

# Lymphedema

The Forgotten Condition

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## Objectives...

- ▶ 1) Understand the etiology, prevalence, and clinical course of lymphedema
- ▶ 2) Understand effective treatment strategies
- ▶ 3) Appreciate the unique variables of acute care lymphedema treatment

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The Functional Lymphatic System

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## Pathophysiology of Lymphedema

- ▶ Lymphedema is an abnormal collection of protein-rich fluid in the interstitial space that results from a disruption of lymphatic flow back into your systemic circulation. This results in water retention and swelling of tissue.
- ▶ Obstruction may occur in both the lymph nodes and the lymphatic vessels; eventually subcutaneous tissue becomes fibrotic, impairing vascular flow and oxygen transfer to tissues.
- ▶ It may result from or be aggravated by radiation therapy, trauma, cancer, morbid obesity, or surgery involving the lymph tissue.

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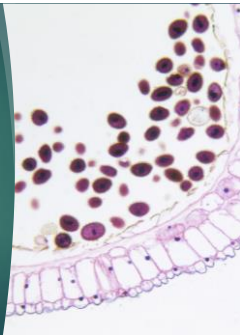
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## Pathophysiology of Lymphedema

- ▶ Depending on the cause of the lymph obstruction, the edema may be unilateral or bilateral.
- ▶ Skin over the lymphedematous area becomes thickened with a peau d'orange appearance (thick and pitted).
- ▶ In chronic disease, the patient is at risk for developing fissures, which act as a port of infection by allowing lymph fluid to leak onto the skin, often causing ulcerations.



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### Peau d'orange skin appearance



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## Pathophysiology of Lymphedema

- ▶ The affected area may develop verrucous cobblestone plaques, also known as Elephantiasis Nostras Verrucosa.



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## Impact of Lymphedema

- ▶ The HRQOL measure is a multidimensional assessment that considers emotional, functional, social/family, and physical domains.
- ▶ Pusic et al completed a systematic review of QOL outcomes in breast cancer related lymphedema. In the 39 studies that met the inclusion criteria, the results showed that exercise and complete decongestive therapy were associated with improved overall QOL in this population.
- ▶ Polic, A., Dembi, T., Alibek, C. et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv. 2015;7:83-92.

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## Causes...

- ▶ Milroy's Disease – Genetic mutation resulting in foot & leg edema
- ▶ Filariasis (roundworm infection)
- ▶ Surgery
- ▶ Radiation
- ▶ Cancer
- ▶ Infection
- ▶ Trauma
- ▶ CHF
- ▶ Portal HTN
- ▶ Burns
- ▶ Insect bites, etc.

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## Risk Factors

- ▶ Axillary radiation or node removal
- ▶ Sentinel node removal
- ▶ Obesity
- ▶ Local radiation to axillary, inguinal, pelvic, or subclavian areas
- ▶ Delayed wound healing
- ▶ Scarring of right or left subclavian ducts
- ▶ Intrapelvic or intra-abdominal tumors that compress lymph system components



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## Signs & Symptoms

- ▶ Difficulty fitting into clothing
- ▶ Fatigue
- ▶ Pain
- ▶ Aching or warmth in the affected arm or leg
- ▶ Feelings of tightness, heaviness, or weakness in the affected arm or leg
- ▶ Fever, chills, and generalized weakness
- ▶ Difficulty with ADL's
- ▶ Social awkwardness due to appearance
- ▶ Recurrent infection (bacterial or fungal)

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## Incidence

- ▶ Between 10% and 40% of patients in the U.S. who undergo breast cancer surgery with lymph node dissection develop some degree of ipsilateral upper extremity edema
- ▶ Congenital lymphedema occurs 70% to 80% more often in females
- ▶ Lymphedema of the upper extremities occurs most often after breast cancer; lower extremity lymphedema occurs most often with uterine or prostate cancer, lymphoma, or melanoma

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## Physical Findings

- ▶ Edema, typically non-pitting, in the affected extremity
- ▶ Fissuring, ulcerations, and skin breakdown, with clear, yellow exudate
- ▶ Thickened skin in the affected area, along with erythema
- ▶ Stemmer sign is positive (inability to lift the thickened skin between the first and second toes or fingers when pinched)

