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REDEFINING THE STANDARD: CURRENT AND EMERGING TRENDS IN THE TREATMENT OF VENOUS ULCERS

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The treatment of venous ulcers (VU) is often a long-term and exhausting process for patients and a significant clinical challenge for healthcare professionals. Despite well-defined pathophysiological mechanisms underlying the development of VUs and the existence of official treatment guidelines issued by professional associations of vascular surgeons and phlebologists, the healing of VUs is still associated with a high rate of therapeutic failure and frequent recurrence. The basis of VU therapy is an adequate diagnostic assessment and the application of compression therapy as the gold standard, while new and advanced concepts of VU treatment can be considered in patients with slow or absent response to initial therapy. Future high-quality clinical studies are essential to define this integrative approach more clearly, determine its role in routine practice, and guide the optimal, individualized use of regenerative therapies treatment strategies.

Key words: venous ulcers, wound healing, therapy, regenerative medicine

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REDEFINISANJE STANDARDA: TRENUTNI I NOVI TRENDOVI U LEČENJU VENSKIH ULKUSA

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Lečenje venskih ulceracija (VU) je dugotrajan i iscrpljujuć proces za pacijenta, a izazov za zdravstvene profesionalce. I pored jasno definisanih patofizioloških mehanizama nastanka VU i postojanja zvaničnih preporuka za njihovo lečenje, koje su izdali relevantna stručna udruženja vaskularnih hirurga i flebologa, proces zarastanja VU i dalje pokazuje visok stepen terapijske neuspešnosti i česte rekurencije. Osnovu terapije VU čine adekvatna dijagnostička procena i primena kompresivne terapije kao zlatnog standarda, dok se novi i napredni koncepti lečenja VU mogu razmatraju kod pacijenata sa sporim ili izostalim odgovorom na inicijalnu terapiju. Dodatne, metodološki kvalitetne kliničke studije biće neophodne kako bi se ovakav integrativni pristup jasno definisao i pronašao svoje mesto u svakodnevnoj kliničkoj praksi, sa posebnim osvrtom na optimalno

i racionalno korišćenje regenerativnog potencijala novih, individualno prilagođenih terapijskih strategija.

Ključne reči: venske ulceracije, zarastanje rana, terapija, regenerativna medicina

INTRODUCTION

Venous ulcers (VU) are chronic, open wounds of the lower leg, representing the most severe stage of chronic venous insufficiency (CVI). Clinically, VU appear as localized loss of skin and subcutaneous tissue, most often on the medial aspect of the distal lower leg, particularly in the region at or below the medial malleolus. VU are frequently associated with other clinical manifestations, including varicose veins, dermatitis, skin hyperpigmentation, and wound exudate (1).

The prevalence of VU in the general population ranges from 0.7% to 2%, with frequency increasing sharply with age. In individuals younger than 40 years, prevalence is approximately 0.18–1%, whereas in those older than 65 years, it rises to around 4%. Given the aging population and rising rates of obesity, a further increase in VU prevalence is anticipated (2,3).

Venous ulcers represent the most common type of chronic wounds, accounting for 60–80% of all chronic lower-extremity wounds. Accurate diagnosis is essential to differentiate VU from other chronic wound types, including arterial ulcers, lymphatic ulcers, diabetic ulcers, inflammatory ulcers, or ulcers associated with malignant syndromes (4). Among chronic ulcers refractory to vascular intervention, 20–23% may result from vasculitis, sickle cell anemia, pyoderma gangrenosum, calciphylaxis, or autoimmune diseases (5). In many cases, clinical examination alone is sufficient for the diagnosis of venous ulcers. Additional diagnostic methods such as ankle-brachial index, Doppler ultrasonography, plethysmography, phlebography, computed tomography (CT), magnetic resonance imaging (MRI), and biopsy are applied selectively to clarify complex or atypical cases (4).

The risk factors for the development of VU are well established. The most significant include CVI, advanced age, female sex, genetic predisposition, history of deep vein thrombosis or phlebitis, diabetes, obesity, smoking, previous traumatic injury, chronic lower-extremity edema, reduced physical activity, and a sedentary lifestyle. The central pathophysiological mechanism underlying VU formation is venous hypertension, which increases the risk of thrombosis and contributes to progressive dysfunction of the venous system. This condition is typically caused by valvular incompetence and/or venous obstruction, resulting in retrograde blood flow and venous reflux that progressively damages the microcirculation (6).

