Going green: using a bio-cellulose membrane for patients with chronic non-healing wounds

ABSTRACT

A 20-patient evaluation was undertaken on the most chronic non-healing wounds that had been present in excess of 6 months. Patients were treated with a biotechnology dressing that is provided in a mesh and gel combination. Eighteen of out 20 patients went on to heal. Cost effectiveness examined the cost associated with maintaining non-healing wounds where all alternative therapies had failed. Nursing time both in outpatients and home visits were included. A wide variety of secondary dressings were applied according to clinical preference as the new dressings are designed as a direct wound contact mesh. This is a very new concept to wound care, with initial unit cost being high, but the possibilities of natural plant extracts that can mimic collagen synthesis is exciting. Both the staff and patients have seen a marked improvement, with up to date no recurrence. Further studies need to be undertaken to establish if these early findings are repeatable.

Key words: Plant extract ■ Chronic non-healing wounds ■ Cost-effectiveness

Research by George Winter in 1962 changed the way both acute and chronic wounds are managed in modern healthcare. He proved that wounds kept moist would heal up to 50% faster than those left dry, and so the development of advanced dressings began. His research, and much that has followed not only confirms that a moist wound healing environment supports the healing process, but it actually reduces the risk of complications (Winter, 1962). Posnett and Franks (2008) suggested that over 80% of chronic wounds heal within a predicted time-frame at an average cost to the health system of around £1900. They surmised that:

> 'One in three chronic wounds had been unhealed for at least six months and one in five for a year or more ... 20% of wounds consume 80% of all resources used in wound healing ... Average cost to heal these wounds was £31 000 – £42 000 per episode of care.'

Posnett and Franks wrote in 2007:

> 'Healing these wounds quicker will have the most significant reduction in costs'.

Difficult to heal wounds are those that began healing by the normal healing process but the rate of closure is delayed for months instead of weeks owing to an attributed intrinsic impairment in healing (Leaper and Harding, 1998; Demling, 2010). A biological definition would be a documented intrinsic impairment to normal healing characterised by a prolonged inflammatory phase, a slow-forming extracellular matrix (ECM) and a decrease in the rate of epithelialisation (Leaper and Harding, 1988; Mast and Schultz, 1996; Bliss, 2003).

Doncaster and Bassetlaw Hospitals NHS Foundation Trust serves a population of over 410 000 people in the areas covered by Bassetlaw District Council and Doncaster Metropolitan Borough Council, as well as from parts of North Derbyshire, Barnsley, Rotherham, and north-west Lincolnshire (NHS Choices, 2015). The wound care service has a dedicated team of four nurses; the equivalent of 2.2 full time nurses, who carry out wound clinics 5 days a week, with an average attendance of 20 patients per clinic. The average case load in one month is 500 patients. Patients are referred from a wide variety of sources that include hospital, community and practice nurses and general practitioners. The majority of the caseload consists of complex chronic non-healing wounds where other treatments have failed.

In 2014, the wound care team were approach by Genadyne Pharma to try a new product called Nanogen Aktiv. The wound care team provide effective treatment supported by new technologies that will improve patient outcomes, while being acutely aware of the need to reduce costs. The challenge was to use this product on the most challenging and difficult-to-heal wounds. Once the team had tried the product and found that it appeared to stimulate healing of a very difficult static venous stasis ulcer, they decided to carry out an evaluation on 20 patients.

Aims of the evaluation

The aim of the evaluation was to robustly test the proposition that the revolutionary nanogen range of bio-cellulose products heal previously unhealed chronic and complex wounds cost effectively.

Following consultation with the wound care team, a validated evaluation form was printed by Genadyne Pharma in concordance with trust protocols and data protection. All patients gave written informed consent for taking part in the evaluation and on the understanding that photographs would be taken at each dressing change and would be used

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Figure 1. Nanogen Aktiv and Nanogen Aktiv Membrane dressing

for education and/or publication. Ethical approval was not required as the wound care team are encouraged to evaluate innovative products as long as they have the required CE registration. All patients were free to withdraw at any time.

Exclusion criteria

Patients under the age of 18, and those not able to give fully informed consent or had wounds that had 100% sloughy tissue were exluded from this evaluation.