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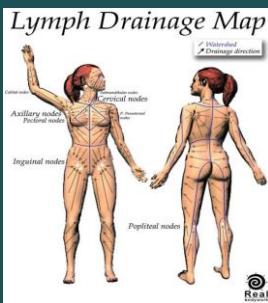
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## Manifestation

- ▶ Manifests as swollen, sometimes disfigured extremities or truncal regions that can cause pain and functional impairment
- ▶ Electron microscopic examination of damaged lymphatics show that the destruction first occurs proximally, at the smooth muscle cells of the vessel walls
- ▶ Functional studies show that when lymphatic drainage is interrupted, it leads to superficial collateralization with retrograde flow to the skin lymphatics.
- ▶ Lymphatic fluid stasis leads to skin thickening and subcutaneous soft tissue fibrosis.

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## Genetics

- ▶ Why only some patients develop secondary lymphedema due to cancer treatment remains unknown.
- ▶ Recent studies have identified polymorphisms in multiple candidate genes that appear to be associated with the development of breast cancer-related lymphedema.<sup>13</sup>
- ▶ A recent study compared the frequency of genetic polymorphisms among breast cancer survivors with or without lymphedema and found significant associations for three genes, all of which are involved with the body's inflammatory response.<sup>14</sup>
- ▶ Genetic polymorphisms associated with immune-deficient states have also been linked with lymphedema.<sup>4</sup>




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## Incidence Breast Cancer

- ▶ At this time there are more than 4 million breast cancer survivors in the United States. This includes women still being treated and those who have completed treatment.<sup>5</sup>
- ▶ One of the largest population-based prospective studies to date, of 631 women living in Pennsylvania, found that the 5-year cumulative incidence of patient-reported lymphedema among breast cancer survivors was 42%. Most was mild lymphedema, but it was found that early-onset correlated with moderate to severe lymphedema.<sup>6</sup>
- ▶ The incidence varies largely with the type of treatment received. In a meta-analysis of 5,354 women, those having a sentinel lymph node biopsy (SLNB) was 6.3% and axillary lymph node dissection (ALND) was 22.3%.<sup>7,8,9</sup>

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## Impact of radiation – difficult to separate effects of radiation from surgery.

- ▶ Radiation targets alone for breast/chest wall was 14.5%
- ▶ Breast/chest wall and supraclavicular was 31.5%
- ▶ Breast/chest wall, supraclavicular, and posterior axillary region was 41.4%
- ▶ Genitourinary cancers was 16%
- ▶ Gynecologic cancers was 34%

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## Measuring Lymphedema

- ▶ Water displacement – Good for quantifying limb volume, not good for localizing lymphedema to a particular limb segment



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## Circumference Measurement

- ▶ Taken at specific anatomic landmarks, accounts for size variations on the limb, and allows for calculating the limb's volume



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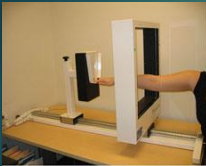
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## Perometry

- ▶ Noninvasive optoelectronic device using infrared light to create an image of the limb and volumetric measurement. Abnormalities in particular regions can be accounted for.



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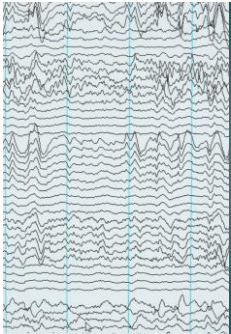
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### Bioelectrical Impedance

- ▶ Measures the opposition of flow of an electrical current through the body
- ▶ The path of electrical current through tissue is frequency-dependent; taking into account the extracellular water compartment.