The resulting venous stasis leads to blood pooling, which in turn causes endothelial injury, activation of inflammatory pathways, leukocyte mobilization, platelets aggregation, and intracellular edema. These processes collectively promote tissue damage and the eventual formation of VU (7).

Extravasation of plasma proteins, such as α2-macroglobulin, fibrinogen, and other biomolecules from the veins into the dermis, is a key mechanism contributing to capillary dilation and endothelial cell damage. At the cellular level, the formation of VU is driven by mast cell degranulation, leukocyte activation, and increases in matrix metalloproteinases (MMPs) and prostacyclin, resulting in microcirculatory alterations and varicose veins formation. Endothelial injury and macrophage-mediated inflammatory activity, involving cytokines such as interleukin-1α (Il), interferon-γ, and transforming growth factor-β1, sustain a chronic inflammatory state. This persistent inflammation promotes fibrosis and progressive venous valve damage, ultimately leading to venous hypertension, impaired microcirculation, and tissue injury, which disrupt the wound-healing process. Additional contributors to VU pathogenesis include increased endothelial permeability, leukocyte infiltration, elevated inflammatory cytokines, MMPs activity, reactive oxygen and nitrogen species, iron deposition, and accumulation of tissue metabolites (8).

Today, VU represent a major medical and economic burden. Treatment costs are estimated to account for approximately 1% of healthcare budgets in many developed countries, reflecting the significant impact of these chronic conditions on healthcare systems. In the United States, the annual costs of VU management are around 16 billion dollars (9); in Great Britain, about 102 million pounds (10); and in Australia, approximately 17 billion dollars (11). Similar trends are observed across Europe (12).

The treatment of VU is often a long and exhausting process for patients and a significant clinical challenge for healthcare professionals. Alarmingly, even with appropriate therapy and care, approximately 20% of VU fail to heal within two years (13). On average, only 60% of venous ulcers heal within 12 weeks, and among those that do heal, up to 75% experience recurrence within three weeks (14). Factors contributing to slow healing of VU include advanced age, obesity, nutritional deficiencies, ulcer size and depth, duration of the ulcer, presence of biofilm, chronic venous insufficiency, history of deep vein thrombosis, and the use of certain medications (15,16). Recurrence of VU most commonly results from non-adherence to compression therapy, failure of surgical interventions, misdiagnosis of the ulcer type, and progression of underlying venous disease (15,17).

Standard therapeutic principles in the treatment of venous ulcers

The management of VU is complex, requiring thorough diagnostic evaluation and a clear understanding of the underlying pathophysiological mechanisms. Treatment strategies encompass conservative therapy, non-pharmacological and non-surgical approaches, compression therapy, wound dressings, pharmacological interventions, and surgical procedures (18,19).

Conservative treatment begins with lifestyle modification, aiming to reduce known risk factors and promote healthy habits. Evidence indicates that regular walking and targeted exercises can have a statistically significant positive effect on wound healing (18-20). Elevation of the affected extremity helps to reduce venous stasis, edema, and venous hypertension, while improving microcirculatory flow, which can support the treatment of CVI (18). However, its direct effect on the healing of VU remains unclear. Some studies report no significant impact on wound closure (21), while others suggest that elevation may reduce the recurrence rate of VU (22). The role of extremity massage, which can help reduce edema and is typically performed around the VU before or after the application of compression therapy, requires further investigation to determine its effectiveness (18).

Compression therapy is a cornerstone in the treatment of VU, aiming to reduce venous hypertension by increasing external pressure on the muscle pump and counteracting gravity, which can impede venous and lymphatic return. This therapy enhances venous blood flow, reduces lower-extremity swelling, improves lymphatic drainage, and stimulates fibrinolytic activity. *The European Society for Vascular Surgery* (ESVS) and the *American Venous Forum* (AVF) provide clear recommendations supporting the use of compression therapy to promote healing of VU (18,19). Optimal therapeutic outcomes are typically achieved with a graduated compression bandage applying 35–40 mmHg of pressure, with a maximum recommended pressure of up to 60 mmHg. Compression materials may be elastic or inelastic, single- or multi-layered, and vary in elasticity, firmness, and the pressure they exert in standing versus lying positions. Various compression devices are available, including graduated compression stockings, bandages, intermittent pneumatic compression (IPC), and adjustable compression wraps (ACW). The use of ACW as a form of inelastic compression has been shown to improve patient quality of life and reduce treatment costs (23,24). Intermittent pneumatic compression (IPC) can provide additional benefits in patients where bandages or stockings fail to achieve the desired effect. IPC is especially useful for patients with limited mobility, helping to

reduce edema, promote VU healing, and enhance arterial blood flow (25). Research indicates that the rate of VU healing is directly correlated with sub-bandage pressure, highlighting the importance of adequate compression levels. Inelastic compression has been shown to be particularly effective for larger VU, while elastic compression is more suitable for medium and smaller VU. Additionally, patient adherence to compression therapy is a critical factor influencing the overall efficacy of VU healing (18,19,26-28).

