The economic impact of hard-to-heal leg ulcers

This paper provides a comprehensive review of the evidence on the outcomes from the use of compression bandaging in treating venous leg ulcers. It shows that after two years about 20% of ulcers will not heal despite being treated with high compression. The paper then reviews the evidence on risk factors for non-healing venous leg ulcers and compares continuing treatment costs with the cost of second-line therapies. It highlights the need for health professionals to raise their awareness of effective options for improved treatment for hard-to-heal venous leg ulcers.

Mark Rippon, Phil Davies, Richard White, Nick Bosanquet

KEY WORDS
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Compression therapy
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A leg ulcer can be defined as a loss of skin on the leg or foot that takes more than six weeks to heal. Leg ulceration is strongly associated with venous reflux or obstruction, both of which lead to poor venous return and venous hypertension (Nelson et al, 2006). It has been reported that more than 80% of leg ulcers are caused by venous insufficiency (Shai and Halevy, 2005).

The causes of chronic venous insufficiency (CVI) include: venous valve incompetence in the deep, perforator, and/or superficial veins; deep vein obstruction and thrombosis; arteriovenous fistula; and calf muscle pump failure resulting from paralysis, a decrease in the range of motion of the ankle and ankle deformity (Wipke-Tevis and Sae-Sia, 2004). CVI leads to pooling of blood and raised blood pressure in the lower leg, causing damage to the walls of the veins allowing blood and proteins to leak into the surrounding tissues (Anderson, 2006). Shear stress within this environment leads to an inflammatory reaction accompanied by leukocyte activation which results in the synthesis and release of pro-inflammatory molecules leading to venous dermatitis and venous ulceration (Pascarella et al, 2005).

The development of an ulcer is thought not necessarily to be 'spontaneous' and solely attributable to the presence of venous insufficiency. A number of specific triggers have been identified including cellulitis, penetrating injury, contact dermatitis, rapidly aggravating leg oedema, dry skin with subsequent scratching, and blunt trauma (Shai and Halevy, 2005).

About 1–2% of the whole population (Anderson, 2006) and 3–5% of the population over 65 years of age (Mekkes et al, 2003) will suffer from a leg ulcer during their lifetime. The prevalence of the population at age 80 years is about 20 per 1,000 (Nelson et al, 2006). Risk factors for the development of venous leg ulcers (VLUs) include a family history of maternal venous insufficiency (Berard et al, 2002), a history of deep vein thrombosis, diabetes mellitus, chronic heart failure, recent oedema, obesity, severe trauma to the leg and, for women, the number of pregnancies (Elder and Greer, 1995; Wipke-Tevis and Stotts, 1996; 1998; 2000). VLUs are characterised by a cyclical pattern of healing and recurrence. VLU recurrences are common with rates ranging from 54–78% (Etufugh and Phillips, 2007).

VLUs are associated with health-related quality-of-life issues such as pain, malodour, itching, altered appearance, loss of sleep, functional limitation and disappointment with treatment (Hareendran et al, 2005). Due to their high prevalence, refractory nature, morbidity, mortality and impact on patients' quality of life, VLUs pose a serious clinical dilemma as well as a large economic burden on health services in many countries (Bouza et al, 2005). The annual cost of CVI is estimated to be between £400m and £600m in the UK (Simka and Majewski, 2003). The average cost of treating one VLU has been reported to vary between €1,332 and €2,585 (£894–£1,735) per annum in Sweden and between £546–£1,338 in the UK (Ragnarson Tennvall and Hjelmgren, 2005).

The standard treatment for VLUs is the application of graduated compression, either in the form of compression

Mark Rippon is Medical Marketing Manager, Mölnlycke Health Care, Gothenburg, Sweden; Phil Davies is Clinical and Scientific Information Manager, Mölnlycke Health Care, Gothenburg, Sweden; Richard White is Professor in Tissue Viability, University of Worcester; Nicolas Bosanquet is Professor of Health Policy, Department of Bioengineering, Imperial College London

bandages or hosiery. Dressings such as foams, hydrocolloids and hydrofibres are usually applied beneath the compression to aid healing, provide comfort and control exudate. Multi-layer, high compression elastic bandaging systems are regarded as the most effective form of compression for treating VLUs (Iglesias et al, 2004). Compression therapy has also been shown to be a cost-effective intervention for the treatment of VLUs (O'Brien et al, 2003; Iglesias et al, 2004) and it has been demonstrated that four-layer bandaging significantly improves the quality of life of patients (Clarke-Moloney et al, 2005).

A position document, *Understanding Compression Therapy*, published by the European Wound Management Association (Franks and Posnett, 2003) reported the total weekly cost of treating a patient with an unhealed VLU to be €44(£29). Based on once-weekly dressing changes, this figure included nursing time, €26.40(£17.40); dressings and bandages, €14.30(£9.43); and other costs, €3.30(£2.18) (Franks and Posnett, 2003). This equates to an estimated yearly cost of treating an unhealed VLU to be in the region of €2,288(£1,544) per patient. The literature also shows that the cost of treating non-healing VLU can be up to three times greater than for healing ulcers (Ragnarson Tennvall and Hjelmgren, 2005).