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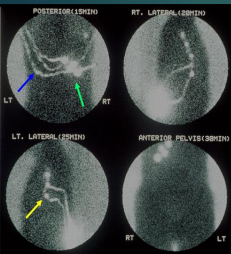
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### Diagnostics: Lymphoscintigraphy

- ▶ Uses radioactive colloid material to detect obstructions or inflammation within the lymphatic system

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### Diagnostics: Lymphangiography

- ▶ Outlines the lymphatic system



(a) (b)

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## Diagnostics: Near-Infrared Fluorescence Imaging (NIRF)

- ▶ Involves intradermal administration of indocyanine green (ICG) dye
- ▶ Immediate uptake into dermal lymphatics and maps the transit through the collecting and conducting lymphatic vessels
- ▶ Can guide lymphedema-relieving surgeries, such as lymphaticovenular anastomoses to redirect drainage toward otherwise unknown, newly formed functional lymphatics, crossing surgical and radiation scars.
- ▶ Used to demonstrate the effectiveness of manual lymphatic drainage (MLD).

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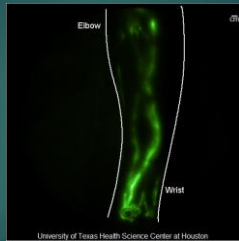
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## Decongestive Lymphatic Therapy (DLT)

- ▶ Lymphatic drainage massage (LDM)
  - ▶ NIRF imaging showed a 23% mean increase in lymph system contraction speed after LDM
- ▶ Compression garment
- ▶ Exercise for those having, or are at risk of developing lymphedema
  - ▶ A meta-analysis of 19 studies using resistance, aerobic, or other types of exercise by patients with breast cancer showed it can be safe and doesn't increase their risk for lymphedema or exacerbate their symptoms when proper supervision is provided.

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### "Up To Date" statement on medications...

- ▶ Pharmacologic treatments are not generally used, as no drug has definitively been shown to be beneficial. In particular, diuretics should not be given.
- ▶ Diuretics may result in volume depletion, with fluid loss coming from the intravascular space.
- ▶ With lymphatic obstruction, the edema cannot be easily mobilized into the vascular space.<sup>17</sup>
- ▶ Some retinoid agents such as Soriatane (can help prevent hyperkeratinization)<sup>18</sup> and Tazarac (can help modulate the differentiation and proliferation of epithelial tissue).<sup>19</sup>



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### Lymphatic Reconstruction

- ▶ Microsurgical reconstruction of the lymphatic system, creating anastomoses between lymphatics and veins.
- ▶ Less invasive than other surgeries and usually only requires one night in the hospital.
- ▶ Seventeen studies enrolling 2,251 patients who had lymphatic venous anastomosis in the upper extremities, lower extremities, or head/neck, reported volume reductions from 23-91.7%.<sup>20</sup>
  - ▶ In studies involving more than 50 patients, I found the following:
    - ▶ Koshima, 2004, 52 patients, LE = 42% reduction.<sup>21</sup>
    - ▶ Compisi, 2010, 1,800 patients, UE's and LE's = 56% reduction.<sup>22</sup>

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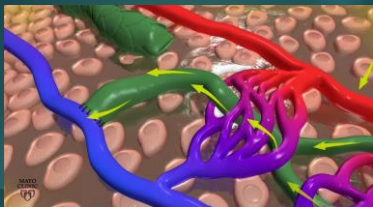
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Lymphovenous anastomosis

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## Recent Research

- ▶ 9-cis and 13-cis retinoic acids have been found to be potent lymphangiogenic factors that stimulates proliferation, migration and lymphatic vessel growth in various animal models. After injection, faster lymphatic drainage and increased lymphatic vessel density was demonstrated.<sup>22,21</sup>
- ▶ This study reviewed data from 4,437 patients who were diagnosed with lower extremity lymphedema at Mayo Clinic in Rochester from 2000 to 2020. Compared with a matched control group, the group with lymphedema had an increased risk of skin cancer, and for patients who had lymphedema in one leg, that extremity was nearly three times as likely to have skin cancer compared with the other leg.<sup>22</sup>

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## Recent Research

- ▶ At present, there are 28 known genes that might harbor causal mutations for primary lymphedema, yet these identified mutations account for <30% of the identified case presentations.<sup>23</sup>
- ▶ Preclinical animal models of acquired lymphedema lend support for therapeutic lymphangiogenesis through VEGF-C/VEGF-R and various other lymphangiogenic growth factor signaling pathways.<sup>24,25</sup>
- ▶ Early human trials of injecting human growth factor, VEGF-C, into newly transplanted lymph nodes in the axilla following mastectomy showed a 46% reduction of excess arm volume after the 12-month follow-up. Lymphedema Quality of Life Inventory (LQOLI) questionnaire showed significant and sustained improvement of quality of life.<sup>26</sup>

