The difficult leg ulcer

A case review illustrating the problems and difficulties associated with treatment

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Through the vehicle of a case study, this paper illustrates the complexity associated with venous leg ulcerations. In order to be effective with treatment regimes, a comprehensive understanding of the pathophysiology of the lower leg venous system, the pathology of venous insufficiency and the pathology of venous leg ulcerations must be fully understood. Compression therapy is the cornerstone to treatment, however, this must only be applied after the patient has been thoroughly investigated to exclude other causes of the leg ulcer. Unlike the United Kingdom and Europe, Australia does not have national guidelines for the management of patients with venous leg ulcers. In view of the high costs associated with this condition, perhaps there may be better outcomes for patients if this approach were adopted in Australia.

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Introduction

Lower leg ulcers are a common and expensive problem [1-3]. Chronic venous insufficiency (CVI) accounts for approximately 70% of leg ulcers; however, the aetiology is often multifactorial [4-6]. In Western countries, the prevalence of chronic leg ulcers has been estimated to be in the region of between 1.1 and 3.0 per thousand of the adult population [4-10]. The cost to treat these chronic wounds has been estimated to be in the region of A$3 billion per annum [11], representing a significant burden on the ever-shrinking health care dollar. Venous ulcers are notorious for recurring despite best practice, with recurrence rates as high as 69% [12-14]. These poor healing rates may be attributed to failure to identify the correct diagnosis, inappropriate compression, or lack of surgical intervention in suitable candidates.

The following case study highlights the problem in treating a gentleman who is known to have a venous leg ulcer for at least 25 years, despite surgical intervention and compression therapy.

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Pathophysiology of the lower leg venous system

In order to understand the abnormal mechanisms associated with venous insufficiency and associated ulceration, an understanding of the anatomy of the venous system of the lower limb and mechanics of its blood flow is required.

There are three major components of the venous system of the lower extremity – deep, superficial and perforator veins [15]. The long and short saphenous veins are located outside the deep fascia, in the subcutaneous tissue. The superficial venous system is also referred to as the saphenous system,

because it is comprised of the greater and lesser saphenous veins. The deep veins include the posterior, anterior tibial and the peroneal veins. The deep veins are encased in a tight musculo-fascial envelope within the calf muscle. Also located within the facia in the soleus and gastrocnemius muscles are dilated valveless sinusoids, which fill with blood when the leg is at rest. The perforators, or communicating veins, penetrate the fascia, linking the superficial system to the deep system [15, 16].

Blood is returned to the heart via the venous system. One-way valves within the venous system support a unidirectional blood flow towards the heart. The valves prevent retrograde blood flow and divides the venous system of the leg into smaller segments, making the gravitational pressures bearable within each segment [17]. The smooth muscle tone within the venous walls, contraction of the skeletal muscles (muscle pump), and the negative intrathoracic pressure created during inspiration are the primary mechanisms by which venous blood is returned to the heart [16]. The blood in the lower extremity must flow uphill against the forces of gravity; this creates a column of hydrostatic pressure, usually 90mmHg while standing. When the calf muscle contracts, this peaks to approximately 120mmHg [16, 18].

The calf muscle pump is the most important pump in the lower extremity. During ambulation, the calf muscle contracts and compresses the blood out of the deep veins. While the blood is being pumped from the deep veins, one-way valves in the perforator system close, preventing backflow into the superficial veins. As the calf muscle relaxes, the valves in the perforator veins open to permit blood from the superficial system to flow into the deep veins [16].

The foot pump and the thigh pump also support venous return to the heart. The foot pump, however, does not depend upon muscle contraction to drain the venous plexus of the foot. During weight bearing, the veins in the foot are stretched and drained [19]. Some patients' mobility is limited by restricted ankle movement, as seen in people with lipodermatosclerosis (hardening of the dermis and underlying subcutaneous fat) or with extensive fibrosis. Restricted ankle movement makes venous return of the blood to the heart much less efficient [15].

Pathology of venous insufficiency

Venous hypertension is the underlying pathologic mechanism for CVI and subsequent ulcerations [16]. Venous hypertension is the result of one or more processes – obstruction (which blocks outflow), valvular incompetence (which permits retrograde flow) or muscle pump failure (which results in incomplete emptying). Venous hypertension can be a result of one or more of these factors [16].