Management of chronic wounds and VU follows the TIME principle: T (tissue management), I (inflammation/infection control), M (moisture balance), and E (epithelial edge advancement) (29). Necrotic tissue present on the surface of a VU acts as a substrate that interferes with the healing process, making its removal essential. This is achieved through debridement, a procedure that reduces the bacterial burden in the wound, stimulates the activity of growth factors, and eliminates senescent cells. Several methods of debridement are available, including surgical, mechanical, autolytic, enzymatic, and biological approaches. Surgical debridement is the fastest method, involving the removal of devitalized tissue down to the level of healthy tissue. Mechanical debridement refers to the physical removal of necrotic tissue during wound bed preparation. In recent years, modern mechanical techniques such as jet lavage and ultrasonic debridement have been increasingly utilized. Autolytic debridement involves the use of modern wound dressings that maintain a moist environment, soften necrotic tissue, and promote natural autolysis. Enzymatic debridement uses topical enzymatic agents such as streptokinase, clostridiopeptidase A, DNAse/fibrinolysin, papain–urea combinations, subtilisin, or trypsin to facilitate the breakdown of necrotic tissue. Biological debridement employs sterile larvae, whose activity increases the wound pH to approximately 8–8.5, producing a bacteriostatic effect. These larvae also secrete proteolytic enzymes that degrade necrotic tissue and enhance tissue oxygenation. Although bacterial colonization is commonly observed in VU, not every wound infection requires immediate systemic antibiotic therapy. In most cases, management should initially focus on modern local dressings and topical antimicrobial therapy, with systemic antibiotics reserved for clearly indicated infections (30-32). The use of modern dressings in the treatment of venous ulcers requires further investigation, and selecting the most appropriate dressing demands careful assessment of the patient's overall condition as well as the local wound status. Current evidence does not clearly confirm the superiority of alginate, foam, hydrocolloid, or silver dressings in the treatment of VU. In contrast, the use of

dressings containing zinc and cadexomer iodine has been recommended (18). Maintaining adequate wound moisture plays a crucial role in the healing process and in the removal of necrotic tissue. Effective control of wound exudate is therefore essential and requires the consistent application of appropriate wound care methods and principles.

Venoactive drugs represent a heterogeneous group of biologically active substances derived either from processed plant materials or through chemical synthesis, and they are widely used in the treatment of VU. Broadly, these agents can be classified into two main groups: natural compounds (of plant or animal origin) and synthetic drugs. Among the agents of animal origin, mesoglycan and sulodexide are polysaccharides isolated from various animal tissues. Synthetic venoactive drugs include calcium dobesylate and naphthazone. In contrast, most herbal venoactive medicines are produced from isolated plant constituents or their semi-synthetic derivatives. The active components of herbal venoactive agents mainly belong to several pharmacological groups, including alpha-benzopyrones (such as coumarin and esculin), flavonoids (including diosmin, hesperidin, rutin, quercetin, and anthocyanins), Ruscus extract, saponosides (such as escin), and other plant-derived substances such as *Centella asiatica* (gotu kola) and *Ginkgo biloba* extracts. These agents are recommended at all stages of CVI, with evidence supporting their beneficial role in promoting the healing of VU. Venoactive drugs exert anti-inflammatory, anti-edematous, venotonic, and vasculoprotective effects, and have been shown to reduce common symptoms of CVI, including pain, cramps, restless legs, a sensation of swelling, paresthesia, and trophic skin changes. Among the available agents, Ruscus derivatives, micronized purified flavonoid fraction, and calcium dobesylate are considered to have the strongest evidence supporting their clinical use (33-34). In addition, medications such as pentoxifylline, acetylsalicylic acid, and iloprost have also demonstrated effectiveness in the treatment of VU (4).

