Lymphedema Strategies for Investigation and Treatment

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A Review

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The goal of this article was to define lymphedema as a disease entity, to introduce the American Lymphedema Framework Project, and to summarize current surgical strategies on the horizon in the surgical treatment of lymphedema.

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LYMPHEDEMA DEFINED

Alongside the arterial and venous vasculature, the lymphatic system is a part of the circulatory system. Lymphatic channels primarily regulate the flow of fluid in the interstitium (Ellis, 2006). Under normal conditions, venous capillaries reabsorb 90% of the fluid in the tissues, and lymphatic channels absorb the remaining 10% of lymph fluid, proteins, and other molecules (Warren, Brorson, Borud, & Slavin, 2007). Lymphatic fluid passes to regional lymph node basins. Ultimately, the lymphatic fluid is transported back into the subclavian vein to enter the venous system via the thoracic duct.

Lymphedema is an external or internal manifestation of lymphatic insufficiency and deranged lymph transport (International Society of Lymphology, 2009). This insufficiency causes an accumulation of protein-rich interstitial fluid, leading to distention, proliferation of fatty tissue, and progressive fibrosis. Skin changes such as thickening and hair loss may occur. Progressive lymphedema without adequate management can lead to functional impairment, compromised quality of life, and deformity. Clinically, lymphedema is noted as swelling of the involved extremity. The head and neck, breast, or genitalia may also be affected (McWayne, & Heiney, 2005; Rockson, 2010; Smeltzer, & Stickler, 1985).

Lymphedema is generally classified as either primary or secondary. Primary lymphedema (hereditary) is related to congenital malformation of the lymphatic channels. Secondary lymphedema results from disruption to the lymphatic system. Primary lymphedema can result from any one of a number of disorders that may be sporadic or hereditary. Syndromes such as Milroy's disease and Prader-Willi syndrome have lymphedema as an element of their clinical manifestations to varying degrees. The estimated prevalence of primary lymphedema is 1.15 in 100,000 persons under the age of 20 years (Smeltzer & Stickler, 1985). In children, the two main causes are Milroy's disease and lymphedema distichiasis (International Society of Lymphology, 2009).

Secondary lymphedema is a consequence of removal or

damage to lymph nodes, fibrosis of the nodes (postradiotherapy), and trauma or infection (Rockson, 2010). Upper extremity lymphedema is commonly associated with the treatment of breast cancer. The degree of lymphedema has been well recognized to correlate with the number of lymph nodes that have been removed and the extent of radiotherapy to the axillary region. Lower extremity lymphedema is most often seen in survivors of uterine and prostate cancer, as well as melanoma and lymphoma survivors (Meneses & McNees, 2007). Most cancer survivors develop lymphedema within 3 years of treatment (Petrek, Senie, Peters, & Rosen, 2001).

In addition to cancer ablation, side effects of advanced diseases such as congestive heart failure, neurological and liver disease, and end-stage renal disease can cause chronic edema. An increase in the bariatric population has also seen an increase in lymphedema incidence. Lympedema caused by the parasite wucheria bancrofti and transmitted by mosquitoes remains the most common cause of lymphedema worldwide. Unfortunately, no strategies employed to prevent the onset of lymphedema have proven fruitful to date. The term *chronic edema* has been adopted by European investigators to define a population of patients with long-standing edema (>3 months). Prevalence estimates for chronic edema are between 1.3 and 1.5 per thousand.

New clinical data suggest that some patients may have a primary disposition to lymphedema but that this first becomes clinically evident after a secondary eliciting event (Rockson, 2010). *Lymphedema tarda* is defined as debut after the age of 35 years. It is often associated with an eliciting factor such as trauma or an inflammatory reaction (Kerchner, Fleischer, & Yosipovitch, 2008).