When outflow obstruction occurs, forward flow is impaired, the veins distal to the obstruction become distended and the venous pressure rises, resulting in venous stasis. The severity and resulting stasis is dependent on the anatomic extent of the venous obstruction and the development of collateral circulation. There are several factors that can cause outflow obstruction – deep venous thrombosis (DVT) resulting in post phlebitic syndrome, pregnancy, obesity, congestive cardiac failure, ascites, severe trauma to the lower leg and tumours. DVT with residual deep vein damage is the most common cause of outflow obstruction [16, 20].

The exact mechanism of valvular incompetence is not yet fully understood. It has been theorised that venous distension, venous hypertension, DVT or valvular agenesis cause damage to valve leaflets [16]. Damage to the valves results in reflux and pooling of the blood in the lower extremities [21].

Failure of the calf muscle pump is thought to be caused by inactivity, neuromuscular abnormalities, or musculoskeletal changes associated with aging, arthritis or sedentary lifestyle. During ambulation, when the muscle pump fails to empty the veins, blood begins to pool and venous hypertension occurs[16].

Pathology of venous ulceration

The exact mechanisms of venous ulceration are not yet fully understood. There are three main theories on the events leading to dermal disruption – the fibrin cuff theory, mechanical theory and the white cell trapping theory [16, 22].

Fibrin cuff theory

Venous hypertension causes the single cell wall of the capillary to be stretched, increasing the size of the capillary pores and allowing the passage of red blood cells and protein (fibrinogen) into the interstitial spaces. Fibrinogen changes to fibrin and forms bands of cuffs around the wall of the capillary. Ulceration to the epidermis is due to these cuffs blocking the diffusion of oxygen and nutrients to the epidermis (Browse & Burnand cited in Moffatt [22]). However, a new theory exists which suggests that the cuffs are a result of and not a cause of the ulceration, and that oxygen and nutrients are able to diffuse through them to the epidermis. This theory suggests that patients who have venous ulceration have less ability to lyse the fibrin which has accumulated (Herrick *et al.* cited in Moffatt [22]).

Mechanical theory

Ulceration is the end result of mechanical stress on the patient's skin. This theory suggests that high pressure in the capillary beds leads to oedema, which in turn raises tissue pressure, resulting in stretching and resultant breakdown of the skin (Chant cited in Moffatt [22]).

White cell entrapment theory

This theory is thought to be the best explanation of venous ulceration. Blood flow through the capillary system becomes reduced in the presence of venous hypertension; this allows leukocytes to adhere to the capillary wall. Tissue damage is caused by some of the leukocytes becoming trapped, blocking the capillaries and causing tissue ischaemia. Other leukocytes migrate out into the tissues, where they become activated and release proteolytic enzymes, oxygen free radicals, and inflammatory mediators that also causes tissue damage (Coleridge *et al.* cited in Moffatt [22]).

Regardless of which theory is correct regarding the pathophysiology of the damage to the microvascular circulation, and subsequent tissue loss, the mainstay of venous ulcer management is graduated compression of the lower limb. The aim is to reduce the pressure within the superficial system, to aid venous return of blood to the heart via the deep venous system, and to reduce local oedema. Graduated compression is considered the gold standard for venous ulcer management [15, 16, 22].

Case study

An 83 year old gentleman was admitted to hospital with CVI, severe ulceration, bacterial infection and fungal colonisation of his left lower leg. He had a history of a motor vehicle accident >25 years ago; the left leg at this time was in external fixation for 3 months and ulceration to this leg developed 2 years later. Over the previous 25 years, he had had several admissions to hospital for management of cellulitis. He had a past medical history of asthma, gout and a recent gastro-intestinal bleed. Medication usage included aspirin EC, sudlinac, temazepam, salmeterol puffer and lanzoprazole. He was allergic to morphine, sulphonamides, and had a perception that he was allergic to normal saline. He lived alone and had two supportive daughters.

Since 1998, surgical procedures included: ligation of the left medial gastronemius vein; exploration of the left popliteal fossa (which revealed that his short saphenous vein was not identified); trapdoor valvuloplasty of the left superficial femoral vein; and split skin graft to the left lateral ulcer. Radiological investigations during the same timeframe included: left lower limb ascending and descending venogram (which demonstrated a grossly incompetent deep venous system); a subsequent venogram 4 years later (which revealed marked reflux); Venous Duplex scans; and a lymphoscintigraphy (which excluded lymphoedema).

