Venous vs Arterial Ulcerations: The Yin & Yang Dilemma When Mixed

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OVERVIEW

The prevalence and costs of lower extremity ulcerations in the US are increasing. Venous leg ulcerations (VLU) are the most common type of leg ulcer, affecting around 1% of the population and 3% of people aged over 80.[1] Ischemic ulcerations, also referred to as arterial ulcerations, are primarily attributed to poor circulation/perfusion to the lower extremities. The overlying soft tissues are deprived of oxygen desiccating the area of vital nutrients and healing capabilities that subsequently form an open wound.

There are a number of causes of lower extremity ulcerations. Additionally, there is even a greater problem in patients who may have several causes for lower extremity ulcerations that evolve with time. For instance, a patient with a long-standing, pure venous ulcer may have arterial insufficiency develop with increasing age, which can make the treatment pathway challenging and problematic if not correctly identified.

VENOUS LEG ULCERATIONS

The Society of Vascular Surgery and American Venous Forum proposed the standard definition of the VLU as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension.[2] Diagnosis of venous leg ulcerations is made by clinical history and examination, and anatomic and physiologic data to confirm venous etiology and rule out other causes, most notably arterial insufficiency. The etiology is attributed to a series of local and systemic factors that include venous valvular incompetence, retrograde blood flow, and venous hypertension **(Figure 1)**. Clinically this can be appreciated with increased lower extremity edema and swelling. These factors lead to an increase in pressure within the deep venous system causing the vein walls to stretch, opening up the valves, and allowing even more blood to fill the veins.[1]

Another factor that influences the development of VLUs is calf muscle pump failure. The calf muscle, through contraction and relaxation, aids in the flow of blood back to the heart through the veins. As the ankle is plantar flexed, the shape of the calf muscle changes, becoming wider and flat, exerting pressure on the veins.[1] Failure of this mechanism causes venous stasis of blood and the aforementioned increased venous pressure.[1] Calf pump failure can potentially arise from paralysis, immobility, sleeping in a chair with legs dependent for long periods of time and fixed ankle joints.[1]

Other potential VLU etiologies include the fibrin cuff and blood cell activation and trap hypothesis theories. The fibrin cuff theory

stipulates that capillary bed distension permits fibrinogen to leak into the dermal tissue forming fibrin cuffs around dermal capillaries and reducing fibrinolytic activity obstructing the healing process.[3] The white blood cell activation theory hypothesizes that venous hypertension reduces velocity of blood through capillary beds resulting in leukocytes adhere to each other and/or capillary walls.[4] Leukocyte aggregation causes "plugging" of the capillaries, resulting in tissue ischemia/migration of cells into the surrounding tissues where they release proteolytic enzymes/inflammatory mediators causing additional

Figure 1. Abnormal anatomy: the main culprit. RBC= red blood cell; WBC= white blood cell. Figure used with permission from Snyder, Ead and Cuffy.

tissue damage.[4] Finally, the trap hypothesis states that fibrin and macro-molecule network leak out of the permeable capillary beds into the dermis traps growth factors and matrix proteins, rendering them unavailable. Many healthcare providers believe that it is actually combination of these potential mechanisms that lead to the recalcitrant nature of these chronic wounds.

VENOUS LEG ULCER DIAGNOSIS

The diagnosis of VLUs is made clinically on the basis of anatomic location, morphology, and characteristic skin changes. Once veins become distended, the venous wall starts to disintegrate often resulting in edema, hemosiderin formation, hyperpigmentation, lipodermatosclerosis, and prominent venous ulcers. Patients with venous insufficiency commonly present an inverted champagne bottle look on the effected leg. It should be noted that the appearance of venous insufficiency could vary. Distention of the veins in the sub-dermal plexus results in varicosities. When smaller sub-dermal capillary networks distend, they form telangiectasia's also known as "spider veins". Cellular senescence has been reported in fibroblasts collected from chronic non-healing ulcers. Lal et al. found that fibroblasts from patients with increasing levels of venous disease by clinical class, etiologic, anatomic, and pathophysiologic (CEAP) criteria displayed a progressively diminishing response to agonist-induced proliferation.[5]

In order to standardize the reporting and treatment of the diverse manifestations of chronic venous disorders, a comprehensive classification system (CEAP) has been developed to allow uniform diagnosis and comparison of patient populations **(Table 1)**.[2] The fundamentals of the CEAP classification include a description of the clinical class (C) based upon objective signs, the etiology (E), the anatomical (A) distribution of reflux and obstruction in the superficial, deep and perforating veins, and the underlying pathophysiology (P), whether due to reflux or obstruction.