AMERICAN LYMPHEDEMA FRAMEWORK PROJECT

As a disease entity, lymphedema can result from a variety of pathologies. The inciting event may be congenital or acquired. Acquired etiologies can be divided into oncologic, infectious, and traumatic. As such, no single discipline has evolved to manage this disease entity in its many manifestations. The American Lymphedema Framework Project (ALFP) was developed to enable partnerships across disciplines and among stakeholders to develop lymphedema best practice initiatives in clinical care, health policy, education, and research (Armer, Stewart, & Shook, 2009).

The ALFP is a national initiative developed under the leadership of recognized clinical experts and investigators in the field of lymphedema. A collaboration of health care providers, researchers, patients, and industry representatives, the ALFP was designed to develop and evaluate appropriate health care services for patients with all forms of lymphedema and advance the quality of lymphedema care (Armer, 2012).

The ALFP mission is to improve the management of lymphedema and related lymphatic disorders in the United States, while contributing to global international improvement in this field with the goal of defining best practices and developing a minimum data set to improve lymphedema outcomes.

The ALFP National Stakeholders Conference, held in Chicago in March 2009, was the initial event for the collaborative input and culminated in proposals, action plans, and targeted goals to drive their initiatives ahead.

During the conference, it was identified that to enhance the current evidence base, various types of research methodologies, including basic, clinical, epidemiological, heath service delivery, and patient-related, must be incorporated into the field of lymphedema (Armer et al., 2009).

ALFP Goals

- Revise and update a Best Practices Document for lymphedema care in the United States.
- Develop and implement a lymphedema minimum data set for clinical and research use nationally and internationally.
- Design a U.S.-based epidemiology protocol to determine the size and complexity of the problem of lymphedema from all causes (primary and secondary lymphedema).
- Develop methods for evaluating patient-based outcome measures and improving patient outcomes.
- Develop and provide appropriate practice-based lymphedema educational programs.
- Contribute to the mission and goals of the International Lymphedema Framework.

A systematic literature review was completed sorting approximately 6,000 articles with content on lymphedema. Databases searched included PubMed, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, PapersFirst, ProceedingsFirst, Worldcat, PEDro, National Guidelines Clearing House, ACP Journal Club, and DARE.

The literature reviews revealed that additional research with quality methods are needed regarding lymphedema and its management.

Imperatives for research to support guidelines for lymphedema are that well-designed studies

- with precise measurements,
- larger well-defined study cohorts,
- followed over longer time periods,
- with stand-alone and bundled interventions, and
- incorporating standard of care versus optimal care guidelines.

Lymphedema research should be considered as a research priority by scientists, health policy experts, and funding sources (ALFP, 2012).

SURGICAL TREATMENT HORIZONS

As the ALFP works to improve our understanding of lymphedema with a data-driven approach to patient care, the efficacy of surgical management techniques will become more readily measured. Already novel surgical treatments have begun to be employed in the management of chronic lymphedema. Although the gold standard for management remains medical and includes decompressive measures, surgical treatments, including excision, lymphaticovenular bypass, and vascularized lymph node transfer, are under active investigation.

Excisional techniques have been used since the 1910s and include debulking and liposuction (Cormier, Rourke, Crosby, Chang, & Armer, 2012). Debulking surgery involves removal of lymphedematous adipose tissue down to fascia, followed by skin grafting or primary closure after elevation of skin flaps (Cormier et al., 2012; Salgado, 2009). While earlier reports of this technique demonstrate its suboptimal outcomes and high complication rates, more recent reports show that debulking can have good functional outcomes and minimal complications (Doscher, Herman, & Garfein, 2012; Karri et al., 2011; Lee et al., 2008; Modolin et al., 2006; Salgado, 2009; van der Walt, Perks, Zeeman, Bruce-Chwatt, & Graewe, 2009). Salgado (2009) reports a 21% volume reduction, using surgical excision in the upper extremity at greater than 1 year postoperation. Liposuction has been utilized more recently to remove subcutaneous lymphedematous fat and has proven to be efficacious for volume reduction (Brorson et al., 2006; Brorson & Svensson, 1998; Brorson, 2003, 2012; Damstra, Voesten, Klinkert, & Brorson, 2009; Greene, Slavin, & Borud, 2006; Liu, Zhou, & Wei, 2005; Schaverien, Munro, Baker, & Munnoch, 2012; Taylor & Brake, 2012). In their study of 37 patients, Damstra, Voesten, Klinkert, et al. (2009) reported that a 118% volume reduction of the upper extremity at 1 year following suction assisted lipectomy. Long-term results have also been reported with an upper extremity volume reduction of 101% at 5 years (Brorson et al., 2006). The most common disadvantage of this method includes transient numbness. An advantage, aside from volume reduction, is increased skin blood flow, which may decrease the incidence of cellulitis (Brorson, 2003).