An extensive literature search was undertaken to identify published articles containing clinical data relating to the healing rates of VLU treated with high compression elastic bandaging systems. Electronic searches of bibliographic

Table 1
Electronic data sources

Bibliographic databases
MEDLINE (National Library of Medicine, Bethesda, USA)
EMBASE (Elsevier BV, Amsterdam, Netherlands)
CINAHL (Cinahl Information Systems, Glendale, USA)
Websites
Cochrane Library
World Wide Wounds

Table 2
Healing rates of VLUs treated with multi-layer high compression elastic bandaging systems (%)

	Treatment (weeks)											
Reference	6	10	12	13	16	22	24	36	40	47	52	104
Meredith and Gray, 1988*	24											
Leaper et al, 1991	6											
Moffatt et al, 1992			69				83					
Duby et al, 1993			44									
Ohlssen et al, 1994*	13											
Franks et al, 1995			69				83					
Lambourne et al, 1996			54				68					
Thomson et al, 1996			40		50		57					80
Armstrong and Ruckley, 1997*	29											
McCollum et al, 1997							82; 84					
Vowden et al, 1997			65				84	91				
Wilkinson et al, 1997			59									
Ghauri et al, 1998								70				
Morrell et al, 1998			34				58				71	
Scriven et al, 1998											55	
Taylor et al, 1998			66.7									
Carr et al, 1999			65; 79				82; 84					
Castineira et al, 1999									50			
Marston et al, 1999		57			75							
Bello et al, 2000											55	
Guest et al, 2000							74					
Vowden et al, 2000			65				80					
Partsch et al, 2001					62							
Moffatt et al, 2003			70				88					
O'Brien et al, 2003			54									
Barwell et al, 2004							65					
Franks et al, 2004			56				85					
Gohel et al, 2005							76					
Bjellerup, 2006				25		50				75		
Unpublished studies cited in NHS Centre for Reviews and Dissemination, University of York (1997)												
Colgan et al			70									
London and Scriven											60	
Morrell et al											65	
Taylor et al	72		75									
Mean (%)	28.8	57	60.9	25	62.3	50	77.1	80.5	50	75	61.2	80
Standard deviation	25.8		12.4		12.5		9.86	14.8			6.87	

*The articles marked with an asterisk do not specify the type of multi-layer high compression bandaging system employed. All other articles refer to the use of four-layer compression bandaging

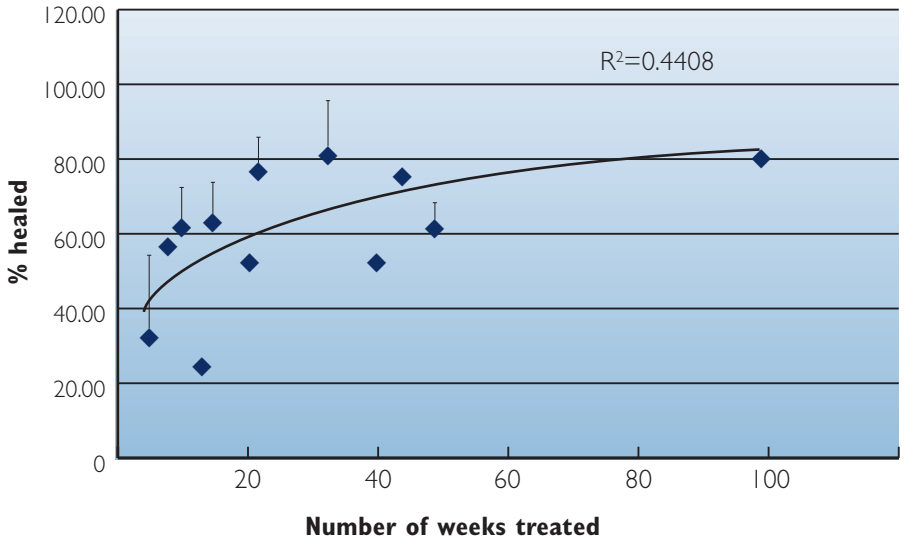

Figure 1. Healing rates of VLUs treated with multi-layer high compression elastic bandaging systems as collated from the available literature, represented using a logarithmic regression analysis.

databases and websites (*Table 1*) were supplemented with manual searches of journals of relevance to wound management.

The literature search identified 30 published articles (including one article that cites data from four unpublished studies) which reported on healing rates over a range of time scales (6, 10, 12, 13, 16, 22, 24, 36, 40, 47, 52 and 104 weeks of treatment). The data from these articles were collated (*Table 2*), the mean percentage healing rates calculated at the different time points, and the data presented graphically as a regression of the mean (standard deviation) of VLUs healed over the range of time points (*Figure 1*).

The data indicate that some VLUs may take in excess of 100 weeks to heal. These findings are similar to work undertaken by Barwell and colleagues who presented a Kaplan-Meier plot produced from their own data which also demonstrated that, after 12 months of treatment, about 70% of VLUs had healed (Barwell et al, 2004). More importantly, the data indicate that about 20% fail to heal despite the use of compression therapy (*Figure 1*). This has been further demonstrated by probability calculations of not healing based on the results of a cohort study using a dataset of more than 20,000 individuals with VLUs. The study, which involved the creation of complex models using logistic regression, as well as simply counting prognostic factors, demonstrated that initial measures of wound size and duration accurately predict which VLUs are likely to heal with compression therapy (Margolis et al, 2004a) (*Table 3*).

Hard-to-heal VLUs

The failure of VLUs to heal in a timely manner may be related to a variety of factors, e.g. bacterial infection (Madsen et al, 1996). A number of pathogenic bacteria have been shown to be associated with VLUs, e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa, Enterococcus faecalis, Proteus mirabilis and Escherichia coli* (Zmudzinska et al, 2005). Control of wound infection is dependent upon many factors, but current treatment is usually centred on the use of topical antibacterial agents, dressings impregnated with antimicrobial agents (e.g. silver) and systemic antibiotics, all of which can add to the baseline costs of management.