On this admission to hospital, the patent presented with extensive tissue loss and cellulitis of the left lower leg (Figures 1-3). Clinical examination revealed that the leg was swollen, with: mild pitting oedema; extensive ulceration over most of the anterior, lateral and posterior aspect; thick adherent

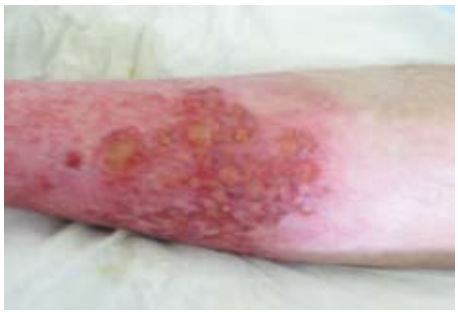

Figure 1. Pre-tibial and medial view of the left lower limb – widespread erythema, partial thickness tissue loss and slough.

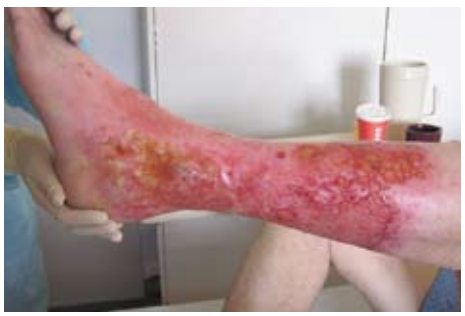

Figure 2. Lateral view of the left lower leg – widespread erythema, partial thickness tissue loss. Ulcer at the supra medial malleoli region 4cmx3cm, partial thickness with adherent slough. One ulcer anterior to medial ankle 5cmx3cm, partial thickness and sloughy. Hyperkeratosis over the medial aspect of the ankle.

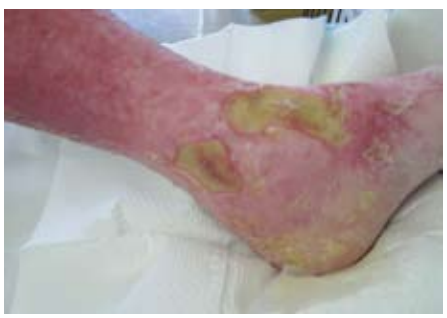

Figure 3. Posterior view of the left lower limb – partial thickness tissue loss, 7cmx5cm, sloughy with surrounding erythema.

slough over the medial and lateral ulcers; hyperkeratosis; lipodermatosclerosis; hemosiderin staining; and moderate serous exudates. His foot was warm and well perfused with palpable pedal pulses. He had a fixed ankle joint, with subsequent decreased range of movement and strength. Ankle brachial indices were not indicative of arterial disease; right: 1.13; left: 1.17. A left arterial duplex scan demonstrated a left 50% popliteal stenosis (not haemodynamically significant) and three-vessel run off to the foot. Left venous duplex scan and venogram demonstrated marked venous reflux and moderated deep and superficial incompetence. Foot x-rays and a white cell scan excluded osteomyelitis.

Other investigations included: inflammatory markers which were elevated; ESR 85mg/L; CRP 53mm/hr; full blood count unremarkable; nuclear autoantibodies, not detected; serology for viral hepatitis non reactive; HIV negative. Wound swab and fungal scrapings revealed that the wound was infected with *Pseudomonas aerginosa* and *Staphylococcus aureus* and critically colonised with *Candida albicans*; punch biopsy for histopathology did not reveal any histological changes.

The patient was commenced on intravenous timentin 3.1g q.i.d., and q.i.d water compresses (the patient had a perception that he was allergic to normal saline) to the areas of tissue loss. The patient refused to have any other type of dressing. Five days later, the wounds showed no clinical signs of improvement and a referral was made to dermatology. They commenced the patient on pentoxifilline 400mg t.d.s. Vitamin supplements were also commenced. The patient had a history of not wearing compression bandages, although nursing and medical staff had spent a great deal of time educating the patient on the importance of compression therapy and its place in wound healing.

Almost a month later, the wounds deteriorated, with an increase in the amount of tissue loss. At this point, the patient agreed to try other dressing modalities, including compression therapy and a primary dressing that contained an antimicrobial agent. The patient was finally discharged home under the care of his general practitioner and community nursing staff some 2 months later.

Discussion

This case illustrates the sequel and long-term consequences of non-compliance with compression therapy in the presence of venous disease. Not only the impact on the patient's quality of life for the last 25 years, there is also the financial drain on the health care dollar to consider. It is generally accepted that venous leg ulcers will heal within 12 weeks with 'best practice', i.e compression therapy. However, in reality, healing rates may be as low as 22% and recurrence rates as high as 69% [12-14]. Other studies have reported that two-thirds of patients' venous leg ulcers recurrence twice or more and 20% of patients have more than six episodes of healing and breaking down [23, 24].