TABLE 1: CEAP CLASSIFICATION

Clinical	Classification	Etiological	Classification
C0	No visible or palpable signs of venous disease	Ec	Congenital
C1	Telangiectasia's or reticular veins	Ep	Primary
C2	Varicose veins	Es	Secondary (post-thrombotic)
C3	Edema	Anatomic	Classification
C4a	Pigmentation and eczema	S	Superficial veins
C4b	Lipodermato-sclerosis atrophy blanche	P	Perforating veins
C5	Healed venous ulcer	D	Deep veins

Pathophysiologic	Classification
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

Adapted from O' Donnell et al.[2]

Other conditions may coexist in a patient with chronic venous insufficiency. A key differential is a Marjolin's ulcer, which may develop when squamous transformation occurs in a preexisting benign chronic wound. A VLU not responding to standard wound care and compression after 4-6 weeks of therapy should be biopsied. The Marjolin's ulcer, other skin neoplasms, vasculitis, vasculopathy, and inflammatory ulcers are differentials to name a few which can be the primary etiology of the ulcer or coexist in a patient with venous hypertension.

VENOUS LEG ULCER MANAGEMENT

The mainstay treatment for VLUs is compression therapy. Gross arterial disease should be ruled out. The degree of compression must be modified when mixed venous/arterial disease is confirmed during the diagnostic work-up. It is important to understand how the diagnosis was made and to understand the limitations of the method. Color duplex ultrasound scanning can be performed to confirm a venous etiology. Venous plethysmography, computed tomography venography, magnetic resonance venography, contrast venography, and intravascular ultrasound may be necessary if duplex venous ultrasound is nondiagnostic. The additional venous imaging can assist in the assessment of venous hypertension due to venous outflow obstruction caused by thrombotic or non-thrombotic iliac vein obstruction.[2] Providers may also opt to use a class high-compression system (three layers, four layers, 'short stretch') or paste-containing bandages-- modified when venous/arterial disease is confirmed.[6] Finally, intermittent pneumatic pressure (IPC) can be used with or without compression dressings.[6]

Adhering to evidence-based wound bed preparation practices is vital for optimal healing. Debride all necrotic or devitalized tissue, control infection (if present), maintain a healthy moisture balance, and maintain proper wound edge and depth. The rate of wound healing should be evaluated to determine whether treatment is optimal and whether progress is being made. Use a dressing that will maintain a moist wound-healing environment, manage exudate, protect peri-ulcer skin, and be cost effective.[7] The dressing material or platform is also important to ensure sustainability and efficacy of the antimicrobial effect. For example, even in low concentrations, ionic silver (Ag+) is highly efficacious on microorganisms in vitro.[7]

The use of cellular therapies, tissue matrices, human matrices, and skin-substitutes should be considered when the VLU has failed to show signs of healing.[7] To decrease the recurrence of venous ulcers, radiofrequency or laser ablation of the incompetent superficial veins in addition to compression therapy is strongly recommended.[2] Vascular interventionists can offer various options with the use of the CEAP

classification and venous ulcer risk including ultrasound-guided sclerotherapy, endo-venous ablation, vein ligation, vein transposition or transplantation, primary valve repair, or open surgery.[2] Adequate nutrition is important to support wound healing including vitamins, minerals and protein.

CLINICAL CASE

A 63-year-old male presented to the university research clinic with a recurrent venous leg wound overlying the gaiter region of the left medial malleolus. The patient had a past medical history significant for chronic venous insufficiency with lower extremity edema, cardiovascular disease, asthma, and obesity. The patient remarked that he discontinued wearing his compression stockings and subsequently developed another venous ulceration that formed approximately 1-2 months ago. After the patient-centered concerns and underlying pathologies had been addressed, and the wound bed had been adequately prepared, a treatment plan was developed to address the systemic and local factors instigating the chronicity of this pathology (**Figure 2**). Initial treatment modalities included compression therapy, non-adherent antimicrobial alginate dressings for two weeks followed by robust collagen-based dressing use until wound closure was observed. Adjunctive therapies including the use of pentoxifyllene and micronized purified flavonoid fraction along with compression were utilized. The combination of these treatment modalities has been reported to potentially help increase the healing rate of chronic venous ulcers.[8] Although the physiology and mechanism of action is not completely understood, these two drugs interact synergistically on leukocyte activation to protect the microcirculation from the deleterious effect of venous hypertension.[2] The patient healed eventfully after 21 days of treatment.