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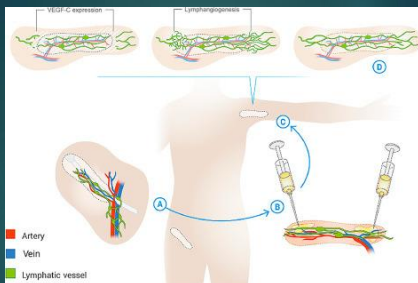
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## "Hot off the Press" Research

- ▶ Stanford University has identified a molecular cause of lymphedema involving the inflammatory molecule leukotriene B4 (LTB4). This discovery has led to the development of a potential drug treatment, *Bestatin* (also known as *Ubenimex*). This drug prevents LTB4 from blocking normal drainage of lymphatic fluid and also prevents further damage to lymphatic vessels. Clinical trials are ongoing, marking the first time a drug treatment is being tested for lymphedema.<sup>35</sup>
- ▶ Surgeons have recently performed the first-ever dual robotic surgery for lymphedema, which combines advanced microsurgical techniques to transplant lymph nodes and reconnect lymphatic vessels. This offers greater precision and reduced recovery time.<sup>36</sup>

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## Levels of Compression

**What are the sock compression levels?**

Compression socks are manufactured with different compression level ranges. This means the amount of pressure will not fall below the bottom number and will not exceed the top number.

15-20 mmHg	20-30 mmHg	30-40 mmHg	40-50 mmHg
<p>Best for everyday compression needs.</p> <p>Helps with swelling and fatigue of the legs.</p> <p>Good for standing or sitting.</p> <p>Does not restrict circulation to legs.</p>	<p>Best for moderate to severe varicose veins.</p> <p>Any medical issues, such as ulcers or sores.</p> <p>Good for long flights.</p> <p>Prevents bruising, swelling and pain in older legs.</p>	<p>Best for moderate to severe varicose veins.</p> <p>For travel and/or after long commutes.</p> <p>Recommended for lymphedema.</p> <p>Good for long flights, travel, pregnancy and longer.</p>	<p>Best for severe varicose veins, ulcers, sores, and other medical conditions.</p> <p>Prevents bruising, swelling and pain in older legs.</p> <p>Used by some women during pregnancy and postpartum.</p>

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## Ankle Brachial Index (ABI)

Right ABI = Highest pressure in the right foot

Highest pressure in both arms

Left ABI = Highest pressure in the left foot

Highest pressure in both arms

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ABI Result	Disease Process	Action
> 1.4	Calcification/vessel hardening	Refer to vascular specialist
1.0 - 1.4	Normal	Compression allowed, 30-40 mmHg
0.9 - 1.0	Borderline	Compression allowed, 30-40 mmHg
0.8 - 0.9	Some arterial disease	Compression allowed, 30-40 mmHg
0.5 - 0.8	Moderate arterial disease	Reduced compression advised, 23-30 mmHg
< 0.5	Severe arterial disease	Compression is contraindicated

Source: Journal of Wound, Ostomy and Continence Nursing 39(2):p 121-129, March/April 2012.  
 | DOI: 10.1097/WON.0b013e31824784de

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## How to Quantify Stretch...

Juzo Pressure Monitor



- ▶ You can slip the pressure monitor under the compression product and measure the amount of pressure being applied.
- ▶ This device costs around \$495.00.




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## What I Consider Before Bandaging

- ▶ Are the wound care orders consistent with the frequency of the compression bandaging?
- ▶ At the end of the patient's time in my facility, is there a capable party to resume this intervention? Can someone be trained?
- ▶ Does an ABI need to be performed to establish a safe amount of compression?
- ▶ I's and O's! How much urine is being produced if fluid isn't being removed during dialysis or Aquapheresis?
- ▶ Is the CHF stable enough to handle the increased fluid burden?
- ▶ Are creatinine levels safe enough to not worsen kidney function?