Methodology

Twenty patients with non-healing wounds of at least 6 months' duration were entered in to a 2-4 weeks of Nanogen Aktiv and Aktigel evaluation (more could be used at clinicians' discretion), until the wound became stable and was progressing to healing. A full holistic assessment was conducted on entry into the evaluation that included gender, age, wound type and underlying comorbidities. Wounds were measured and photographed at every dressing change with observations made on peri-wound skin, exudate type and colour. A numerical pain score using Wong and Baker's faces scale (1988) was used during dressing change and wear time. Documentation included current medication and whether patients were on antibiotics or not. Quality of life was also measured, this considered reduction in wound fluid, pain, mobility and number of attendances at the clinic.

Secondary dressings were applied at the clinicians' discretion, along with compression therapy. Clinicians changed the secondary dressing as required, but were advised by Genadyne Pharma to leave the Nanogen Aktiv membrane in situ for a period of 1 week between changes. All patients were reviewed by 3 days after application. The wounds would only be redressed at weekly intervals at either Doncaster or Bassetlaw outpatient departments. All clinicians assessed the time the wound had been unhealed before treatment with nanogen and estimated the cost to maintain the wound to date. 'Maintaining the wound' in this article refers to the time the patient received continuous treatment (in this study all had chronic wounds in excess of 6 months). A retrospective cost analysis was undertaken, taking into consideration the number of home visits, attendance to the clinic and costs of dressings and various treatments such as topical negative pressure. Each patient was given a 90 ml bottle of Aktiv Gel, which they brought to clinic for each dressing change. A few drops of the gel were applied to the membrane sheet before application.

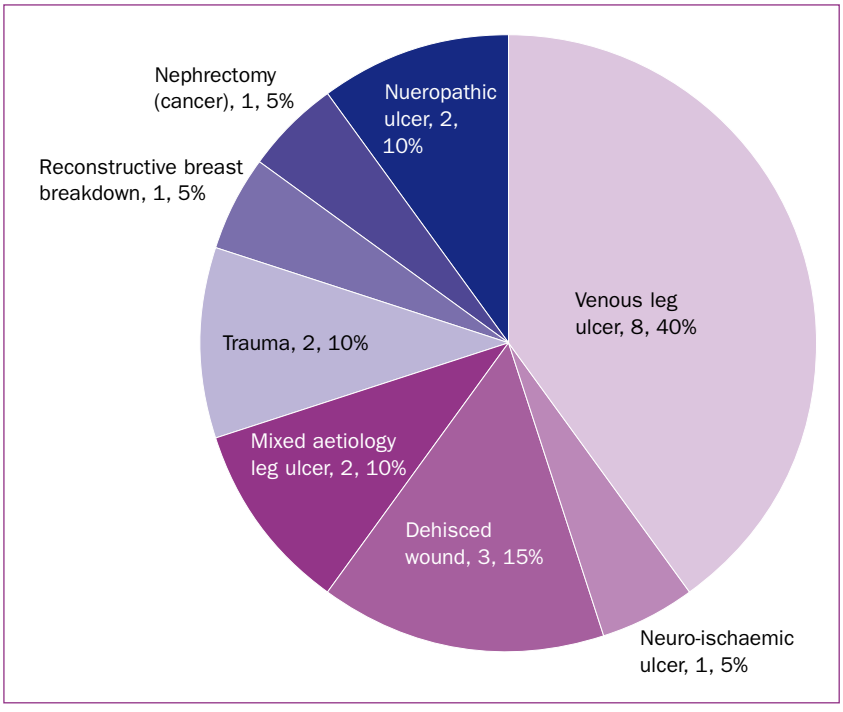

Figure 2. Wound types

Feeding the wound

Nanogen Aktiv is a bio-cellulose membrane that is a plant-based collagen, manufactured from plant extract, that has the ability to mimic the ECM in the wound. The membrane provides an abundance of nutrients, enzymes and vitamins to the wound. It is rich in acetic and lactic acid, glucouronic acid, usinic acid, enzymes vitamins B1, B2, B3, B6 and B12, vitamins C, D, E and K, biotine and folic acid. The antioxidants act as additional nutrition, helping create the optimum environment for healing (Data on file, Genadyne Pharma 2015).

