



Leg ulcer update

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The venous ulcer pipeline: a novel approach to refractory venous ulcers



Authors (left to right): Robert Kirsner and Herbert Slade

Patients experiencing venous leg ulcers are common^[1], but unfortunately, standard treatment including infection control, primary dressings, and high-strength compression achieves healing in only 30–75% of cases^[2]. Guidelines suggest that wounds that are not healing, as determined by insufficient

wound size reduction following four weeks of standard care, should receive adjunctive therapy^[3]. The adjunctive therapy with the longest history of use is autologous skin grafting^[4], which requires the creation of a second wound at the donor site and can be problematic as ulcers tend to recur.

Attempts to develop 'off-the-shelf' products have produced monolayer constructs, such as cultured allogeneic adult keratinocytes^[5], which suffer from construct fragility^[6], and bilayered constructs. Systematic reviews of cell-based therapies for venous leg ulcers have found limited high-quality evidence of benefit, with inherent challenges of blinding engineered tissue application^[7,8]. A recent Cochrane review found 15 of 17 qualifying randomised controlled trials to be underpowered^[9]. Most successful of these products is a tissue-engineered skin product, which is conceived as a bilayered 'human skin equivalent' (Apligraf®, Organogenesis). It contains bovine collagen and allogeneic cells, which work to heal venous ulcers and it bears histological similarity to skin^[10,11], but as the allogeneic cells do not engraft, the need for an elaborate tissue construct is uncertain.

The authors recently reported the efficacy and safety of the HP802-247 trial (Healthpoint Biotherapeutics), which consists of cryopreserved allogeneic, growth-arrested neonatal fibroblasts and keratinocytes in a format that allowed the evaluation of various doses^[12]. After rapid thawing, the cells are delivered to

the wound surface in a modified fibrin spray. *In vitro* studies have allowed optimisation of the cellular formulation to enhance the release of essential growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), transforming growth factor alpha (TGFα) and, when the cells are combined, granulocyte-macrophage colony-stimulating factor (GM-CSF).

The authors studied patients with confirmed and refractory venous ulcers between 2–12cm² in area that had been present for 6–104 weeks. Using a double blind, parallel group design, we compared weekly, or biweekly, application of 5.0×10⁶ cells/mL (N=45, 44) or 0.5×10⁶ cells/mL (N=46, 43) to the weekly application of fibrin vehicle without any cells (N=50), with all five groups receiving four-layer compression bandages. Two hundred twenty-eight patients across 28 centres were enrolled and 205 completed all visits. Using Intent to Treat (ITT) analysis, the authors found that treatment with spray cell therapy produced significantly greater reduction in wound area (p=0.0446), shorter time to healing (p=0.0058) and a higher proportion of wounds closed (p=0.0267), than standard care alone. The best results were seen with 0.5×10⁶/mL, given bi-weekly.

This is the first report documenting benefit using neonatal cell (as opposed to tissue) therapy for venous ulcers. Phase 3 studies are now ongoing for this first-in-class, cell-based therapy that holds promise for better outcomes compared with current standard care. In contrast to numerous publications of small trials and case series suggesting the benefit of allogeneic cells, the present trial was sufficiently large, properly randomised and well-masked, with complete reporting of prospectively determined outcomes and using ITT analyses. To date, this experimental therapy has generated the best results seen in the treatment of refractory venous ulcers, and informs understanding of how to take into account the typical pharmaceutical parameters of dose, duration and frequency when testing cell-based therapeutics.

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Expert Commentary

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Lower limb venous ulceration is one of the cutaneous manifestations of chronic venous disease and, as such, its management consist of three basic strategies:

- **The management of the wound itself**
- **The management of the abnormal periwound skin**
- **The management of the underlying venous disease.**

Only by addressing all of these three elements of the disease process can acceptable healing rates be achieved and low ulcer recurrence rates obtained. It is now widely agreed that high-compression bandaging should form the mainstay of treatment for the majority of patients with venous ulceration, the level of compression being determined by patient tolerance and a measure of lower limb perfusion, such as the Doppler ankle brachial pressure index (ABPI). In selected patients, early venous surgery or ablation therapy may be appropriate to assist healing, but in general such treatment is used, with the application of compression hosiery, to reduce the risk of ulcer recurrence rather than assist with healing. Despite effective high-compression therapy, whether by bandaging or hosiery, some venous ulcers fail to heal and these wounds, often referred to as 'hard to heal' have increasingly been the target of studies aimed at identifying adjuvant therapies that may assist in the healing. The challenge with all such treatments is:

- **The early identification of the sub-group of patients whose wounds will fail to heal in an acceptable timeframe with 'standard' care**
- **To offer such patients a practical and cost-effective alternative or adjuvant treatment.**

*In this paper on spray-applied cell therapy, Kirsner and Slade highlight both the advantages and disadvantages of currently available tissue-engineered constructs and autologous skin grafts as vectors to assist healing in this group of patients in whom the challenge is often not just to achieve healing, but to produce a wound bed likely to support healing or the application of a skin or an engineered skin substitute. Their phase 2 dosing study, originally reported in the *Lancet*¹¹, successfully demonstrated the potential for cryopreserved allogeneic, growth-arrested neonatal fibroblasts and keratinocytes delivered in a modified fibrin spray to assist healing. The challenge now is to demonstrate the efficacy and cost effectiveness of this treatment when applied as part of a larger clinical trial and to confirm effectiveness as the treatment is extended to general use.*

A clinically and cost-effective bio-engineered solution to address non-healing or delayed healing continues to elude us. Many elegant potential solutions have been developed but most have failed to make a successful transition from early concept or construct to practical and widely applicable device. Early results with this formulation of spray-applied cell therapy have been encouraging and storage, shelf-life, product handling and wound bed status constraints seem to be less of a problem than those encountered with some bio-engineered products. I await with interest the next report on this therapy, which I hope will contain a health economic model outlining the benefits of this form of treatment as this will give a clear indication of the true potential of this treatment to impact on the care of the wider leg ulcer population.

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Barbara Kaiser

German Leg Club inaugurated

Based on the English 'Leg Club' model established by Ellie Lindsay, the first Leg Club in Germany was founded in April 2012 by Barbara Kaiser. She works as a nurse in Munich with

a focus on wound care in Ambulatory Nursing and has studied at the private medical university, Paracelsus, in Salzburg for a Master's in scientific Wound Care Management.

The health system in Germany differs greatly from the English health care system. The benefits of the German system are based on various pillars, such as health insurance, pension insurance, unemployment insurance and accident insurance. Due to the rising population in Germany, the number of age-related diseases is growing, resulting in the healthcare system, despite the many reforms in recent years, being put under increasing strain to improve the care of patients.

The risk of developing leg ulcers increases with age and around 1.5 million people are said to be suffering from ulcers in Germany^[1]. After a patient has been discharged, problems with providing the correct care/treatment have been known to arise. Patients are cared for primarily by their GP and, if requested, by an Outpatient Nursing Service (Ambulatory Nursing). Further treatment depends on the expertise of the family physician and the outpatient care service provider.

Due to the low recognition of the treatment of ulcers by the health insurance companies and, as a consequence, the low potential financial gain, patients with leg ulcers are not prioritised, either by physicians or the outpatient care service providers. Therefore, patients that are well cared for in hospitals, tend to receive a lower level of special disease-related care at home and can move from an optimal treatment environment in the hospital to minimal and mostly inefficient treatment at home.

The Leg Club model can provide a bridge between the stakeholders and the various medical fields outside of the clinics. Through weekly meetings, the Leg Club provides contact with other sufferers, as well as access to expert nursing staff and volunteers, all of whom are advised and educated, following the model established by Ellie Lindsay.

Her model consists of four major pillars:

- **Professionally competent care in a non-medical institution that has the atmosphere of a club, with refreshments provided**
- **Treatment of all patients together in one room, in order to promote the exchange of knowledge**
- **Visits without appointments to enable patients to access the Leg Club at their own pace, so as to avoid artificial barriers**
- **Follow-up is available as long as the patient wants it. This means that, even after the wound is healed, the individual can still visit the club and get further advice and/or training.**

The model not only incorporates training and presentations for patients, but also involves a range of clinicians, to raise awareness of the issue and to promote the sharing of knowledge. The motivation to start a Leg Club in Germany arose during a lecture at the University of Salzburg by Dr Zemlin, who became aware of the Leg Club in England and saw this model as a benefit in terms of the care of chronic wounds. Dr Zemlin's presentation encouraged the author to become familiar with the model through site units. Ms Kaiser was then invited by Professor Helen

Edwards to a four-week internship at the Queensland University of Technology (QUT) in Brisbane, in January 2011.

In Brisbane, the model is integrated into the Health Care Service Center within the QUT University. The unit in Brisbane is headed by Michelle Gibb, who founded another Leg Club in a local outpatient care service, which is also integrated into the research with the University. The experiences of the author during her internship raised the question of whether it was possible to implement a Leg Club in Germany.