Factors that influence delayed wound healing include failure to investigate and identify the correct underlying aetiology of the ulcer, inadequate compression, lack of patient education and compliance, and failure to reassess and evaluate wound healing rates. Poor healing rates may also be due to senescence of fibroblasts which have reduced response to proliferative stimuli after a prolonged exposure to the chronic venous environment [25-27].

Clinical evaluation

The cornerstone to wound healing is accurate diagnosis. The diagnosis of a venous leg ulcer is comprehensively covered in two recent review articles [28, 29]; in our case study over the last 25 years, repeated invasive and non-invasive investigation confirmed that the underlying aetiology of the leg ulcer was venous in origin. Other differential diagnoses such as arterial, vasculitis, lymphatic, neuropathic, haematological, neoplastic, pyoderma gangrenousum, and osteomylitis were all fully investigated and excluded.

One independent group, the Scottish Intercollegiate Guideline Network (SIGN) [30], gathered evidence, assembled multidisciplinary panels, reached consensus and issued guidelines regarding the management of leg ulcers. Based on the available evidence in the literature [31], they recommend that non-healing ulcers be biopsied because, in 2% of these cases, ulcers are malignant and the correct diagnosis is often missed. Based on these guidelines, a punch biopsy was performed; however, it failed to detect any histological changes.

Compression therapy

In the presence of arterial disease, compression therapy, or bandaging at is otherwise known, will cause tissue necrosis and, in severe cases, potentate the need for amputation. It is beyond the scope of this paper to discuss modified compression for patients with mixed leg ulcers. Prior to applying compression bandaging in our case study, arterial disease was carefully excluded and, over the years, reassessed.

At least two extensive literature reviews and SIGN support the evidence for compression bandaging [28, 30, 32, 33]. The aim of compression bandaging is to provide sustained graduated

external compression, thereby reducing blood pressure in the superficial venous system, aiding venous return of blood to the heart by increasing velocity of flow in the deep veins, and reducing oedema by reducing the pressure differences between the capillaries [34, 35].

The principles of compression bandaging are based on Laplace's law: P=T/R. The pressure (P) exerted by an elastic bandage in proportional to the tension of the bandage (T) and the inverse of the radius of the skin surface area (R). Therefore, when the surface area is convex (ankle), compression is stronger than when it is rounded (middle leg) [36]. Therefore sub-bandage pressure is directly proportional to bandage tension, but inversely proportional to the radius of the limb's curvature to which it is applied [37].

$$P = \text{proportional to} \quad \frac{N \times T}{C \times W}$$

P = pressure exerted by the bandage
N = number of layers of bandage
T = bandage tension
C = circumference of the limb
W = bandage width

The ideal amount of compression for wound healing to occur is approximately 30-40mmHg at the ankle, reducing to 15-20mmHg at the calf, and will lead to healing in a normal shaped leg in 70-80% of cases [38]. However, compression bandaging should only be applied by a skilled professional operator, otherwise there is no benefit; it may in fact be detrimental to the patient if not applied in the correct way [39].

There are various types of compression bandages available on the market – high compression elastic, high compression inelastic, multi-layer bandaging and dynamic compression [40]. There is a lack of evidence to support the use of elastic multi-layer versus inelastic multi-layer high compression [41]. Cullum *et al.*, based on an extensive literature search of 22 trials evaluating compression therapy, concluded that there were higher healing rates with compression therapy compared to no compression, that high compression (35-45mmHg) was more effective than lower compression (15-25mmHg), and that elastic or inelastic multi-layer systems were more effective that single compression [42].

Based on these results, expert opinion and patient-related factors, The International Leg Ulcer Advisory Board recommends a multi-layer high compression system for venous leg ulcers [42]. For active/mobile patients, multi-layer (elastic or inelastic) systems are recommended – elastic expands and contracts to accommodate changes in leg geometry during activity and maintains a resting pressure. Inelastic bandages (short-stretch) do not accommodate changes in limb circumference, have low resting pressures, and therefore require the calf pump muscle action to activate the pressure beneath the bandages. These bandages are therefore unsuitable for inactive patients. For immobile/fixed ankle patients, the recommendation is for multi-layer (elastic) compression bandages [40]. However, it is documented in the literature that independent factors also affect healing rates such as the duration and ulcer size, reduced mobility and reduced ankle function [43, 44].