The primary goal of surgical therapy in the treatment of VU is to eliminate the underlying pathophysiological mechanisms namely venous reflux and/or obstruction that lead to the development of venous hypertension. Ablative surgical approaches include both open surgical techniques and endovenous procedures. Traditional open surgery involves high ligation and vein stripping, while minimally invasive endovenous methods include endovenous laser therapy (EVLT/EVLA), radiofrequency ablation (RFA), and mechanochemical ablation (MOCA). In cases where venous stenosis or obstruction is present, endovascular procedures play an important role in reducing

venous hypertension and improving venous outflow[35]. Surgical interventions have demonstrated beneficial effects in accelerating VU healing and reducing the risk of recurrence (36-37). In addition to these approaches, sclerotherapy also has a recognized role in the management of VU (4).

The use of skin grafting in the treatment of VU has not consistently demonstrated convincing effectiveness. However, evidence from a Cochrane review indicates that the use of bilayer artificial skin, when combined with compression therapy, can increase the likelihood of VU healing (38).

New concepts in venous ulcer therapy

Despite well-defined pathophysiological mechanisms underlying the development of VU and the existence of official treatment guidelines issued by professional associations of vascular surgeons and phlebologists, the healing of VU is still associated with a high rate of therapeutic failure and frequent recurrence. This highlights the need for continued research and the development of innovative therapeutic approaches that may provide improved clinical outcomes.

Negative pressure therapy (NPT) involves the use of a specialized device that creates controlled negative pressure within the wound, typically ranging from 40 to 125 mmHg. The therapeutic effects of NPT include stimulation of capillary growth and granulation tissue formation, contraction of wound edges, continuous drainage of wound exudate and inhibitory factors, and a reduction in bacterial load (32). However, NPT is not considered a primary treatment modality for VU. One limitation of this method is that it may interfere with the application of compression therapy, which remains a cornerstone in the management of VU. Nevertheless, NPT may be selectively applied in certain clinical situations, including: large VU (12–40 cm^2), VU larger than 40 cm^2 that fail to show at least a 40% reduction in wound area after four weeks of treatment and deep VU with significant wound exudation, in combination with compression therapy whenever feasible (39,40).

Hyperbaric oxygen therapy (HBO) has been recognized as an important adjunctive method in the treatment of chronic wounds. Its therapeutic effects are primarily related to increased local tissue oxygenation, which improves tissue perfusion and supports several processes essential for wound healing. HBO promotes antibacterial activity, enhances the regeneration of ischemic tissue, and accelerates fibroblast proliferation, granulation tissue formation, epithelialization, and angiogenesis. In addition, it stimulates growth factor activity, reduces the concentration of

inflammatory cytokines, limits leukocyte migration, and may contribute to improved venous blood drainage. Although HBO therapy has demonstrated benefits such as reduction of VU area, pain relief, and improvement in patients' quality of life, most studies indicate that it does not significantly increase the rate of complete VU healing (41,42).

Low-level light therapy (LLLT) is a therapeutic modality based on photochemical and photophysical effects, without generating significant heat. Through photochemical activation of cells, LLLT stimulates the synthesis of serotonin, histamine, and bradykinin, leading to increased ATP production and cellular activity. These processes promote cellular repair, stimulate granulation tissue formation, and reduce the levels of inflammatory cytokines. In addition, LLLT has demonstrated antibacterial effects and a beneficial impact on pain reduction in patients with chronic wounds (43). However, literature findings regarding the effectiveness of LLLT in VU healing remain inconsistent. Research conducted by Fraccalvieri et al. (44) reported positive outcomes with blue light LLLT, showing an increased rate of VU healing over a 10-week treatment period. In contrast, the analysis by Flemming et al. (45) based on data from the Cochrane database, suggested a potential preference for infrared light therapy, but without statistically significant evidence confirming that LLLT improves VU healing. Overall, additional well-designed studies are needed to clearly define the role and effectiveness of LLLT in the treatment of VU.