Studies have indicated that infection in wounds can increase the cost of treatment significantly, for example the additional cost of infection in a surgical wound has been shown to range between US$1,617–$3,152 (£828–£1,614) (Agency for Health Care Policy and Research, 1989). Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is an increasing problem, particularly in community care (Miller et al, 2007). The contamination of chronic wounds with MRSA represents an increasing problem worldwide. If MRSA contamination progresses towards a systemic infection, then this will be detrimental to the patient as well as having an adverse effect on the cost of treatment (Dissemond et al, 2005). The additional cost of treatment for a patient infected with MRSA on a trauma and orthopaedic ward has been reported to be £13,972 compared with the cost of prevention which is reported as £3,200 (Nixon et al, 2006).

Table 3
Prognostic models for non-healing VLUs (Margolis et al, 2004)

Ulcer size (cm^2)	Ulcer duration (months)	Chance of not healing (%)
<10	<12	29
<10	>12	44
>10	<12	56
>10	>12	78

It has been shown that there are other medical conditions which are associated with patients who have recently developed a VLU. These conditions include: asthma, cellulitis of the lower extremity, congestive heart failure, diabetes, deep venous thrombosis, lower-limb oedema, osteoarthritis, peripheral vascular arterial disease of the lower extremity, rheumatoid arthritis, history of hip surgery, and history of venous surgery or ligation (Margolis et al, 2004b). The association between chronic ulcers and cancers such as squamous cell carcinoma is well established and, if present, will impair healing (Enoch et al, 2004).

Cost of treating hard-to-heal VLUs

Using data presented in this paper along with published population statistics, it is possible to identify the overall and individual UK costs associated with the treatment of VLUs that do not heal (*Table 4*). These VLUs can be identified by using the prognostic indicators (ulcer size >10cm^2 and ulcer duration >12 months) (*Table 3*).

Multiplying the average annual cost of treatment — €2,288 (£1,541) as estimated by EWMA (2003) — by the number of years the patients with hard-to-heal VLUs are likely to live e.g. x5,

Table 4
Cost calculation of treating difficult-to-heal VLU in the UK

Incidence of VLU: 1.5–2.0 per 1,000 of the whole population (Anderson, 2006)
Population of the UK: 60,139,274 (The European Union Internet Statistics, March 2006)
Number of patients with VLU (Population x VLU incidence): 90,209–120,279
If, as the reference data indicate, 20% of VLU will not heal despite being treated with high compression therapy, then the number of patients that will require alternative therapies to initiate a healing response, or ongoing compression therapy, will be in the region of 20,000
Average cost of ongoing treatment of 20,000 VLUs that will not heal with compression therapy: €2,288 (£1,541) per patient per annum (Franks and Posnett, 2003)
Annual cost of treating 20,000 VLU that will not heal with compression therapy: €46m (£30m)

x10 and x15 years, then per patient this equates to a total maintenance cost of €11,444 (£7,705), €22,880 (£15,410) and €34,320 (£23,115) respectively.

When taking this into consideration, it allows a serious comparison of the more expensive advanced treatments for VLUs that are currently on the market all of which are discussed later. If an advanced treatment is effective in initiating a healing response, then it very quickly appears to be cost-effective. A hypothetical advanced therapy costing €1,500 in total for a complete course of treatment per patient will be cost-effective even if it only has a 10% success rate. This figure was loosely based on the cost of using amelogenin (Xelma, Mölnlycke Health Care) which costs in the region of €1,700 for a course of once-weekly treatments over a period of 12 weeks. It has not been possible to establish an accurate average cost for advanced therapies for treating venous leg ulcers, for the following reasons:

- Many of the advanced therapies are not reimbursable against NHS prescriptions and, as such, are not listed in the Drug Tariff therefore making it very hard to establish the cost of treatment with these modalities in the United Kingdom
- Duration of treatment with advanced therapies varies.

As described earlier, the treatment costs for one patient with standard therapy (high compression) over a period of 15 years is €34,320 and for 10 patients who have been accurately predicted to have a hard-to-heal VLU is €343,200. If all 10 patients were additionally treated with a hypothetical advanced therapy costing €1,500 per complete course of treatment, then this would equate to €15,000, resulting in a total cost of €358,200 (standard therapy plus advanced therapy). In order to calculate the potential savings associated with the use of the advanced therapy (assuming a zero rate of VLU recurrence), the following equations have been applied and the results are presented in *Table 5*. Equation 1: cost of advanced therapy and 15 years of standard therapy for 10 patients – cost of 15 years of standard therapy for patients with healed VLUs = cost of standard plus advanced therapy for patients with VLUs remaining unhealed.

Equation 2: total cost saving = total cost of 15 years of standard therapy for 10 patients – cost of advanced therapy for 10 patients plus the cost of 15 years of standard therapy for patients with unhealed VLUs. For example, a success rate of 10% (i.e. 1/10 VLUs healed) results in a cost saving of €19,320

- Equation 1:
  €358,200 – €34,320 = 323,880
- Equation 2
  343,200 – 323,880 = 19,320

Based on potentially different success rates (i.e. 10%, 50% and 100%) with this advanced therapy, calculations of the potential cost savings over 15 years associated with its use are presented in *Table 5*.