ARTERIAL LOWER EXTREMITY ULCERS

Arterial leg ulcers occur as a result of reduced arterial blood flow and subsequent tissue perfusion. Atherosclerosis or peripheral vascular disease is the most common cause of arterial leg ulceration.[9] Atheroma or plaque development can be caused by tobacco use, obesity, hyperlipidemia, hypertension and/or diabetes. Arterial leg ulcers usually affect men over 45 years and women over 55 years.[10] As the arterial blood supply reduces, patients experience an increase in pain. Their ability to walk distances and uphill causes pain, which is also present on leg elevation. This is known as intermittent claudication. The treatment of patients with chronic non-healing leg ulcers associated with arterial insufficiency involves a critical assessment of the patient's suitability for invasive procedures and the potential risk of limb loss based on ulcer characteristics.

Arterial ulcerations occur distal to impaired arterial supply most commonly on the lateral aspect of the leg, when presenting on the lower extremity. However, they can occur anywhere that is susceptible to trauma such as the interphalangeal joints of the toes. Wound margins are even, sharply demarcated and punched out and have minimum exudate and are very painful in nature.[11] The Society for Vascular Surgery Lower Extremity Guidelines Committee formed a classification system to take into account the change in demographics over the years, the increased incidence of diabetes mellitus in this population, and the advances in revascularization techniques.[12]

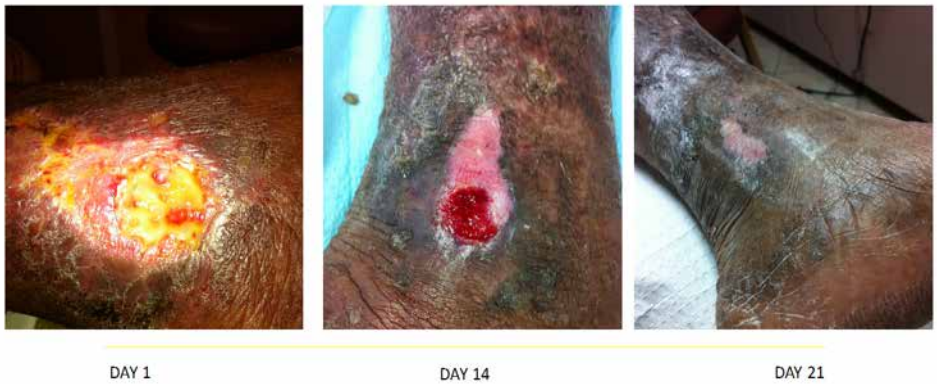

Figure 2. Venous leg ulcer wound healing: Photo used with permission from Snyder, Ead and Cuffy.

Specifically, this protocol was developed to support clinicians in their management of patients whose comorbidities increase their risk of lower extremity amputation.[12] The three main risk stratification factors for arterial ulcers are: wound extent, ischemia, and foot infection (WIfi). Hicks et al found that with the progression through each stage of WIfi there is a strong association with prolonged wound healing time, a higher number of surgical procedures, and an increased cost of care.[13]