Dynamic compression or intermittent pneumatic compression (IPC) in the management of lower limb venous ulcers has yet to be fully proven [45]. There is no statistically significant evidence to support the routine use of IPC; eight small studies concluded that IPC may be of some benefit when used in conjunction with compression bandaging [46]. The European Wound Management Association (EWMA) postulate that the use of IPC may be of advantage in the immobile patient with a slow non-healing ulcer [40].

Primary dressing choice

There is a lack of evidence to recommend one dressing type over the other [42]. Conversely, there is good evidence to suggest that the type of dressing has no effect on wound healing rates [30]. Dressing choice should therefore be based on a thorough wound assessment, taking into account the presence of viable and non-viable tissue, the presence of infection, the amount and of exudate, the surrounding skin, allergies, pain, and the clinician's knowledge of the mode of action of dressing selection. A recent Cochrane systematic review and SIGN recommend that the use of a simple non-adherent dressing may be sufficient for the majority of venous ulcers [30, 42].

Care must be taken prior to using any product that will come in contact with the patient's skin – many patients are prone to contact dermatitis, particularly from wool (used in the under padding of compression bandaging systems), lanolin, antiseptics, preservatives, emulsifiers, resins (in hydrocolloid dressings), and rubber [30]. Patients should therefore be patch tested prior to the application of these products.

Prior to applying a dressing, the leg ulcer should be washed in tap water. A lower infection rate was found in a randomised study using tap water versus sterile saline to clean acute traumatic soft tissue wounds [47]. The use of antibiotics is

not recommended routinely unless there is there is evidence of infection such as cellulitis and pain, and may in fact be harmful by encouraging colonisation of resistant organisms [30]. Wound swabbing should be discouraged unless there is a clinical indication of infection (cellulitis, pyrexia, excessive pain) because all chronic wounds are colonised with bacteria [30]. There is no evidence that the use of topical antibiotics have any bearing on wound healing [30].

Over the many years that our patient had his leg ulcer whilst an inpatient for the treatment of cellulitis and venous surgery, the leg was washed with tap water and dressings were kept as bland and simple as possible due to the patient's known sensitivities. Unfortunately, the author does not have access to the client's record whilst being managed in the community to make any comment on the management of his leg ulcer.

Community versus specialised leg ulcer clinics

There is emerging literature, particularly from the United Kingdom, to suggest the healing rates are improved when patients attend specialised leg ulcer clinics [13, 30, 48-51]. In one study, following the implementation of a community based leg ulcer clinic, healing rates improved to 67% at 12 weeks and 82% at 24 weeks, compared with healing rates of 22% prior to the implementation of the service [13].

Providing such a service not only ensures that there are clinical practice guidelines or protocols in place, thus ensuring consistency with practice, but also that nurses are trained in the application of compression therapy. A structured multidisciplinary approach also ensures that patients have been properly investigated to exclude other cause of leg ulcers and therefore have an accurate diagnosis of venous disease prior to the application of compression therapy. Within such a service, there is the provision for regular secondary follow up by a vascular specialist for reassessment and investigation, particularly when leg ulcers are not healing in a timely manner.

In our case study, the patient did not attend a specialised leg ulcer clinic – this may have contributed to the non-healing nature of the leg ulcer. Due to the patient's geographical location, a specialised clinic was unavailable to him. One can hypothesis that this may have facilitated wound healing over the years and prevented recurrence.

Medical and surgical options

Over the years our patient underwent venous surgical procedures to no avail. The place for surgery, compared with graduated compression, is yet to be fully established [30]. To date, there have been no randomised controlled trials which compare both. However, there is consensus that, if the deep venous system is normal, superficial surgery may be helpful [30]. In the case of CVI, there is usually incompetence of the superficial, deep and perforators in both the affected limb and the contralateral limb; therefore, the place for surgery is complex [30].

The use of systemic pharmacotherapy may be helpful in improving healing rates, particularly in ulcers, which are difficult to heal. Pentoxifyline inhibits cytokine mediated neutrophil activation and adhesion. A meta-analysis conducted by Margolis [52] suggests that there is sufficient evidence to support the use of pentoxifyline as an adjunctive with compression therapy. We commenced our patient on this agent following advice from the dermatologist. Other agents such as stanozol, ergotamine, aspirin, prostaglandin E1, and hydroxethirutosides are available on the market. However, there is a lack of any evidence to support their routine use to improve ulcer healing.

We did not trial the use of skin substitutes on our patient; however, there does appear to be new evidence that skin substitutes may be beneficial, particularly in ulcers that have been present for >1 year when used with graduated compression bandaging [53, 54]. Other clinical evaluations currently in progress include evaluating the efficacy of growth factors and protease inhibitors in wound healing rates in venous leg ulcers [54].