This calculation provides a justification for the use of more advanced therapies in an attempt to initiate healing in patients who have a VLU that will otherwise not heal. These advanced therapies include drugs, such as pentoxifylline, surgery (grafting, meshing and vein surgery), biologically active agents (growth factors, scaffolds/matrices), and the use of in vitro autologous/heterologous cells. All of these treatments have met with varying levels of success, details of which are summarised below with cost-effectiveness data, if available.

Advanced therapies

Pharmacological agents

Various pharmacological agents have been used as adjuvant therapy in the

Table 5
Costs and potential savings associated with the treatment of 10 patients with VLUs accurately predicted to be hard to heal over a period of 15 years

A	B	C	D	E	F
Success rate (proportion healed VLUs)	Cost for advanced treatment and 15 years worth of standard therapy for 10 patients	Cost of 15 years of standard therapy for patients with healed VLUs	Cost of advanced therapy for 10 patients plus the cost of 15 years of standard therapy for patients with unhealed VLUs	Total cost of 15 years of standard therapy for 10 patients	Cost savings (E-D)
10% (1/10 patients)	€358,200	€34,320	€323,880	€343,200	€19,320
50% (5/10 patients)	€358,200	€171,600	€186,600	€343,200	€156,600
100% (10/10 patients)	€358,200	€343,200	€15,000	€343,200	€328,200

management of VLUs but in many cases there is no definitive evidence of their efficacy (Simka and Majewski, 2003). Some recent clinical studies have evaluated the use of oral pentoxifylline, an anti-inflammatory drug that improves blood flow, down-regulates leukocyte activation, reduces leukocyte adhesion and has fibrinolytic effects (Dormandy, 1995). It is thought that this agent might be directed against leukocyte activation in order to regulate the magnitude of the inflammatory response (Pascarella et al, 2005). Oral pentoxifylline has been shown to be beneficial in conjunction with compression therapy in the treatment of VLUs (Jull et al, 2002). It has also been shown to be cost-effective when compared with a placebo treatment (Iglesias and Claxton, 2006). Although significantly better than the placebo in that complete healing occurred in 23 of the 38 patients treated with pentoxifylline, it is worth noting that a percentage of patients still remained unhealed.

Controlled studies have demonstrated that the cost-effectiveness ratio of another pharmacological agent, micronised purified flavonoid fraction (MPFF) adjuvant therapy, is substantially better than that for conventional therapy (US$1,061.8 (£543) versus US$1871.9 (£957) per ulcer healed) in the treatment of VLUs (Simka and Majewski, 2003).

Surgery

Surgical intervention, such as sub-fascial endoscopic perforator vein surgery (SEPS), can be used as a treatment for VLUs (Chong et al, 2005). This type of surgery utilises techniques to interrupt (e.g. ligate) incompetent perforators. It is a procedure which is generally reserved for patients with hard-to-heal leg ulcers. Patients who benefit from surgical treatment and the addition of SEPS are those with ulcers resulting from primary valvular incompetence of the superficial and perforating veins, with or without deep venous incompetence (Kalra and Gloviczki, 2002). Recent studies have shown that SEPS is a cost-effective surgical management with complete ulcer healing occurring in 57% of patients (at a mean healing time of 14 weeks) with a reduction in ulcer size in 29% and with no recurrent ulceration. Although SEPS incurs increased operating room costs, it is considered to be cost-effective due to the patients' shortened length of hospital stay and diminished wound complications (Iafrati et al, 1997).

Other surgical interventions that have been used include the use of grafts such as those taken from the patient's own uninjured skin. A study evaluated the use of shave therapy, which involves the removal of ulcers together with the surrounding lipodermatosclerosis and covering the wounds with meshed split-skin grafts, and demonstrated a healing rate of ulcers classified as non-healing of 67% versus 76% for ulcers associated with primary deep vein incompetence and 58% for ulcers associated with post-thrombotic syndrome (Schmeller and Gaber, 2000). A Swedish study evaluated the effect of split-skin grafting on VLUs. The results showed that 88% healed after a mean of 15 days, with a cost for treating one leg ulcer of SEK89,000 (£6,451) (Turczynski and Tarpila, 1999). Another study demonstrated that the cost of treating a VLU over a 12-week period with pinch grafting was £5,552 in hospital care, versus £2,504 in primary care (Ragnarson et al, 2005a).

Alternatively, skin may be grown from the patient's skin cells into a dressing (autografts), or applied as a sheet of bioengineered skin grown from donor cells (allograft). Preserved skin from other animals, such as pigs, has also been used; these grafts are known as xenografts. Generally, there is little evidence to suggest that artificial bilayered skin may be beneficial to wound healing (Jones and Nelson, 2005). However, a clinical study using a bilayered bioengineered skin substitute (BBSS) demonstrated cost-effective management in patients with ulcers of duration greater than one year. The results showed that the costs of BBSS plus compression therapy were US$20,041 (£10,247) per patient whereas the costs of compression therapy alone was US$27,493 (£14,057) per patient (Curran and Plosker, 2002).

Growth factors

Other biologically active agents that have been used to treat recalcitrant ulcers include growth factors, such as recombinant human platelet-derived growth factor-BB (rhPDGF-BB) which has been shown to have some beneficial effect in the treatment of non-diabetic ulcers (Harrison-Balestra et al, 2002). Generally, however, growth factors appear to have limited clinical usage in the treatment of VLUs (Nelson et al, 2006).