Ultrasound therapy has been reported to have beneficial effects in the treatment of chronic wounds. Its therapeutic action includes stimulation of protein synthesis and fibroblast activity involved in collagen production, acceleration of cell proliferation and angiogenesis, and support of enzymatic fibrinolysis. In addition, ultrasound therapy may exert anti-inflammatory and anti-edematous effects, contributing to an improved wound-healing environment. Based on the frequency of the emitted waves, ultrasound therapy can be classified into high-frequency ultrasound (HFU) (1–3 MHz) and low-frequency ultrasound (LFU) (30–40 kHz) (46). Evidence regarding the effectiveness of ultrasound therapy in the healing of VU remains inconclusive. An analysis of the Cochrane Wounds Specialized Register conducted by Cullum et al. (47) did not find clear evidence supporting the effectiveness of either HFU or LFU in promoting VU healing. In contrast, research by Beheshti et al. (48) demonstrated positive effects, including reduction in wound surface area, pain, and edema, suggesting potential benefits in VU healing. Furthermore, a study by Shapiro et al. (49) reported improved healing outcomes and symptom reduction when ultrasound therapy was combined with

electric field stimulation therapies. Overall, additional studies and further analysis are required to better define the role and clinical effectiveness of ultrasound therapy in the treatment of VU.

Electromagnetic stimulation (EMS) is a therapeutic modality that can induce electrical impulses across damaged cell membranes. This stimulation promotes an increase in fibroblast and macrophage activity within the wound, leading to activation of reparative mechanisms, enhanced fibrin and collagen deposition, and reduction of local inflammation (50). However, the evidence regarding the effectiveness of EMS in VU healing remains inconsistent. Some studies suggest that EMS may contribute to reduction of VU surface area and improvement in patients' quality of life. Nevertheless, the overall level of evidence remains limited due to methodological constraints and small sample sizes, making definitive conclusions difficult (51,52).

Platelet-rich plasma (PRP) therapy represents another emerging therapeutic approach. PRP contains platelet concentrations approximately 2–6 times higher than those found in whole blood, along with numerous inflammatory modulators, growth factors, and signaling cytokines. These components play an important role in granulation tissue formation, angiogenesis, and modulation of the inflammatory response. Meta-analyses conducted by Fang et al. (53) and Oliveira et al. (54) indicate that PRP therapy may accelerate the healing process and increase the healing rate of VU, while also contributing to improvements in patients' quality of life. However, further well-designed studies are required to establish clearer clinical recommendations regarding the use of PRP in the treatment of VU.

Stem cell therapy (SCT) is a promising approach in the treatment of chronic wounds, based on the capacity of undifferentiated cells to self-renew and differentiate into multiple cell types, which play a critical role in the wound-healing process. Stem cells contribute to healing by secreting growth factors, cytokines, and chemokines, modulating inflammation, promoting angiogenesis and re-epithelialization, differentiating into myofibroblasts, and enhancing collagen deposition, thereby accelerating tissue repair and improving tissue quality. Clinical studies have shown that SCT can significantly reduce the surface area of chronic VU and improve tissue regeneration. The primary sources of adult stem cells used in VU treatment are adipose tissue, bone marrow, and peripheral blood, with adipose-derived stem cells (ADSCs) being particularly advantageous due to their ease of collection and abundance. Overall, SCT represents a promising adjunctive treatment for chronic VU, with numerous studies indicating its safety and potential clinical benefits. However, current evidence

is limited by methodological weaknesses and heterogeneity among studies, highlighting the need for high-quality randomized controlled trials to definitively establish the effectiveness of SCT in VU management (50,55,56).

Biological therapy represents a potentially promising approach in the treatment of VU because it targets specific immune system cytokines that play a central role in chronic wound inflammation (57). Elevated levels of proinflammatory cytokines including IL-1α, IL-6, IL-8, IL-17, TNF-α, and VEGF, are associated with impaired collagen synthesis and delayed wound healing (58). Studies have shown that TNF-α levels are increased in VU compared to healthy skin, particularly in non-healing wounds. Anti-TNF agents such as adalimumab, etanercept, and infliximab have demonstrated the ability to reduce inflammation, limit fibroblast apoptosis, and enhance collagen synthesis, thereby promoting faster healing and reducing wound size (59). Research is also ongoing into the use of inhibitors targeting other proinflammatory cytokines, such as IL-17, in VU therapy; however, clinical evidence confirming their effectiveness is not yet available (60). If future studies validate their efficacy, biologic therapies could become a powerful tool to accelerate healing and improve outcomes in VU management.

Exosomes, the smallest subpopulation of **extracellular vesicles (EVs),** have become a major focus of research in regenerative medicine in recent years. These vesicles—whether of natural origin (animal or plant), modified, or synthetic (artificial)—exhibit a broad range of biological activities essential for tissue regeneration. Their anti-inflammatory, immunomodulatory, and antioxidant properties, combined with the ability to stimulate angiogenesis, enhance intercellular communication, and support extracellular matrix remodeling, make them a highly promising therapeutic tool (61).