Beginning on 1 November 2011, a one-year Leg Club project in Germany began. In order to run the project successfully, a project management system was put in place, which comprised the project start-up phase, the planning and execution phase, the coordination and modification phase and the consolidation of the project.

During the Australian internship and following a visit to Worcester in England, it became clear that the Leg Clubs were primarily set up in church institutions. It was, therefore, suggested that this be the case in Germany as well. However, the Ambulanter Pflegedienst Diakonie Immanuelkirche e.V. München-Ost — a mobile nursing centre under the patronage of the Dean of Bavaria — was in fact able to implement the project.

The aforementioned outpatient care service has existed for 15 years. It caters for approximately 90 patients, including those with chronic wounds. As a result of a presentation on the Leg Club model and the already existing arrangements in the care of chronic wounds, it was found that there was considerable interest in enhancing the level of care relating to chronic wounds. Thus, the head of nursing and the management of the outpatient care service joined in the project to implement a Leg Club. It was decided that a meeting place should be created to promote the sharing of knowledge in individuals with leg ulcers. Through a network of various medical specialties, the aim of the club was to improve the quality of life of patients with ulcers and to promote healing of these wounds. The focus was put on education and the promotion of self-care skills, accompanied by a professionally competent wound care specialist.

This social project is in line with the philosophy and facilities of the outpatient care service. Involved in the project are the the Board of the Ambulatory Care service, the administrative management, the nursing team and of course the patients, while potential visitors include GPs, clinics, podiatry, physiotherapy, nutritional therapy, and wound experts, representatives of the pharmaceutical industry, pharmacies and medical supply stores.

It should be noted, that the implementation of the Leg Club model in Germany was only possible with the approval and support of Ellie Lindsay. Ellie personally checked the implementation — both before and after opening — and gave permission for the use of the Leg Club's official logo.

It became clear that shared experience was beneficial to patients, as they were not left alone with their condition. The knowledge patients gained while frequenting the club, helped improve trust in the high-quality work of specialist nurses and helped promote cooperation.

Unfortunately, due to the different health systems in the UK and Germany, the Leg Club model cannot be implemented in its UK format in Germany. The ankle-brachial pressure index

(ABPI) value is, for example, not usually measured by the nurse in Germany. Also, in Germany, bandages and medical aid can only be prescribed by a doctor. To implement Ellie Lindsay's model in Germany in its entirety will require more time.

The issues that emerge from ulceration can be distressing for patients. To prevent ongoing suffering, the most important issue is for the patient to further their knowledge of the disease. Only then can long-term problems be solved.

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The Leg Club reaches Tasmania

Tasmania is an island state 240km south of the Australian continent. It has a population of around 508,000, of whom about half live in the south, in the greater Hobart area.

Community Nursing Services within the Southern Tasmania Area Health Services (STAHS) provide both generalist and specialist services. General community nurses provide long and short-term care, monitoring and support to people who are post-acute, aged, disabled, undergoing palliative care, those with chronic diseases and their carers.

They are supported by specialist nurses, who are employed in the areas of palliative care, breast care, continence, spinal injury and mental health. A large part of the work undertaken by community nurses is wound care^[1], but local practices, skills and resources vary from area to area^[2] and specialist wound management nurses are not yet employed in community health to support the teams.

The STAHS-funded service for assessment of people with chronic wounds, such as leg ulcers, is the hospital out-patient wound clinic. The clinic is held on two half-days each week, one for new and returning patients to be assessed by a consultant, while a Registered Nurse reviews returning patients on the other half-day. Access requires a General Practitioner (GP) referral and usually involves a four- to eight-week wait for an appointment^[2]. At other times, nurses may contact the hospital Clinical Nurse Consultant for Wounds for general advice. Patients have often had a non-healing wound for many months or years before being referred to the clinic.

Although there is no local data available, it has been suggested that this is often the result of a general lack of wound management education, training, and nationalised treatment and referral plans^[3]. Once a patient's wound has healed, they are discharged from the clinic, with compression hosiery when applicable, but there is no access to follow-up for those with healed wounds for advice regarding wound prevention strategies or early intervention and the treatment of new wounds. Further clinic visits require another referral from the GP and presentation of a new wound.

Why set up a Leg Club?

An Australian randomised controlled trial^[4] demonstrated a significant improvement after 24 weeks in people attending a Leg Club, compared with the control group, which received traditional home care by the same group of nurses, using identical protocols. Improvements were seen in healing rates, quality of life, morale, self-esteem, pain and functional ability. Running alongside the trial was a participatory action research study from which the results were very positive in favour of the Leg Club model, not only in relation to leg ulcer management, but also in empowering clients to make positive changes through increasing their knowledge^[1].