Biological matrices and scaffolds

Tissue ischaemia has been linked to elevated extracellular matrix (ECM) turnover, associated with matrix failure when compounded with problems of matrix stabilisation likely in ischaemia (Dalton et al, 2005). This represents a potential mechanism for ulcer formation and therefore the use of an artificial matrix or scaffold may help to alleviate this condition and be beneficial to the healing of chronic wounds. Thus wounds with a large loss of deep tissue can be repaired using a dermal substitute. A number of such products are available commercially (Campitiello et al, 2005). In a recent study, allogenic cultured dermal substitute (CDS) was shown to achieve healing in 95% of various wounds treated, including 100% healing in a sub-population of chronic skin ulcers although only six patients were evaluated in this group (Kuroyanagi et al, 2001).

Recently, a matrix protein used in dental surgery has been identified to have beneficial effects in the treatment of chronic wounds such as VLUs. This is a low molecular weight protein (amelogenin) found in developing tooth enamel, and it belongs to a family of ECM proteins. It has been used successfully to treat VLUs as has been demonstrated in a single-blinded, randomised multi-centre study (Vowden et al, 2006). Both treatment groups maintained compression therapy throughout the investigation. In a more recent study, VLU patients were treated with either amelogenin plus high compression or high compression alone (the control group). The results demonstrated that the percentage reduction in ulcer size was significantly ($p=0.03$) greater in the amelogenin group (-33.11) than in the control (-11.07) from baseline to final visit. Additionally, the number of improved ulcers was significantly ($p=0.01$) greater

in the group treated with amelogenin (Vowden et al, 2007).

In order to gain the maximum advantage from using advanced therapies to treat hard-to-heal VLUs it is imperative that the potential non-healing ulcer (that will not respond to compression therapy) is identified at an early stage. A number of studies have used prognostic indicators to identify 'at-risk' patients who will probably not heal. Initial ulcer size and moderate arterial insufficiency were identified as factors that were independently associated with delayed healing (Marston et al, 1999). In a recent study in which data from 20,000 patients were evaluated, Margolis et al (2004a) showed that ulcer size (>10cm^2) and duration (longer than 12 months) could be used as accurate predictors of a non-healing wound. In effect these patients have a 78% chance of their wound not healing. Other studies have shown that baseline ulcer area, and duration of over six months, are important predictors of non-healing (Philips et al, 2000; Tennvall and Hjelmgren 2005; Vowden et al, 2007).

Other predictors for not healing were identified as the presence of an arterial lower-limb disease, an ulcer duration of more than three months and an initial ulcer length of 10cm or more. The use of linear regression has demonstrated that old age and a high body mass index are independent predictors of a delayed or non-healing wound (Meaume et al, 2005).

Discussion

Data obtained from the literature show that, even when treated with the 'gold standard' of compression therapy, 10–20% of VLUs will remain unhealed after two years (Thomson et al, 1996; Pfeffer et al, 2004), and will probably not go on to heal with their current therapy. It has also been shown that this sub-population of (non-healing) patients can be identified by using prognostic indicators e.g. healing rate (wound area reduction) during the first few weeks of treatment.

It is thought that such long-standing wounds may require active agents to initiate the healing process. A variety of biological agents are currently available to do this. Such has been the success of these agents in treating the hard-to-heal wound, that the use of biological agents in conjunction with compression therapy has been recommended as 'best practice' by some authors (Kunimoto et al, 2001) and their use for specific chronic wound indications, such as diabetic wounds, is well supported (Falanga, 2005). Amelogenins are biological agents that have also recently been shown to promote healing in acute experimental models (Mirastschijski et al, 2004) and in trials have been shown to be clinically beneficial to the healing of hard-to-heal VLUs (Vowden et al, 2006; 2007).

In order for advanced therapies to be presented as cost-effective, the expense implications of the patients' remaining treatment lifetime have to be taken into consideration and weighed against the overall expenditure of such a therapy.

Conclusion

About 20% of patients with VLUs will not heal, even when treated with compression therapy — the so-called gold standard. Using prognostic indicators, the patients with these types of VLU can be identified. The use of advanced therapies, even though initially more expensive, may be fully justified in treatment from a cost-effective and efficacy perspective, when all the associated costs over the patient's treatment lifetime are taken into consideration. By giving these treatments to patients who have been accurately identified as having hard-to-heal ulcers these treatments can be considered cost effective.

The costs of leg ulcer treatment are no exception to Pareto's law that 20% of patients generate 80% of the cost — and these are the patients who have the worst experience, the greatest pain and the most serious reductions in social functioning. Some may be involved in a number of hospital admissions every year with poor outcomes, leading ultimately to long-term care.

There has been considerable progress in using compression bandaging for many ulcer patients, but there is a substantial minority who cannot be helped by such methods and this minority incur some of the greatest costs and worst outcomes. This paper points the way forward to a situation where health services could offer greater help to these patients who have a high level of need. It is not fully appreciated that there are already cost-effective ways for improving outcomes for such patients. If funding and resources are to be used effectively, health services need to develop much more systematic ways of identifying and targeting treatment for patients with hard-to-heal ulcers. WUK

**All currency conversions were calculated on 20th February 2007 using Xe.com*

Key Points

- A review of the literature indicates that 20% of VLUs do not heal despite being treated with high compression.
- Significant costs are associated with the treatment of chronic VLUs and associated conditions.
- The literature indicates that the cost of compression therapy for one patient with a VLU over a period of 15 years is approximately €34,320.
- The use of advanced therapies, although initially appear expensive, may result in significant cost savings in the management of chronic VLUs.

