applied to edematous areas by technicians and provide a high degree of compression. They are then worn for several hours to several days, and are often used in conjunction with exercise of the limb.

Contraindications to the use of compression garments are few. Insensate extremities need to be inspected often to ensure skin integrity. Infections within the limb may make the use of garments more difficult because of pain. Open wounds should not be considered a contraindication. Complications from the use of compression garments include inducing or worsening hand swelling. Skin irritation may occur from contact dermatitis.

Pneumatic Compression

The application of external pneumatic "pumps" has been recommended for a number of years in the management of lymphedema. Several controlled studies exist that support

their use in this population.³¹⁻³⁶ However, the optimum pumping pressures, the length and frequency of pumping sessions, and the need for continuation of pumping after initial reduction has been attained have yet to be determined.

A number of commercially available pumps exist, which range widely in cost and complexity. Cost can vary from several hundred dollars for simpler devices to several thousand for more complex units. Pumps are available with both single chambers and multiple compartments. Multiple-chamber pumps are generally sequential in nature; they produce pressure on the limb by initially inflating distally and then moving proximally. This action theoretically forces edematous fluid to more proximal portions of the limb wherein better lymph removal may occur. Newer sequential pumps are capable of generating gradient pressures.

Pump selection and guidelines for their use are controversial. No individual pump appears to have a distinct advantage or to be inherently superior over any other. Studies exist in which individual pumps have been found to be beneficial in the treatment of edema; however, comparative studies assessing the relative efficacy of these pumps are lacking. One study in a small sample found a multichambered device effective in patients who had previously not responded to a single-chamber device.³² However, one group reported superior response to devices with a single chamber as compared to those with multiple chambers.³⁶ Because of this confusion, it has been recommended that a trial comparing pumping devices be made before a unit is obtained for patients to use at home.¹⁰

Pumping regimens may be done on an inpatient or outpatient basis.^{10,19,34} Pressures to be used as well as the length and frequency of individual pumping sessions have not been established. In a nonrandomized study, statistically significant reduction in edema was described with a sequential gradient pump when administered over a 48-hour period. The maximum distal pressures used were determined by calculating the mean of the systolic and diastolic blood pressures (mean 88.3mm Hg and most proximal, 48.7mm Hg).³² This approach to determining pumping pressure was also reported by Kim-Sing et al.³³ Pappas and O'Donnell³⁴ suggested using pressures ranging from 80 to 110mm Hg, pumping 4 to 8 hours per day. Yamakazi et al³⁷ recommended pressure settings at or near 80mm Hg. Long-term benefits of pumping and compression garments have been reported, including at least partial maintenance of reduction in edema in 36 of 49 patients treated for lower extremity edema for a mean of 25 months.³⁴

Proponents of massage therapy suggest that pumping is ineffective and perhaps dangerous.^{9,28,30} However, an extensive clinical experience exists that does not support these claims.

Complications from pumping therapy are few. Pain may limit the maximum pressure employed. Contraindications include infection in the limb, local or proximate malignancy, anticoagulated patients, and deep vein thrombosis. Use of palliative pumping has been described in patients with advanced cancer in order to restore function and as an adjunct to pain control.¹⁰

Massage Therapies

Traditional massage techniques, including self-administered retrograde massage, are routinely prescribed as part

of a multidisciplinary treatment approach to lymphedema.^{1,9,10,24,29} As described by Földi et al²⁹, Vodder developed manual lymph drainage as a specific technique for lymphedema. This approach suggests that in order to remove lymphedema from a body segment, treatment and "decongestion" of more proximal portions of the body, so called lymphotomes, must occur.²⁸

A comprehensive treatment regimen has been advocated by certain authors which has been termed "complex physical therapy" (CPT) or "complex decongestive therapy."^{9,28,30} These programs comprise four components: meticulous skin hygiene, manual lymph drainage, exercises, and bandaging and use of compression garments. The typical protocol calls for intensive therapy for 4 to 5 weeks, followed by discharge to a maintenance program consisting of bandaging and garments. The garments and bandages used have very little elasticity. Protocols employed call for garments to be worn at all times and typically at a compression ranging from 40 to 60mm Hg.

Various authors claim impressive results with CPT. In several noncontrolled series, reductions in limb size following a 4-week course of CPT have ranged from 60% to 90% reduction, with maintenance of reduction at 1 year of 60% to 100%.^{9,28-30} Földi et al⁹ reported that 54% of patients maintained reduction at 3 years; 35% had partial relapse and 10% total relapse.