Lymphaticovenular bypass is another surgical treatment of lymphedema. Supermicrosurgery with the aid of high-power microscopy has been used to anastomose lymphatic channels to subdermal venules of less than 0.8 mm in diameter (Campisi et al., 2010; Chang, 2010; Cormier et al., 2012; Damstra, Voesten, van Schelven, & van der Lei, 2009; David & Chang, 2010; Demirtas, Ozturk, Yapici, & Topalan, 2009; O'Brien et al., 1990; Yamamoto, & Sugihara, 1998). This method is based on two concepts, first that subdermal lymphatics are less affected by lymphedema and can be used for bypass, and second that pressure in subdermal venules is low and therefore venous backflow is minimized (David & Chang, 2010). Chang prospectively utilized this technique in 20 patients with upper extremity lymphedema (Chang, 2010). He created two to five anastomoses for each patient. Nineteen patients reported symptom improvement following surgery, and a mean volume reduction of 35% was seen at 1 year postoperation (David & Chang, 2010). In the largest retrospective study of 1,800 patients over 10 years, Campisi et al. (2010) demonstrate a volume reduction of 67% and note that 85% of patients were able to discontinue conservative treatment modalities. Disadvantages to this procedure are that it is technically challenging and results are currently unpredictable (Auba, Marre, Rodríguez-Losada, & Hontanilla, 2012). Advantages of lymphaticovenular bypass include minimal invasiveness and a low rate of complications (David & Chang, 2010).

The most recent advancement in surgical lymphedema treatment is vascularized lymph node transfer. Healthy lymph nodes, artery, and vein are transplanted from the axilla, groin, or submental region to the affected area of lymphedema (Becker, Assouad, Riquet, & Hidden, 2006; Cheng et al., 2012; Lin et al., 2009; Saaristo et al., 2012; Viitanen, Mäki, Seppänen, Suominen, & Saaristo, 2010). One hypothesis is that the transferred lymph nodes act as a pump and suction pathway for lymphatic clearance (Lin et al., 2009). Lin et al. (2009) report, at over 4 years postoperation, a 51% reduction in upper extremity volume when transferring groin lymph nodes to the wrist. Cheng et al. (2012) report a reduction in circumference of more than 60% in the lower extremity when utilizing submental lymph nodes transferred to the ankle. In Becker and colleagues' study of 24 patients with groin lymph node transfer to axilla for upper extremity lymphedema, physiotherapy was able to be discontinued in 62.5% of patients (Becker et al., 2006). Although development of lymphedema in the donor site is a concern, literature has shown morbidity to be minimal. In a study of 13 patients utilizing lymphatic groin flaps, none of the patients experienced an increase in lower limb circumference (Viitanen et al., 2010). Disadvantages of this procedure

include potential flap loss and bulkiness of the recipient site (Cormier et al., 2012).

CONCLUSION

Multidisciplinary data-gathering efforts such as the ALFP will serve to improve our understanding of the diagnosis and management of lymphedema. We must better define the disease process for each affected individual with improved diagnostic techniques. Surgical intervention remains in its infancy but offers promising techniques to achieve long-term management.

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