References

Agency for Health Care Policy and Research (1989) Omnibus Reconciliation Act of (OBRA). *Public Law:* 101–239

Anderson I (2006) Aetiology, assessment and management of leg ulcers. *Wound Essentials* **1**: 20–36

Armstrong SH, Ruckley CV (1997) Use of a fibrous dressing in exuding leg ulcers. *J Wound Care* **6**(7): 322–4

Barwell JR, Davies CE, Deacon J et al (2004) Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised

controlled trial. *Lancet* **363(9424)**: 1854–9

Bello M, Naik J, Scriven MJ, Hartshorne T, London NJ (2000) The clinical management and outcome of venous ulcers in legs with deep-venous obstruction. *Eur J Vasc Endovasc Surg* **19(1)**: 62–4

Berard A, Abenhaim L, Platt R, Kahn SR, Steinmetz O (2002) Risk factors for the first-time development of venous ulcers of the lower limbs: the influence of heredity and physical activity. *Angiology* **53(6)**: 647–57

Bjellerup M (2006) Determining venous incompetence: a report from a specialised leg ulcer clinic. *J Wound Care* **15(10)**: 429–30; 433–6

Bouza C, Munoz A, Amate JM (2005) Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. *Wound Repair Regen* **13(3)**: 218–29

Campitiello E, Della Corte A, Fattopace A, D'Acunzi D, Canonico S (2005) The use of artificial dermis in the treatment of chronic and acute wounds: regeneration of dermis and wound healing. *Acta Biomed* **76(Suppl 1)**: 69–71

Carr L, Philips Z, Posnett J (1999) Comparative cost-effectiveness of four-layer bandaging in the treatment of venous leg ulceration. *J Wound Care* **8(5)**: 243–8

Castineira F, Fisher H, Coleman D, Grace PA, Burke P (1999) The Limerick Leg-Ulcer Project: early results. *Ir J Med Sci* **168(1)**: 17–20

Chong TW, Bott MJ, Kern JA, Peeler BB, Tribble CG, Harthun NL (2005) Subfascial endoscopic perforating vein surgery (SEPS) for the treatment of venous ulcers. *Ostomy Wound Manage* **51(9)**: 26–31

Clarke-Moloney M, O'Brien JF, Grace PA, Burke PA (2005) Health-related quality of life during four-layer compression bandaging for venous ulcer disease: a randomised controlled trial. *Ir J Med Sci* **174(2)**: 21–5

Colgan MP, Teevan M, McBride C Cost comparisons in the management of venous ulceration. Unpublished report In: NHS Centre for Reviews and Dissemination, University of York (1997) Compression therapy for venous leg ulcers. *Effective Health Care* **3(4)**: 1–12

Curran MP, Plosker GL (2002) Bilayered bioengineered skin substitute (Apligraf): a review of its use in the treatment of venous leg ulcers and diabetic foot ulcers. *BioDrugs* **16(6)**: 439–55

Dalton SJ, Mitchell DC, Whiting CV, Tarlton JF (2005) Abnormal extracellular matrix metabolism in chronically ischemic skin: a mechanism for dermal failure in leg ulcers. *J Invest Dermatol* **125(2)**: 373–9

Dissemond J, Korber A, Lehnen M, Grabbe S (2005) Methicillin-resistant *Staphylococcus aureus* (MRSA) in chronic wounds: therapeutic options and perspectives. *J Dtsch Dermatol Ges* **3(4)**: 256–62

Dormandy JA (1995) Pharmacologic treatment of venous leg ulcers. *J Cardiovasc Pharmacol* **25(Suppl 2)**: S61–5

Duby T, Hoffman D, Cameron J, Dobloff-Brown D, Ryan T (1993) A randomised trial in the treatment of venous leg ulcers comparing short stretch bandages, four layer bandage system, and long stretch-paste bandage system. *Wounds* **5**: 276–9

Elder DM, Greer KE (1995) Venous disease: how to heal and prevent chronic leg ulcers. *Geriatrics* **50(8)**: 30–6

Enoch S, Miller DR, Price PE, Harding KG (2004) Early diagnosis is vital in the management of squamous cell carcinomas associated with chronic non healing ulcers: a case series and review of the literature. *Int Wound J* **1(3)**: 165–75

Etufugh CN, Phillips TJ (2007) Venous ulcers. *Clin Dermatol* **25(1)**: 121–30

The European Union Internet Statistics, (2006) www.internetworldstats.com/stats4.htm#europe (last accessed March 2006)

Falanga V (2005) Wound healing and its impairment in the diabetic foot. *Lancet* **366 (9498)**: 1736–43

Franks PJ, Moody M, Moffatt CJ et al (2004) Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. *Wound Repair Regen* **12(2)**: 157–62

Franks PJ, Oldroyd MI, Dickson D, Sharp EJ, Moffatt CJ (1995) Risk factors for leg ulcer recurrence: a randomized trial of two types of compression stocking. *Age Ageing* **24(6)**: 490–4

Franks PJ, Posnett J (2003) Cost-effectiveness of compression therapy. In: Calne, S et al eds. *European Wound Management Association Position Document: Understanding Compression Therapy.* Medical Education Partnership, London: 8–10

Ghauri AS, Nyamekye I, Grabs AJ, Farndon JR, Poskitt KR (1998) The diagnosis and management of mixed arterial/venous leg ulcers in community-based clinics. *Eur J Vasc Endovasc Surg* **16(4)**: 350–5

Gohel MS, Taylor M, Earnshaw JJ, Heather BP, Poskitt KR, Whyman MR (2005) Risk factors for delayed healing and recurrence of chronic venous leg ulcers – an analysis of 1324 legs. *Eur J Vasc Endovasc Surg* **29(1)**: 74–7

