Shifting the Focus: Late-Stage Venous Disease

Organizational and research priorities for treating patients with advanced venous disease.

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Late-stage chronic venous disease is the most common cause of leg ulceration in the United Kingdom.[1] Although numerous treatment options for symptomatic venous disease exist, disease progression to skin changes and ulceration (CEAP [clinical, etiology, anatomy, and pathophysiology] C4 and higher disease) is an ongoing issue for those affected. A prospective cohort study demonstrated that over a 6-year period, approximately 20% to 30% of patients with C2 disease progressed to higher CEAP stages.[2] Although further longitudinal studies are required to delineate the rate of progression, the health care burden of advanced venous disease and venous leg ulcers (VLUs) is expected to increase.[3] This has stimulated a drive to further our understanding of the pathophysiology leading to progression to advanced disease and identify how best to manage late-stage chronic venous disease.

VLUs are estimated to affect 1% of the population, with an increase to 2% in those ≥ 65 years.[1,4,5] However, these estimates are often derived from old, small data sets. Similarly, the cost of VLUs has been estimated at approximately 2% of the annual health care budget in western European countries and the United States.[6] Such estimates may be derived from historical incidence rates and by extrapolating from small-scale studies. A team in Wales attempted to derive the true cost of all chronic wounds by utilizing linked patient-level data. They identified an estimated prevalence of 6%, with chronic wounds responsible for 5.5% of the total budget expenditure.[7] Accurate national and international prevalence rates and costs to the health care service are required if services are to evolve their capacity to optimally manage patients with VLUs.

Therefore, late-stage venous disease contributes to significant morbidity, reduced quality of life, social isolation, and health care expenditure. Despite the profound impact of VLUs on patients and health care resources, they are largely managed in the community by general practitioners and community nurses who spend 50% of their time caring for patients with ulcerations, the majority of which will be venous in origin.[8] Alongside community practitioners, VLUs are managed by several other members of the multidisciplinary team, including vascular surgeons, phlebologists, and dermatologists. The diverse multidisciplinary team involvement may lead to heterogeneous management of VLUs,[9] which may contribute to poor service provision in managing ulcers.[10] Unifying the clinical practice of clinicians from different specialties could help ensure that evidence-based, best practice treatment is administered. There are numerous clinical practice guidelines for VLUs that can help achieve this.[1,11-14] A recent review highlighted the diverse focus of several guidelines, reflecting not only the expertise of each guideline development group but also a lack of methodologically high-quality clinical practice guidelines.[15] It has been suggested that the use of guideline quality checklists may help improve the quality of clinical practice guidelines.

ORGANIZATIONAL CHALLENGES

The 2013 National Institute for Health and Care Excellence (NICE) guidelines outline that patients with nonhealing venous ulcers should be referred to a vas-

cular center within 2 weeks,[16] yet no significant changes in clinical practice have been observed since those guidelines were published.[17] In 2018, the results of the large, multicenter EVRA randomized controlled trial (RCT) showed that early endovenous ablation of refluxing veins improved leg ulcer healing and increased the length of time free from leg ulceration.[18] In combination with the ESCHAR trial, which found that intervention reduces recurrence rates for VLUs,[19] this provides level 1 evidence for the early treatment of superficial venous incompetence in this cohort of patients. Nonetheless, the real-world application of these trial findings remains a challenge.

In the EVRA trial, participants had VLUs for an average of just over 3 months before intervention. This highlights the issue of delayed referral, and if the trial followed the NICE guidance regarding a 2-week pathway, the outcomes of the EVRA trial may have been better. However, obtaining referrals in this time frame is a challenge in clinical practice. To evolve service provision in venous ulceration, further research is required to understand the real-life barriers to timely referrals and management of ulcers, which are likely multifactorial.

VLUs often affect the elderly, who may experience isolation in society and may be unaware of the available treatment modalities. Methods of optimizing patient education with the goal of empowering patients to seek such treatment are important. This education should extend to clinicians in the community who may be unaware of possible treatment outcomes or may consider their patients to be too infirmed to undergo intervention.