Biomimetics

The nanogen fibres within the membrane are the same size as collagen fibres. The nanogen membrane mimics collagen in creating an ECM in the wound that does not originate from animals or is synthetically produced, so is described as artificial biology. This supports the body's own healing mechanism, stimulating fibroblast production and subsequently transforming growth factor (TGF) beta 1 (TGF-ß1) production is stimulated. TGF-ß1 is a polypeptide member of the TGF- beta superfamily of cytokines. It is a secreted protein that performs many cellular functions, including the control of cell growth, cell proliferation, cell differentiation and apoptosis.

Fibroblasts are present in the healthy healing wound, from the late inflammatory phase to epithelialisation (Forrest, 1985; Bainbridge, 2013). They are summoned to migrate to the wound area, proliferate and carry out a number of key activities under the progressively changing environment of the healing wound, which is critical to the end state of the wound (Schultz et al, 2011). In chronic non-healing wounds, fibroblasts are thought to be inactivated, or sub-optimally migrate into the provisional matrix. In chronic non-healing wounds, fibroblasts are thought to be inactivated, or slow to respond. Bainbridge (2013) suggests that this reduces the fibroblast's ability to break down fibrin through fibrinolysis, which

Table 1. Cost effectiveness

Wound type	Wound duration (weeks)	Traditional costs (to date)	Weeks to healing	Total cost to heal (£)	Saving (£)
Neuropathic ulcer	104	15496	16	2096	13400
Venous leg ulcer	26	3874	16	3258	616
Venous leg ulcer	52	7748	20	3620	4128
Neuropathic ulcer	60	8940	5	649	8291
Neuro-ischaemic ulcer	104	15496	20	2820	12676
Mixed wound ulcer	100	14900	16	2224	12676
Dehisced ulcer	30	4470	12	1943	2527
Venous leg ulcer	104	15496	8	1096	14400
Venous leg ulcer	28	4172	8	1196	2976
Mixed aetiology leg ulcer	104	15496	Stopped		
Dehisced wound	208	30992	12	10196.0	20796
Trauma	208	30992	Stopped (nearly healed)		
Dehisced wound	17	2533	11	2215	318
Venous leg ulcer	24	3576	9	1347	2229
Venous leg ulcer	104	15496	9	1053	14443
Traumatic cavity	26	3874	9	1053	2821
Venous leg ulcer	150	22350	11	1856	20494
Venous leg ulcer	28	4172	14	1734	2438
Kidney cancer	6	894	0	900	(6)
Breast mesh	16	2384	6	987	1397
Average	75 weeks	11168	11	2236	7590

supports autolytic debridement and results in proliferative and remodelling phases of healing being disorganised. When the fibroblasts are stimulated or present in the wound, the new matrix will be able to support angiogenesis and granulation (characterised by the light red and moist tissue, with the new buds or granules of capillary growth). Epithelialisation is also observed as new pink epithelial tissue grows from the wound edge as the keratinocytes migrate over the new granulation tissue. At this time, the tissue strength is sub-optimal, since the fibroblasts are laying down and remodelling the ECM. It is thought that the nanogen fibres provide a fibronectin scaffold, that stimulates fibroblast to support the cellular structures by providing a platform for collagen to be remodelled (Data on file, Genadayne Pharma, 2015).

Nanogen Aktiv

The Genadyne Pharma nanogen products come in two preparations; Nanogen Aktigel and Nanogen Aktiv (*Figure 1*). Nanogen Aktigel comes in bottles of 15 ml and 90 ml solutions, it is not a hydrogel or a wound cleanser. It includes approximately 40% nanogen fibres in suspension and can be used at all stages of wound healing (Data on File, Genadyne Pharma, 2015). It can be used with Nanogen Aktiv membrane for 2-6 weeks. Once healing had occurred only the Aktigel was applied as it appeared to improve the quality of the scar tissue and surrounding skin.

Participants and wound types

A total of 11 female and 9 male patients took part in the evaluation. The youngest was an 18-year-old male with a traumatic wound and the eldest was a 90-year-old female with a complex leg ulcer. The mean age was 59.

The most common chronic wound type in this study was venous leg ulcers (n=8; 40%). One (5%) was a breast reconstruction mesh breakdown (Case study 2), this patient also had a nephrectomy for a secondary tumour that had broken down as she was on a combination of chemotherapy and radiotherapy during her wound care treatment. A full breakdown of wound types is shown in *Table 1*.