Guest M, Smith JJ, Sira MS et al (2000) Venous ulcer healing by four-layer compression bandaging is not influenced by the pattern of venous incompetence. *Br J Surg* **87(8)**: 1114

Hareendran A, Bradbury A, Budd J et al (2005) Measuring the impact of venous leg ulcers of quality of life. *J Wound Care* **14(2)**: 53–7

Harrison-Balestra C, Eaglstein WH, Falabela AF et al (2002) Recombinant human platelet-derived growth factor for refractory nondiabetic ulcers: a retrospective series *Dermatol Surg* **28(8)**: 755–9; discussion 759–60

Iafrati MD, Welch HJ, O'Donnell TF Jr (1997) Subfascial endoscopic perforator ligation: analysis of early clinical outcomes and cost. *J Vasc Surg* **25(6)**: 995–1000

Iglesias CP, Claxton K (2006) Comprehensive decision-analytic model and Bayesian value-of-information analysis: pentoxifylline in the treatment of chronic venous leg ulcers. *Pharmacoeconomics* **24 (5)**: 465–78

Iglesias C, Nelson EA, Cullum NA, Torgerson DJ; VenUS Team (2004) VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. *Health Technol Assess* **8(29)**: iii, 1–105

Jones JE, Nelson EA (2005) Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev* **25(1)**: CD001737

Jull A, Waters J, Arroll B (2002) Pentoxifylline for treatment of venous leg ulcers: a systematic review. *Lancet* **359 (9317)**: 1550–4

Kalra M, Gloviczki P (2002) Subfascial endoscopic perforator vein surgery: who benefits? *Semin Vasc Surg* **15(1)**: 39–49

Kunimoto B, Cooling M, Gulliver W, Houghton P, Orsted H, Sibbald RG (2001) Best practices for the prevention and treatment of venous leg ulcers. *Ostomy Wound Manage* **47(2)**: 34–50

Kuroyanagi Y, Yamada N, Yamashita R, Uchinuma E (2001) Tissue-engineered product: allogeneic cultured dermal substitute composed of spongy collagen with fibroblasts. *Artif Organs* **25(3)**: 180–6

Lambourne LA, Moffatt CJ, Jones AC, Dorman MC, Franks PJ (1996) Clinical audit and effective change in leg ulcer services. *J Wound Care* **5(8)**: 348–51

Leaper DJ, Cameron S, Hewitt H, Winter A, Lucarotti ME (1991) A community- and hospital-based comparative evaluation of Comfeel Ulcer Dressing for chronic leg ulcers. *J Dermatolog Treat* **2(3)**: 103–6

London N, Scriven JM. Unpublished report In: NHS Centre for Reviews and Dissemination, University of York (1997) Compression therapy for venous leg ulcers. *Effective Health Care* **3(4)**: 1–12

Madsen SM, Westh H, Danielsen L, Rosdahl VT (1996) Bacterial colonization and healing of venous leg ulcers. *APMIS* **104(12)**: 895–9

Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA (2004a) The accuracy of venous leg ulcer prognostic models in a wound care system. *Wound Repair Regen* **12(2)**: 163–8

Margolis DJ, Knauss J, Bilker W (2004b) Medical conditions associated with venous leg ulcers. *Br J Dermatol* **150(2)**: 267–73

Marston WA, Carlin RE, Passman MA, Farber MA, Keagy BA (1999) Healing rates and cost efficacy of outpatient compression treatment for leg ulcers associated with venous insufficiency. *J Vasc Surg* **30(3)**: 491–8

McCollum CN, Ellison DA, Groarke L et al (1997) *Randomised trial comparing Profore and the original four layer bandage. Presented at European Wound Management Association, Milan 1997*. Macmillan, London

Meaume S, Couilliet D, Vin F (2005) Prognostic factors for venous ulcer healing in a non-selected population of ambulatory patients. *J Wound Care* **14(1)**: 31–4

Mekkes JR, Loots MA, van der Wal AC, Bos JD (2003) Causes, investigation and treatment of leg ulceration. *Br J Dermatol* **148 (3)**: 388–401

Meredith K, Gray E (1988) Dressed to heal. *J Dist Nurs* **7(3)**: 8–10

Miller LG, Quan C, Shay A et al (2007) A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and –susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis* **44(4)**: 483–92

Mirastschijski U, Kourad D, Lundberg E, Lyngstadaas SP, Jorgensen LN, Agren MS (2004) Effects of a topical enamel matrix derivative on skin wound healing. *Wound Repair Regen* **12(1)**: 100–8

Moffatt CJ, Franks PJ, Oldroyd M, Bosanquet N, Brown P, Greenhalgh RM, McCollum CN (1992) Community clinics for leg ulcers and impact on healing. *BMJ* **305(6866)**: 1389–92

Moffatt CJ, McCullagh L, O'Connor T et al (2003) Randomized trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration. *Wound Repair Regen* **11(3)**: 166–71

Morrell J, Collins K, Walters S Cost-effectiveness of community leg ulcer clinics. Unpublished report In: NHS Centre for Reviews and Dissemination, University of York (1997) Compression therapy for venous leg ulcers. *Effective Health Care* **3(4)**: 1–12

Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LM, Peters J, Brooker CG (1998) Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* **316 (7143)**: 1487–91

Nelson EA, Cullum N, Jones, J (2006) Venous leg ulcers. Clinical Evidence http://www.clinicalevidence.com/ceweb/conditions/wnd/1902/1902.jsp Last accessed Feb 2007