Research on exosome therapy for VU remains limited. However, current evidence suggests a beneficial effect, demonstrated by a higher proportion of granulation tissue formation and a lower proportion of necrotic tissue in VU treated with exosomes (62,63). Continued investigation into functionally optimized exosome-based therapies could provide a novel and effective strategy to enhance healing in patients with VU.

Considering the high prevalence of VU, their potential for serious complications, and their substantial impact on quality of life and work capacity, VU represent a significant medical and socioeconomic challenge. Effective modern therapy requires a multidisciplinary approach, thorough

knowledge of therapeutic protocols and options, and an individualized treatment strategy (64) (Figure 1).

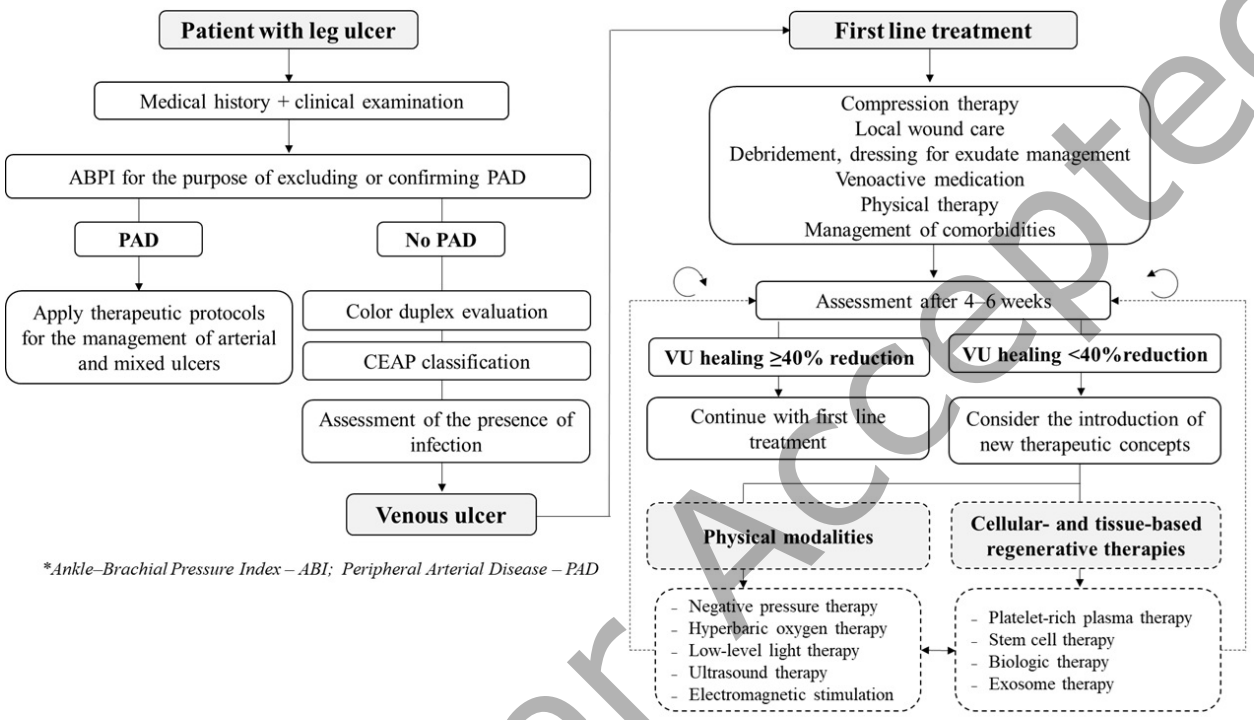

Figure 1. Stepwise therapeutic algorithm for the management of venous ulcers

CONCLUSION

To organize contemporary wound management, the use of a stepped therapeutic model that integrates both standard and advanced treatment modalities may provide a rational and clinically justified approach. The foundation of therapy of VU includes comprehensive diagnostic assessment and the implementation of compression therapy, which remains the gold standard. Advanced or innovative treatments can be considered in patients with VU who show slow or absent response to initial therapy. Future high-quality clinical studies are essential to define this integrative approach more clearly, determine its role in routine practice, and guide the optimal, individualized use of regenerative therapies treatment strategies.

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