Wound duration

Patients were recruited if their wounds had not healed in excess of 6 months. It is important to understand why wounds fail to heal, taking a full holistic approach is essential and understanding the underlying diseases or treatments helps clinicians decide an appropriate care pathway (European Wound Management Association (EWMA), 2008; Fletcher, 2008). The complexity of patients requiring chronic wound care can be challenging for staff and the wound team are constantly trying different approaches to support patients and encourage healing. This will often involve a multidisciplinary team (MDT) approach, offering a variety of treatments such as topical negative pressure, larvae and surgical debridement.

Costs can be high, particularly if there is a delay in discharge, or patients need high-cost interventions (Storm-Versloot et al, 2010).

Demling (2010) suggested that in chronic non-healing wounds, the orchestrated repair of cells within the ECM senescent are slow to respond. This affects the quality and strength of the ECM is compromised. In an attempt to establish cost savings, it was important to confirm how many weeks patients had their chronic wounds and calculating the cost before the evaluation.

Patient 11 had a dehisced surgical wound and, despite the use of topical negative pressure therapy, antimicrobial silver dressings and several courses of antibiotics, failed to progress in 208 weeks. In addition, patient 12 had a non-healing traumatic wound for the same period. These were the wounds that had the longest duration in the evaluation (*Table 1*).

Cost effectiveness

The authors calculated the cost to treat these chronic wounds with one outpatient appointment per week (even though on the first week all patients were asked to return after 3 days). The cost was £84 plus dressing costs (secondary dressings were chosen at the clinician's discretion) and one visit by community nurses at £55 per visit plus dressing costs. This is a conservative

FIGURE 3. CASE STUDY 1

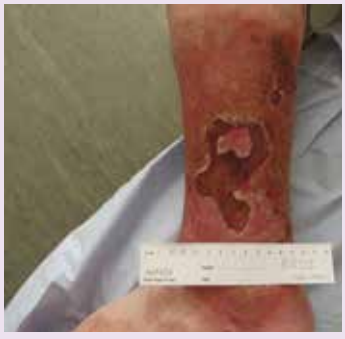

Figure 3a. Static non-healing leg ulcer at 3 years (6.8.14), commenced Nanogen Aktiv mesh and gel

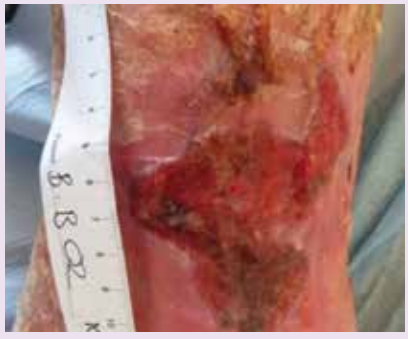

Figure 3b. Week 3 of treatment with Nanogen (27.8.14): wound showed improvement, change in shape, peri-wound condition (where the product had been applied) and reduction in exudate

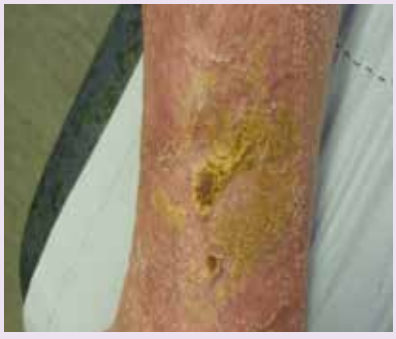

Figure 3c. Week 11 (10.9.14). Healing achieved, with good surrounding skin condition. The Aktigel was used after healing to remove the last of the flaky skin

calculation, but it is important to consider the costs of maintaining the wound over the cost to heal and prevent the wound from breaking down again. It is important to note that it is more than just a dressing that can do this. It is about understanding the underlying causes and treatment options. It would be impossible to say that the biotechnology dressing will stop a wound from reoccurring, particularly in fungating tumours, leg ulcers and pressure ulcers, as aetiology is key.

More detailed information on cost effectiveness is provided in *Table 1, and Tables 2–4* break down the cost of the case studies.