BASIC SCIENCE RESEARCH

Several emerging technologies and areas of further research may aid the tailored management of patients with late-stage venous disease. This includes identifying biomarkers that may detect which patients are at risk of progressing to advanced disease and, in particular, developing recurrent or resistant ulceration.[20] A number of biomarkers have been identified in the wound fluid of healing and nonhealing ulcers, although more work is required to translate these findings to the clinical arena. These biomarkers will be crucial in furthering our understanding of the pathophysiology of VLUs and may help develop possible translational applications, such as predicting the likelihood of healing/nonhealing ulcers and the development of novel, targeted, personalized therapies.[21]

Understanding the wound microenvironment may also help identify factors associated with nonhealing, recalcitrant, or recurrent ulcers. The microbial load, presence of pathogenic organisms, and bacterial diversity have all been implicated in delayed venous wound healing,[22] but further studies linking the microbiome to the clinical status of the ulcer and evaluating the effects of treatment are required.

Technologies in wound imaging can help visualize the wound microenvironment. Trials utilizing fluorescence imaging to identify bacteria that may hinder wound healing are in progress. Such technologies can be used to perform accurate image-guided wound tissue biopsies to identify pathogenic bacteria.[23] They may also enable faster recognition of infected wound ulcers and tailoring of treatment.[24] These devices, among others such as digital planimetry and stereophotogrammetry,[25] are also being used for accurate, objective measurement of wound ulcer size. This may be helpful in reviewing the progression of venous ulcers in treatment, but it is unclear whether these technologies demonstrate superiority over traditional manual planimetry.[26]

CLINICAL RESEARCH

The role of perforator intervention on venous ulcer healing or recurrence remains unclear. The presence of new or recurrent perforating veins has been implicated in varicose vein recurrence.[27] One prospective observational study suggested that the treatment of perforator veins enabled the healing of recalcitrant venous ulcers,[28] although another study suggested that recurrent perforators may lead to ulcer recurrence.[29] There are currently no level 1 data that support the closure of perforating veins.

The EVRA trial focused on the effect that treating the main refluxing truncal veins had on wound healing; the impact of treating perforators was not investigated.[18] This also applied to the ESCHAR study, where only six patients underwent isolated calf perforator intervention.[19] Prospective RCTs are necessary to better characterize the impact of perforator vein treatment on VLU outcomes.

Similarly, the role of treating the subulcer venous plexus with foam sclerotherapy remains unclear. In the EVRA trial, ablation of the subulcer plexus was acknowledged to be a source of clinical practice heterogeneity across different institutions.[18] The impact of this practice on venous ulcer healing has yet to be investigated in the context of an RCT.

Compression is a key component in the management of venous ulcers, and multicomponent systems, high-compression stockings, and four-layer bandages are of particular benefit.[30] Nonetheless, compliance is

a major issue and is affected by factors such as patient education, pain associated with compression, and aesthetics.[31] Further work is required to better characterize compliance and incentivize stocking use.

There is ongoing interest in the treatment of deep venous obstruction in the context of venous ulceration, although it remains unclear if and when this should be treated. A number of retrospective studies have explored the use of deep venous stenting in chronic venous insufficiency and concluded that stenting could be helpful, especially in healing recalcitrant ulcers.[32-34] Although these studies explore the use of deep venous stenting in combination with superficial interventions, it is unclear whether superficial reflux or deep venous occlusion should be treated first. Future research should investigate the efficacy and cost-effectiveness of deep venous stenting in venous ulcer disease compared with current standard treatment.

Alternative treatments, including pharmacologic therapy,[35] extracorporeal shockwave therapy,[36] and alternative skin substitutes for ulcer grafting[37-40] may also be important in later-stage venous disease and will require further elucidation.

Finally, nonthermal and nontumescent ablation techniques may have an increasingly important role in managing patients with skin changes and VLUs. Radiofrequency ablation and endovenous laser ablation require tumescent anesthesia, which can cause discomfort. Current data suggest that nonthermal truncal ablation techniques are comparable to thermal ablation[41,42] and appear to be less painful.[42] Comparisons between these nonthermal techniques are underway[43]; however, research into the efficacy of nonthermal interventions compared with thermal methods in late-stage venous disease should be considered.

CONCLUSION

The health care burden of late-stage venous disease is set to increase, and numerous challenges regarding its management remain. Epidemiologic research is required to provide up-to-date estimates of the prevalence of venous ulcers and the rate of progression to advanced disease. Basic science research is needed to investigate the microbiome and identify biomarkers that might be useful in identifying factors associated with nonhealing, recurrent, and recalcitrant ulcers. These factors may be useful in developing novel therapies. Clinical research is also needed to determine the optimal interventional strategy. A unified effort from the multidisciplinary team is required to promote patient education in venous ulceration and promote organizational changes that will drive evidence-based practices into the clinical setting to improve service provision and quality of care. ■

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