Preventing recurrence

Once ulcers have healed, preventing recurrence is vitally important [5, 8]. This includes regular follow up and ensuring that the patient has been fitted for graduated compression hosiery [30]. Over a 5 year period, studies have demonstrated that well fitted compression garments reduce the recurrence rate [30, 55]. A compression of 35-45mmHg at the ankle is required; however, if patients are unable to tolerate this, then a lower compression may be used 25-35mmHg [40]. Lower rates of recurrence are associated with higher levels of compression hosiery [40]. Hosiery should be refitted and replaced at regular intervals. Unless there is a prevention programme in place, then the time and effort spent on healing venous leg ulcers is futile.

Concordance

Often patients are labelled non-compliant with treatment regimes, yet one must take into consideration that a key component of evidence-based health care is patient choice. We as practitioners have a responsibility to the patient to

ensure that, before labelling a patient as non-compliant, we have provided enough education aimed at their level of understanding to allow them to make an informed choice with regard to treatment regimes. Treatment regimes should also be individual.

Venous leg ulcers are a complex condition and therefore education may need to be repeated. Treatment regimes must be individually tailored and the patients must be actively encouraged to participate in their treatment. Over the years, in our case study, the patient was labelled non-compliant. In order to remove this 'label' from our patient, even although the leg ulcer had been present for many years, we found that starting from the beginning and reaffirming prior education of the cause of venous disease and the rational behind treatment regimens was beneficial to concordance. The level of compression was gradually reintroduced to the patient over a period of weeks, until the patient was in full compression (Figure 4).

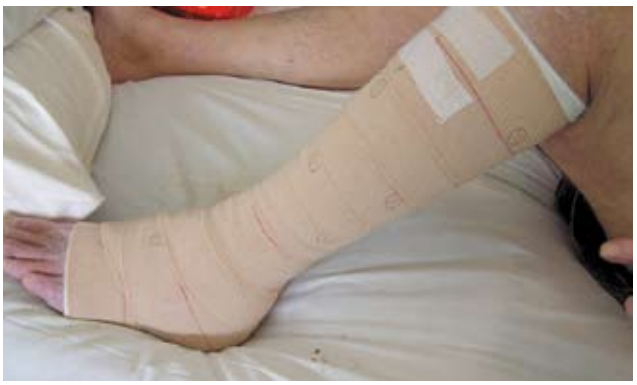

Figure 4. Patient wearing compression bandaging.

It is important that the patient has a full understanding of the consequences of reduced compression and the impact on delayed healing. Ensuring that dressing products are patch tested first is also vitally important since allergic reactions will cause the leg and ulcer to deteriorate and will contribute to the patient being reluctant to participate in other treatment regimes. Good communication is vitally important; if we are expecting compliance with treatment regimes, then we must take the time to listen to any concerns our patients may express.

Pain is often underestimated in the patient with venous leg ulcers and must be addressed; this can be done with appropriate analgesic agents and careful selection of dressings. This will not only improve the patient's quality of life but also improve tolerance of compression therapy [40]. One must also consider assessing the wound for signs of infection and arterial disease.

Conclusion

This case study illustrates the complexity associated with venous leg ulcerations. There are many factors to be taken into account when treating a patient with venous leg ulcers. An understanding of the pathopysiology of the lower leg venous system is vital in order to understand the pathology of venous insufficiency and subsequent ulceration.

Compression therapy is the cornerstone to treatment and must only be applied after the patient has been thoroughly investigated by a vascular specialist to exclude other cause of leg ulceration. Compression therapy should only be applied by a trained operator.

Specialised leg ulcer clinics are associated with better outcomes for the patient; however, due to our patient's geographical location, this service was unavailable to him. Before health care professionals label patients as being non-compliant with treatment regimes, we need to ensure that patients are sufficiently well educated and understand the complexity of venous disease to make this decision.

Unlike the United Kingdom and Europe [30, 56, 57], Australia does not as yet have national guidelines for the management of patients with venous leg ulcers. With the high costs associated with this condition, perhaps motivated health care professionals should consider being actively involved in establishing and implementing a national approach to venous leg ulcers such as those adopted in the United Kingdom.