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## Lymphatic Pneumatic Pump

- ▶ Provides peristaltic compression, distal to proximal
- ▶ Typical wearing schedule is one hour in the morning and one hour in the evening



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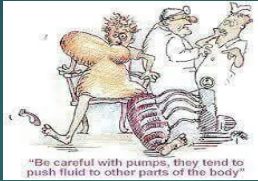
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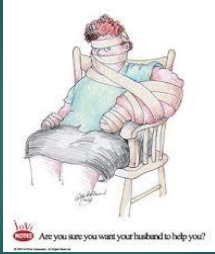
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MEDIGRIP® LF		MEDIGRIP LATEX FREE (LF) SIZING CHART FOR COMPRESSION						
ITEM#	SIZE	LEGGING MEASUREMENT*				COMPRESSION LEVEL FOR DOUBLE LAYER		
		Waist (inches)	Hip (inches)	Thigh (inches)	Calf (inches)	ankle (inches)	Pressure (mm Hg)	Height (inches)
MSC9500LF	A - 1.75 in (4.5 cm)	5	5.5	13	14	A	-	-
MSC9501LF	B - 2.5 in (6.4 cm)	5.5	6	14	15	B	A	-
MSC9502LF	C - 2.63 in (6.7 cm)	6	7	15	16	C	B	A
MSC9503LF	D - 3 in (7.6 cm)	6.5	8	16	17	D	B	A
MSC9504LF	E - 3.5 in (8.9 cm)	7	9	17	18	E	C	B
MSC9505LF	F - 4 in (10.2 cm)	8	10	18	19	F	D	B
MSC9506LF	G - 4.75 in (12.1 cm)	9	11	19	20	G	E	C
MSC9507LF	J - 6.75 in (17.2 cm)	15	18	25	30	F	E	C
MSC9508LF	K - 9.25 in (23.6 cm)	23	28	32	37	J	G	-
		25	30	35	40	K	J	-

**CONTRAINDICATIONS:** Exercise caution when applying compression to patients with severe arterial disease. Always conduct a patient assessment to ensure the safety of compression therapy.

**CHANGE FREQUENCY:** Up to 7 days.

Not made with Natural Rubber Latex. Non-Sterile. Single patient use for each cut piece.

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MEDIGRIP™ SIZE RANGE		
ITEM#	SIZE	USAGE
MSC9500	A - 1.75 in (4.45cm)	Small extremities
MSC9501	B - 2.5 in (6.35cm)	Hands or small arms
MSC9502	C - 2.63 in (6.67cm)	Arms or small legs
MSC9503	D - 3 in (7.62 cm)	Legs or large arms
MSC9504	E - 3.5 in (8.89 cm)	Legs or small thighs
MSC9505	F - 4 in (10.16cm)	Large knees or thighs
MSC9506	G - 4.75 in (12.07cm)	Large thighs
MSC9507	J - 6.75 in (17.15cm)	Small trunks
MSC9508	K - 8.25 in (20.96cm)	Medium trunks

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### Popular Types of Compression



**TED hose**  
\$10-40/pair. Offers graduated compression, offers between 8-18 mmHg, lasts around two months.



**Unna Boot**  
\$10-30/boot, one-time use. Typically provides 20-30 mmHg stretch.



**3M 2 Layer Coban Compression**  
Around \$18.30/box, one-time use. Can offer up to 30-40 mmHg stretch.

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### Popular Types of Compression



**Tubigrip**  
Approximately \$50/roll, to be changed out every 7 days, offers up to 30 mmHg if double layered.



**Rosidal K**  
Around \$20-25/roll, intended for single use, changed every few days, offers 20-30 mmHg stretch.



**Comprilan**  
Around \$10-20/roll, refill every 2-3 days, can be reused, designed to offer up to 30-40 mmHg stretch.

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## Popular Types of Compression

### Circaid



- Costs on average of \$225/pair.
- Offers 20-50 mmHg stretch.
- Easier to apply than traditional stockings.
- Typically last 6-12 months.
- Stretch can be graded with a color-coded system.

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## Jobst Compression Stocking Donning Tool



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Myth Buster Question... True or False?