Surgical Therapy

Surgical therapy for lymphedema may be divided into two general categories: physiological and reduction surgery. The goal of physiological surgery is to restore some level of lymphatic function to the affected limb. Reduction therapy attempts to remove excess tissue and edema with the hope of returning a limb to a more functional size, at which point more conservative treatments may be employed to control swelling.

Physiological surgery. A variety of techniques have been described, including lymphangioplasty,³⁸ omental flaps and pedicle flaps^{39,40}, and myocutaneous flaps.⁴¹ The preferred technique is the microlymphatic-venous anastomosis (LVA), as described by Degni.³⁸ This procedure entails grafts between lymphatic vessels or nodes and proximate venous systems to allow removal of lymph. Several studies of involved upper extremities found good relief in 50% to 77% of patients treated with LVA.^{38,42-48} Unfortunately, the number of patients with acquired lymphedema due to breast cancer was small in all of these studies. Also, recurrence to some degree was reported to have occurred in most patients undergoing this procedure, likely due to decreased lymph flow through anastomoses.⁴³ One group recommended that further studies be done before LVA is endorsed in the general management of lymphedema.⁴³ O'Brien et al⁴⁴ proposed a combination of LVA with reduction surgery; they reported 60% reduction in patients treated with the combined technique versus 40% treated with LVA alone.

Excisional surgery. Removal of excessive tissue has been performed since early in the 20th century. The Charles procedure was first described in 1912. Though variations of this procedure are still performed,⁴⁹ significant drawbacks

have been associated with it.^{39,40} More recently, suction lipectomy has been reported as a means of reducing the size of the involved extremity.⁵⁰⁻⁵² Zelikovski et al⁵³ suggested a combination of excisional reduction surgery and conservative interventions for certain severe cases.

Surgical therapy remains an option in the treatment of acquired lymphedema. However, it is likely best reserved for severe cases when conservative therapy has failed.^{10,39} The procedure chosen should be one that reduces the size of the limb and thereby allows conservative therapy such as garments to be properly fitted and worn.

Drug Therapy

Several classes of drugs have been utilized in the treatment of lymphedema and associated infection. There are no data supporting the use of diuretics for long-term management of this type of swelling. Some authors suggest, in fact, that use of these agents may be detrimental, though these claims are equally unsubstantiated.⁹

Use of antibiotics is obligatory in the management of cellulitis and lymphangitis. Larger doses may be needed because of the impaired lymphatic function in these patients.³⁶ No controlled data exist that support the treatment of all patients with acquired lymphedema with antibiotics. These drugs should be reserved for patients with known or suspected infection.

Benzo-pyrones are among a group of drugs that reportedly have a salubrious effect on lymphedema. They appear to stimulate proteolysis by macrophages as well as increase the absolute number of macrophages within the affected limb.⁵⁴ Two recent randomized, placebo-controlled crossover studies found statistically significant reduction in patients with lymphedema who received benzo-pyrones for several months.^{54,55} These findings suggest that this class of drugs may be clinically beneficial in the management of lymphedema, while at the same time having very little toxicity. Unfortunately, there are no data about the long-term effects, potential toxicity, or efficacy of these agents.

CONCLUSION

Acquired lymphedema is a relatively frequent complication of axillary node dissection. Patients afflicted with this condition are prone to physical and psychological consequences, including pain, lost function, and depression. There is no cure for acquired lymphedema, but treatment options are available. Unfortunately, the evidence supporting many of these forms of treatment is less than optimal. Claims and counterclaims from biased practitioners have served to further muddy the waters, leaving many clinicians confused about the best options for their patients.

A combination of garments, massage, and the appropriate use of sequential pumps at a sufficient pressure should form the core program for most patients with lymphedema. Though data supporting complex decongestive therapy is primarily anecdotal, it may be an option for some patients. However, its limited availability and significant cost preclude many patients from receiving it. Medications at this time should be used judiciously. Antibiotics are indicated

for patients with a high likelihood of infection. There is little role for widespread use of diuretics. Surgery is best reserved for those in whom conservative care was ineffective. Surveillance for infection and other complications, including psychological concerns, should be maintained after a patient has been placed on a home program.

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