The Clarence Integrated Care Centre has been developed with a view to improving access to a wider range of well-coordinated health services for people on Hobart's Eastern Shore, with extra emphasis on people with chronic and complex conditions^[5]. This makes it an ideal venue to hold a Leg Club for the local community. There are successful clubs based upon the Lindsay Leg Club model established in four other Australian states, but this is the first in Tasmania^[6].

Studies have reported that leg ulcer care is sometimes less than optimal, due to lack of time, support and appropriate education/training^[7]. Locally, wound management education is available for a fee from various organisations. Nurses not attending education sessions are still required to provide a wound management service, however, this cannot be as effective as the one provided by a nurse with specific training^[8]. Education is essential to nurses being able to provide effective and appropriate care^[9]. One of the aims of Eastern Shore Leg Club is to provide an informal environment for staff education. Leg Club protocols and practices are based on evidence-based guidelines to provide research-based wound management in a friendly, non-threatening social environment and give a standardised approach to leg ulcer assessment and treatment^[10].

The Eastern Shore Leg Club lead nurse is endorsed as a Wound Management Nurse Practitioner and the other staff are increasing their knowledge through completing the education programme provided by the Leg Club Foundation^[11] and modules from an Australian online wound education programme^[12]. Graduate



Figure 1. Left to right: Kris Penney, Lea Young, Di Lyons, Jayarne King.

nurses placed with the Community Nursing services will have the opportunity to spend time at the Leg Club to increase their wound management knowledge and skills.

Many patients discharged from the hospital wound clinic require ongoing review of ankle brachial pressure index (ABPI) and measuring or advice for new compression hosiery. As they are unsure about their needs, they often use the same stockings for many years until they develop another leg ulcer. Then the whole cycle begins again. The Leg Club model of care helps reduce recurrence by providing post-healing monitoring and 'well-leg' checks. It has been widely documented that chronic leg ulcers affect quality of life by restricting mobility leading to social isolation and increasing anxiety and depression^[5] and the Leg Club model aims to meet the social needs of isolated clients by facilitating an informal support network and providing the setting for social interaction and for treatment.

The drop-in system with no GP referral required encourages people to attend for information and advice, facilitating early diagnosis, treatment and education. Eastern Shore Leg Club is held in a general activities room used at other times by allied health services and other community groups. It is ideally placed close to a local shopping centre and has free parking at the door.

One of the aims of the Australian Wound Management Association is to raise public and professional awareness of the problems associated with chronic wounds^[13]. Through promotion of the Leg Club and the provision of informal and formal health promotion and education, awareness may be increased in both of these areas. This, in turn, de-stigmatises the condition, increasing self-esteem and self-respect.

Open day

Staff present on the open day included the lead nurse and three other community nurses, while the volunteers provided the refreshments. As this is a club, rather than a clinic, people are called members rather than patients or clients. Three members were expected to join on the day and other clinicians were invited to look at how the system works. The first three members arrived, as well as interested staff from podiatry, community transport, community nursing, child health, social work, aged services and a local GP.

The three members included two women with venous leg ulcers and a man with an above knee amputation, but no current wounds. They stayed varying lengths of time from one-and-a-half to three hours, happily chatting to volunteers and enjoying the company, with all three eager to return the following week. Two extra people popped in following their podiatry visits, and also said that they would return the following week.

Of the two people with wounds requiring dressing changes, one woman was happy to be treated in the collective treatment area, while the other opted for a private area. Both were accommodated, but after realising that the treatment area was not easily viewed by everyone, the woman seen privately opted to be treated in the collective treatment area the following week. On week two, all members returned, and two new people joined, one requesting wound treatment and the other requiring assessment and measuring for new compression

hosiery after noticing a potential new wound developing.

What lies ahead?

There are two treatment chairs and two staff available most weeks, so to prevent long waiting periods for those not wishing to stay longer it was decided to arrange appointment times for people requiring treatment. It remains a drop-in club, so members are free to arrive and leave whenever suits them.

Once there are more members, occasional guest speakers will be organised. Initial plans include a physiotherapist to discuss the importance of exercise, a podiatrist to demonstrate footwear essentials and other professionals to talk about compression hosiery, self-care and nutrition. The Club is in the very early stage and changes will be made as and when the need arises. However, things are looking positive at present and staff are very excited at the prospect of membership growing and being able to make a positive impact to the lives of those with chronic leg ulcers.

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