It is NOT appropriate to apply compression bandaging to a weeping extremity that has been saturating through all of the wound dressings.

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False!

The best way to stop the weeping is to apply compression to the limb.

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### When NOT to compress

- ▶ **Acute Infection** (e.g., Cellulitis). Compression should not be applied if there is an active infection in the affected limb, as it can worsen the infection or cause systemic spread. Treating the infection first is essential.
- ▶ **Untreated or unstable CHF**: Compression can shift fluid back into the circulation, which may overload the heart, worsening symptoms and potentially leading to heart failure decompensation.
- ▶ **Arterial Insufficiency**: Contraindicated in patients with significant peripheral arterial disease (PAD), usually defined by an ABI (Ankle-Brachial Index) of less than 0.5, as it can further restrict blood flow and lead to ischemia or tissue damage.




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### When NOT to compress

- ▶ **Acute DVT**: Compression should be avoided in a limb with an untreated or newly diagnosed blood clot, as it may dislodge the clot and cause complications like a pulmonary embolism. Compression can be reconsidered after anticoagulation therapy is well-established.
- ▶ **Uncontrolled Hypertension**: Compression therapy can increase venous return and elevate blood pressure. In patients with poorly controlled hypertension, compression therapy may aggravate the condition and needs to be used cautiously.




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## How long for blood thinners to become therapeutic?

1. **Heparin (Intravenous):** Starts working almost immediately, with therapeutic effects observed within minutes.
2. **Heparin (Subcutaneous):** Takes about 1 to 2 hours to achieve therapeutic levels.
3. **Low Molecular Weight Heparin (e.g., Enoxaparin):** Takes about 3 to 5 hours to reach peak levels, and therapeutic effects are generally observed within a few hours.
4. **Warfarin (Coumadin):** Takes several days (typically 3 to 5 days) to reach therapeutic levels due to its impact on vitamin K-dependent clotting factors, which have varying half-lives.
5. **Direct Oral Anticoagulants (DOACs):**
  1. **Eliquis (Apixaban):** Reaches peak levels within 3 to 4 hours, with therapeutic effects often noted within a few hours.
  2. **Xarelto (Rivaroxaban):** Reaches peak levels within 2 to 4 hours, with therapeutic effects typically observed within a few hours.
  3. **Pradaxa (Dabigatran):** Reaches peak levels within 1 to 2 hours, with therapeutic effects usually occurring within a few hours.
  4. **Savaysa (Edoxaban):** Reaches peak levels within 1 to 2 hours, with therapeutic effects observed within a few hours.

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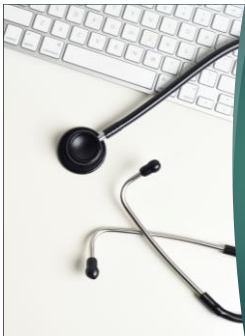
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## Inpatient Lymphedema Reminders

- ▶ If appropriate, have the patient's wound care needs coincide with the scheduled days to re-bandage, typically Monday, Wed, and Friday.
- ▶ In CV/ICU, if the physician writes an order accordingly, the compression bandaging can cover the areas where pedal pulses would otherwise need to be taken each shift.
- ▶ If the patient doesn't tolerate the compression bandaging or it gets wet or soiled, it can be removed and placed in a location where it will not be thrown away. The material used is often very expensive and can be laundered.

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## Lymphedema Referrals



- ▶ Last minute referrals are very difficult, unless there is a capable family member who is available to be trained.
- ▶ Ideally, the patient will be able to continue their progress post-discharge by transitioning to an outpatient or home health care specialist.
- ▶ Unfortunately, follow-through and know-how with compression bandaging in the home health and SNF setting is greatly lacking.

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## Info for Referral Sources

- ▶ It is never appropriate for a patient to be measured for compression stockings before they have regained their baseline size.
- ▶ Beginning January 1st, 2024, Medicare finally began paying for compression stockings. Assuming the store-front business can bill Medicare, they will require the prescription, sizing measurements, and necessary insurance information for billing purposes.
- ▶ Often, VA benefits will cover the cost of the recommended compression stockings.

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## That's a Wrap!




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## Seriously, more references?!

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