TREATMENT OF PATIENTS WITH MIXED ARTERIAL AND VENOUS ULCERS

A thorough clinical history, focusing on the duration and size of the ulcer with any associated lower extremity symptoms is the first step in patient management. In clinical studies, the reported incidence of arterial insufficiency in patients with VLUs has ranged from 15% to 30%.[10] Utilizing an evidence-based diagnostic guideline is critical in order to differentiate between the two etiologies (**Figure 3**). A comprehensive evaluation of the patient's comorbidities and overall health is vital, as patients with arterial disease are likely to be older with significant cardiovascular comorbidities. Typical characteristics of each type of leg ulcer are described in **Table 2** to help guide accurate diagnosis.[11] The literature has been clear in regard to reducing the strength of compression for treatment of VLUs. However, it is critical in patients with significant arterial insufficiency to minimize the risk of compression-related complications including pain and compression-related necrosis. The exact level of arterial insufficiency that warrants modified compression is debatable, ranging from 0.7 mmHg to 0.9 mmHg.[10] Tissue necrosis typically occurs over bony prominences including the malleoli and anterior tibia, or over the posterior heel and tendons.[11] Additional padding is recommended to these areas underneath compression to reduce the potential risk of tissue injury. Most experts recommend against high strength compression in patients with an ankle pressure below 80 mmHg or ABI below 0.7 mmHg to 0.85 mmHg.[10] If the ankle pressure is below 60 mmHg or the ABI is below 0.5 mmHg, revascularization is recommended prior to compression therapy.[10] Furthermore, doppler ultrasound to measure ankle-brachial pressure index should be performed when the ulcer is

TABLE 2. WOUND CHARACTERISTICS OF VENOUS LEG ULCERS AND ARTERIAL INSUFFICIENCY ULCERS

Characteristic	Venous Leg Ulcer	Arterial Insufficiency Ulcer
Sensation	Throbbing, aching, heavy feeling in legs Improves with elevation and rest	• Very painful, especially while exercising, at rest, or during night • Improves with dependency
Typical Location	• Lower leg (mid-calf or below) • Ankle • Adjacent to or above the medial or lateral malleoli area	• Between or on tips of toes • Outer ankle • Lateral foot over pressure points
Exposure of Deep Structures	• None	• Often extends to underlying tendon, muscle, or bone
Wound Appearance	• Often covered with fibrinous layer mixed with granulation tissue • Shallow, superficial • Varying depths within ulcer • Small to large • May be discrete or circumferential	• Base of wound typically does not bleed and is yellow, brown, grey or black • Characteristically deep • Punched-out, usually round, with well defined, even wound margins
Periwound	• Hemosiderine staining • Lipodermatosclerosis in long-term • Venous insufficiency • Variable pigmentation • Venous eczema (erythema, scaling, weeping, itching) is common	• Skin and nails of extremity appear atrophic • Skin is pale, shiny, taut, and thing • Minimal to no hair growth • Extremity may turn red when dangled dependent rubor) and pale when elevated
Foot/leg temperature and pulses	• Higher temperature consistent with chronic venous insufficiency	• Lower limb cool or cold to touch • Little to no distinguishable pulse
Exudate and edema	• Heavy exudate • Pitting edema often present and may predate ulcer (often worse toward end of day)	• Minimal exudate • Limited edema

Adapted from Gupta et al[11]

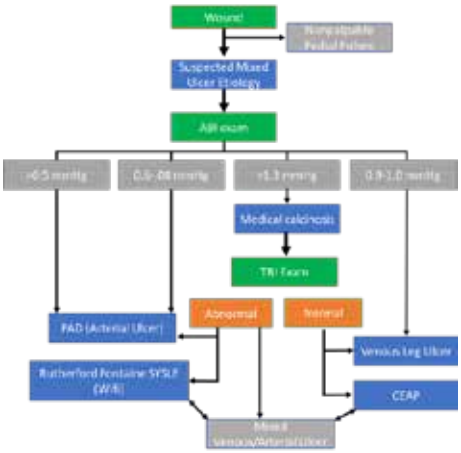

Figure 3. Diagnostic pathway for patients with mixed etiologies
Adapted from Snyder et al. [15]

regressing, no signs of healing by 12 weeks, sudden increase in size of ulcer, sudden increase in pain, foot color or temperature change, or there is recurrence of ulcer. [6, 14]

CONCLUSION

A comprehensive methodology of wound assessment, treatment of patient- and wound-centered concerns, and follow-up should be adhered to for all chronic wounds, irrespective of wound type. Patient-centered factors including nutrition, etiology, obesity management, nicotine use, uncontrolled infection, circulation, incontinence, pain, and psychosocial factors, among others, can all impede healing and need to be addressed for successful treatment. The management of patients with mixed ulcerative pathologies requires a multidisciplinary team approach, educating patients on issues of correct foot care, and the importance of seeking early medical advice. It cannot be overstated that venous disease and arterial disease can exist in the same patient, therefore utilizing evidence-based guidelines can only optimize patient outcomes.

Patient data and photos courtesy of Snyder, Ead and Cuffy.

As with any case study, the results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary depending on the patient's circumstances and condition.

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