References

1. Fowkes F. Epidemiology of chronic venous insufficiency. Phlebology 1996; **11**:2-5.
2. Nelzen O, Bergqvist D & Lindhagen A. The prevalence of chronic lower limb ulceration has been underestimated: results of a validated population questionnaire. Br J Surg 1996; **83**:255-8.
3. Nelzen O & Bergqvist D. Chronic venous insufficiency and leg ulcers: how big is the problem? In: Goldstone J (Ed). Perspectives in Vascular Surgery. St Louis, Missouri: Quality Medical Publishing, 1994.
4. Baker SR, Stacey MC, Singh G, Hoskins SE & Thompson PJ. Aetiology of chronic leg ulcers. Eur J Vasc Surg 1992; 245-51.
5. Nelzen O, Bergqvist D & Lindhagen A. leg ulcer etiology: a cross sectional population study. J Vasc Surg 1991; 557-64.
6. Baker SR, Stacey MC, Jopp-McKay AG, Hoskins SE & Thompson PJ. Epidemiology of chronic venous ulcers. Br J Surg 1991; 864-7.
7. Cornwall JV, Dore CJ & Lewis JD. Leg ulcers: epidemiology and aetiology. Br J Surg 1986; 693-6.
8. Callam MT, Harper DR, Dale JJ & Ruckley CV. Chronic ulcer of the leg: clinical history. BMJ 1987; 1389-91.
9. Nelzen O, Bergqvist D, Lindhagen A & Hallbook T. Chronic ulcers: an underestimated problem in primary health among elderly patients. J

Epidemiol Community Health 1991; 184-7.