Nixon M, Jackson B, Varghese P, Jenkins D, Taylor G (2006) Methicillin-resistant Staphylococcus aureus on orthopaedic wards: incidence, spread, mortality, cost and control. *J Bone Joint Surg Br* **88(6)**: 812–7

O'Brien JF, Grace PA, Perry IJ, Hannigan A, Clarke Moloney M, Burke PE (2003) Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. *Br J Surg* **90(7)**: 794–8

Ohlsson P, Larsson K, Lindholm C et al (1994) A cost-effectiveness study of leg ulcer treatment in primary care. Comparison of saline-gauze and hydrocolloid treatment in a prospective, randomized study. *Scand J Prim Health Care* **12(4)**: 295–9

Partsch H, Damstra RJ, Tazelaar DJ et al (2001) Multicentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. *Vasa* **30(2)**: 108–13

Pascarella L, Schonbein GW, Bergan JJ (2005) Microcirculation and venous ulcers: a review. *Ann Vasc Surg* **19(6)**: 921–7

Pfeffer F, von Dobschuetz E, Riediger H Moosmann C, Hopt UT (2004) The non-healing wound. *MMW Fortsch Med* **146(44)**: 45–8

Phillips TJ, Machado F, Trout R, Porter J, Olin J, Falanga V (2000) Prognostic indicators in venous ulcers. *J Am Acad Dermatol* **43(4)**: 627–30

Ragnarson Tennvall G, Hjelmgren J (2005) Annual costs of treatment for venous leg ulcers in Sweden and the United Kingdom. *Wound Repair Regen* **13(1)**: 13–8

Ragnarson Tennvall G, Hjelmgren J (2005a) [Treatment of venous leg ulcers is costly for the health care and the society. The value of preventive measures should be further investigated according to a study] *Lakartidningen* **102(42)**: 3027–9

Schmeller W, Gaber Y (2000) Surgical removal of ulcer and lipodermatosclerosis followed by split-skin grafting (shave therapy) yields good long-term results in 'non-healing' venous leg ulcers. *Acta Derm Venereol* **80(4)**: 267–71

Scriven JM, Taylor LE, Wood AJ, Bell PR, Naylor AR, London NJ (1998) A prospective randomised trial of four-layer versus short stretch compression bandages for the treatment of venous leg ulcers. *Ann R Coll Surg Engl* **80(3)**: 215–20

Shai A, Halevy S (2005) Direct triggers for ulceration in patients with venous insufficiency. *Int J Dermatol* 44(12): 1006–9

Simka M, Majewski E (2003) The social and economic burden of venous leg ulcers: focus on the role of micronized purified fraction adjuvant therapy. *Am J Clin Dermatol* **4(8)**: 573–81

Taylor AD, Taylor RJ, Marcuson, RW Prospective comparison of healing rates and therapy costs for conventional and four layer high compression bandaging treatments of venous leg ulcers. Unpublished report. In: NHS Centre for Reviews and Dissemination, University of York (1997) Compression therapy for venous leg ulcers. *Effective Health Care* **3(4)**: 1–12

Taylor A, Taylor RJ, Marcuson RW et al (1998) Prospective comparison of healing rates and therapy costs for conventional and four layer high compression bandaging treatments of venous leg ulcers. *Phlebology* **13(1)**: 20–4

Thomson B, Hooper P, Powell R et al (1996) Four-layer bandaging and healing rates of venous leg ulcers. *J Wound Care* **5(5)**: 213–6

Turczynski R, Tarpila E (1999) Treatment of leg ulcers with split skin grafts: early and late results. *Scand J Plast Reconstr Surg Hand Surg* **33(3)**: 301–5

Vowden KR, Barker A, Vowden P (1997) Leg ulcer management in a nurse-led, hospital-based clinic. *J Wound Care* **6(5)**: 233–6

Vowden KR, Mason A, Wilkinson D, Vowden P (2000) Comparison of the healing rates and complications of three four-layer bandage regimes. *J Wound Care* **9(6)**: 269–72

Vowden P, Romanelli M, Peter R, Bostrom A, Josefsson A, Stege H (2006) The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. *Wound Repair Regen* **14 (3)**: 240–6

Vowden P, Romanelli M, Price P et al (2007) Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers. *J Wound Care* **16(5)**: 189–95

Wilkinson E, Buttfield S, Cooper S et al (1997) Trial of two bandaging systems for chronic venous leg ulcers. *J Wound Care* **6 (7)**: 339–40

Wipke-Tevis DD, Rantz MJ, Mehr DR (2000) Prevalence, incidence, management, and predictors of venous ulcers in the long-term care population using the MDS. *Adv Skin Wound Care* **13(5)**: 218–24

Wipke-Tevis DD, Sae-Sia W (2004) Caring for vascular leg ulcers. *Home Healthc Nurse* **22(4)**: 237–49

Wipke-Tevis DD, Stotts NA (1996) Nutritional risk, status, and intake of individuals with venous ulcers: a pilot study. *J Vasc Nurs* **14(2)**: 27–33

Wipke-Tevis DD, Stotts NA (1998) Nutrition, tissue oxygenation and healing of venous leg ulcers. *J Vasc Nurs* **16(3)**: 48–56

Zmudzinska M, Czarnecka-Operacz M, Silny W (2005) Bacterial flora of leg ulcers in patients admitted to Department of Dermatology, Poznan University of Medical Sciences, during the 1998-2002 period. *Acta Dermatovenerol Croat* **13(3)**: 168–72