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.

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KEY WORDS
Venous leg ulcer
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Health economics
Advanced wound therapies

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 Tenvall and Hjemgrem, 2005).

The standard treatment for VLUs is the application of graduated compression, either in the form of compression...
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 T ennvall 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 databases are listed in Table 1.
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).

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 £2300 (Nixon et al, 2006).

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 legation (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 3). These VLUs can be identified by using the prognostic indicators (ulcer size >10 cm² 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,
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

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### 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

### 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

<table>
<thead>
<tr>
<th>Success rate (proportion healed VLUs)</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% (1/10 patients)</td>
<td>€358,200</td>
<td>€34,320</td>
<td>€333,880</td>
<td>€343,200</td>
<td>€19,320</td>
</tr>
<tr>
<td>50% (5/10 patients)</td>
<td>€358,200</td>
<td>€171,400</td>
<td>€186,600</td>
<td>€343,200</td>
<td>€156,600</td>
</tr>
<tr>
<td>100% (10/10 patients)</td>
<td>€358,200</td>
<td>€343,200</td>
<td>€15,000</td>
<td>€343,200</td>
<td>€328,200</td>
</tr>
</tbody>
</table>
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 (Iafriati 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 Gáber, 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).

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.

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 (Campitelli 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 (>10cm²) 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 (Mirastchijski 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.

“*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**


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