10. Nelzen O, Bergqvist D & Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. Br J Surg 1994; 182-7.
11. Bennett G & Moody M. Wound Care for Health Professionals. London: Chapman Hall, 1995.
12. Douglas WS & Simpson NB. Guidelines for the management of chronic venous leg ulceration. Report of multidisciplinary workshop. British Association of Dermatologists and the Research Unit of the Royal College of Physicians. Br J Dermatol 1995; 446-52.
13. Moffatt CJ, Franks PJ, Oldroyd M *et al.* Community clinics for leg ulcers and impact on healing. BMJ 1992; 1389-92.
14. Wright DDI, Franks PJ, Blair SD, Backhouse CM, Moffatt C & McCollum CN. Oxerutins in the prevention of recurrence in chronic venous ulceration: randomised controlled trial. Br J Surg 1991; 1269-70.
15. Cameron J. Venous leg ulcers. Nursing Standard 1996; **10**:48-56.
16. Doughty D, Waldrop J & Ramundo J. Lower-extremity ulcers of vascular etiology. In: Bryant R (Ed). Acute and Chronic Wounds: Nursing Management. St Louis: Mosby, 2000, p265-300.
17. Vanhouttee P & Pikoulis E. Venous disease from pathophysiology to quality of life. Angiology 1997; **48**:559-605.
18. Reichardt L. Venous ulceration: compression as the mainstay of therapy. J Wound Ostomy Cont 1999; **26**:39.
19. Lopez A & Philips T. Venous ulcers. Wounds 1998; **10**:149.
20. Cordts P & Gawley T. Anatomic and physiologic changes in lower extremity venous hemodynamics associated with pregnancy. J Vasc Surg 1996; **24**:763-770.
21. Sales C, Rosenthal D & Pertrillo K. The valvular apparatus in venous insufficiency: a problem of quantity? Ann Vasc Surg 1998; **12**:153-155.
22. Moffatt C & Harper P. Leg Ulcers. London: Churchill Livingstone, 1997.
23. Dale J & Gibson B. The epidemiology of leg ulcers. Prof Nurse 1986; **1**:215-216.
24. Cornwall J, Dove CJ & Lewis JD. Leg ulcers: the epidemiology and aetiology. Br J Surg 1986; **73**:693-696.
25. Lal BK, Saito S, Pappas PJ *et al.* Altered proliferative response of dermal fibroblasts to TGF-beta 1 may contribute to chronic venous stasis ulcer. J Vasc Surg 2003; **37**:1285-1293.
26. Mendez MV, Raffetto JD, Phillips T, Menzoian JO & Park HY. The proliferative capacity of neonatel skin fibroblasts is reduced after exposure to venous ulcer wound fluid: a potential mechanism for senescence in venous ulcers. J Vasc Surg 1999; **30**:734-743.
27. Seidman C, Raffetto JD, Marian B, Croon C, Seah CC & Menzoian JO. bFGF-induced alterations in cellular markers of senescence in growth-rescued fibroblasts from chronic venous ulcer and reflux patients. Ann Vasc Surg 2003; **17**:239-244.
28. Weingarten MS. State of the art treatment of chronic venous disease. Clin Infect Dis 2001; 32.
29. de Arujo T, Valencia I, Federman DG *et al.* Managing the patient with venous ulcers. Ann Intern Med 2001; **138**:326-334.
30. Scottish-Intercollegiate-Guidelines-Network. The Care of Patients with Chronic Leg Ulcers. A National Clinical Guideline. SIGN publication number 26. Edinburgh: Royal College of Physicians, 1998.
31. Yang D, Morrison BD, Vandogen YK & Stacey MC. Malignancy in chronic leg ulcers. Med J Aust 1996; **164**:718-20.
32. Margolis DJ & Cohen JH. Management of chronic venous leg ulcers: a literature-guided approach. Clin Dermatol 1994; **12**:19-26.
33. Fletcher A, Cullum F & Sheldon TA. A systematic review of compression treatment for venous leg ulcers. BMJ 1997; **315**:576-580.
34. Eagle M. Compression bandaging. Nursing Standard 2001; **15**:47-52.
35. Morrison M & Moffatt C. A Colour Guide to the Assessment and Management of Leg Ulcers. London: Mosby, 1994.
36. Ramelet AA. Compression therapy. Dermatol Surg 2002; **28**:6-10.
37. Thomas S. The use of Laplace equation in the calculation of sub-bandage pressure. EWMA J 2003; **3**:21-23.
38. Simon D. Approaches to venous leg ulcer care within the community, pinch skin grafts and simple venous surgery. Ostomy/Wound Management 1996; **42**:34-40.
39. Alexander House Group. Consensus paper on venous leg ulcers. Phlebology 1992; **7**:48-58.
40. Marston W & Vowden K. Compression therapy: a guide to safe practice. Understanding compression therapy (EWMA position document): Medical Education Partnership Ltd 2003; 11-17.
41. Partsch H, Damstra RJ, Tazelaar DJ, Schuller-Petrovich S *et al.* Multicentre randomized controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. Vasa 2001; **30**:108-13.
42. Cullum F, Nelson EA., Fletcher AW & Sheldon TA. Compression for Venous Leg Ulcers (Cochrane Review). The Cochrane Library. Vol. 2. Oxford: Update software, 2001.
43. Franks PJ & Moffatt CJ. Factors associated with healing ulceration with high compression. Age Ageing 1995; **24**:407-410.
44. Margolis DJ, Berlin JA & Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. Archives of Dermatology 1999; **135**:920-926.
45. Vowden K. The use of intermittent pneumatic compression in venous ulceration. Br J Nurs 2001; **10**:491-509.
46. Mani R, Vowden K & Nelson EA. Intermittent Pneumatic Compression for the Treatment of Venous Leg Ulcers (protocol for a Cochrane Review). The Cochrane Library. Oxford: Update Software, 2001.
47. Hall Angeras M, Brandberg A & Seeman T. Comparison between sterile saline and tap water for the cleaning of acute traumatic soft tissue wounds. Eur J Vasc Surg 1992; **158**:347-50.
48. Ghauri ASK, Taylor MC, Deacon JE *et al.* Influence of a specialized leg ulcer service on management and outcome. Br J Surg 2000; **87**:1048-1056.
49. Stevens J, Franks PJ & Harrington MA. A community/hospital leg ulcer service. J Wound Care 1997; **2**:62-8.
50. Simon D, Freak L, Kinsella A *et al.* Community leg ulcer clinics: a comparative study in two health authorities. BMJ 1996; **312**:1648-51.
51. Scriven JM, Hartshorne T, Bell PR, Naylor AR & London NJ. Single-visit venous ulcer assessment clinic: the first year. Br J Surg 1997; **84**:334-6.
52. Margolis DJ. Should pentoxifyline be used as an adjuvant for the treatment of venous leg ulcer? Arch Dermatol 2002; **138**:1597.
53. Falanga V & Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair Regen 1999; **Jul-Aug 7**:201-7.
54. Stacey MC, Falanga V, Marston W, Moffatt CJ *et al.* The use of compression therapy in the treatment of venous leg ulcers: a recommended management pathway. EWMA Journal 2002; **2**:9-13.
55. Moffatt CJ & Dorman MC. Recurrence of leg ulcers within a community ulcer service. J Wound Care 1995; **4**:57-61.
56. Benbow M, Burg G, Camacho Martinez F *et al.* Compliance Network Physicians/HFL. Guidelines for the Outpatient Treatment of Chronic Wounds and Burns. Berlin: Blackwell Science, 1999.
57. RCN Institute. Clinical Practice Guidelines: The Management of Patients with Venous Leg Ulcers. London: RCN Institute, 1998.