Table 2. Case study 1. Cost to maintain

	Prior Cost
Weeks	150
Appointment	20850
Dressing materials	300
Compression	1200
Cost to maintain	**22350**

Table 3. Case study 1. Cost to heal with Nanogen

	Nanogen cost
Weeks	11
Appointment	924
Nanogen Aktiv	877
Dressing materials	55
Compression	88
Cost to heal	**1944**

Quality of life

There was a marked improvement in 18 out 20 of the wounds in wound exudate, pain, frequency of dressing changes, and consequently visits to the clinic. The documentation of wound pain scores were not consistent and it was impossible to establish a statistically significant difference. The rapid improvement in both tissue type and wound size reduction was clearly visible within the first week. One clinician said:

> 'After just one week it looked like a different wound in both colour and shape—that really excited us!'

Another member of staff stated:

> 'Another patient came in to see me and demanded to have treatment with the 'magic paper'. "Why do you call it magic paper?" I asked. "That's what the other patients call it, they told me they when you had put it on them, it quickly got rid of the pain and was healing their wounds for the first time in years.'
>
> *(Kathy Leak, lead investigator)*

Case studies

Case study 1 (*Figure 3*) was a 90-year old male with a 3-year duration non-healing venous leg ulcer. The wound care team had been treating the wound for nearly 3 years and the district nursing team before that. There was no progression towards healing at all (the would care team had 100 photographs that all look identical) despite application of 'gold standard' four-layer bandage compression. The team had tried most wound care products including Allevyn, Acticoat, Pico, (topical negative wound therapy and others. The wound measured 8.5 cm x 5.5 cm). It had deep edges, dry scaly friable peri-wound skin, a dry wound bed and little exudate. The patient was in a lot of pain.

Case study 2 (*Figure 4*) was a female aged 58 who had been diagnosed with breast cancer. After a routine mastectomy, the breast wound subsequently dehisced, as the patient had a BMI close to 40. The wound was debrided and then placed in negative pressure wound therapy for 4 weeks. The wound granulated quickly but then stalled. The MDT decided they

FIGURE 4. CASE STUDY 2

Figure 4a. Breast wound after 4 weeks of NPWT—now stalled. Placed in Nanogen Aktiv and started chemotherapy

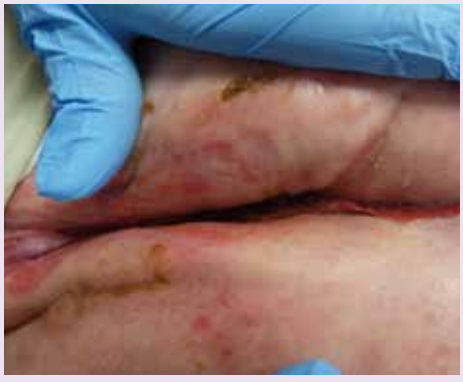

Figure 4b. Breast wound 3 weeks after starting Nanogen Aktiv treatment

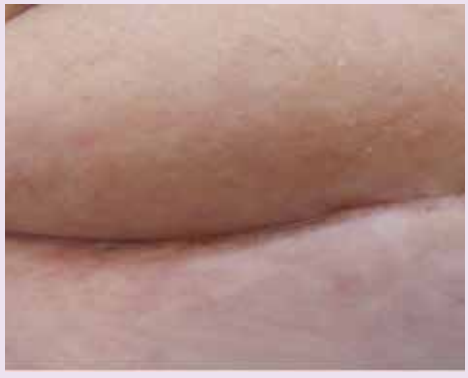

Figure 4c. Wound healed in 6 weeks with strong healthy scar line present

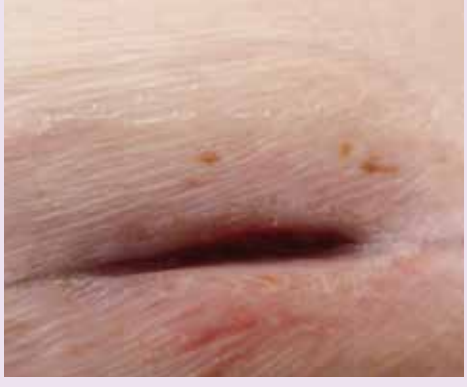

Figure 4d. Kidney cancer suture line not healing, patient undergoing chemotherapy

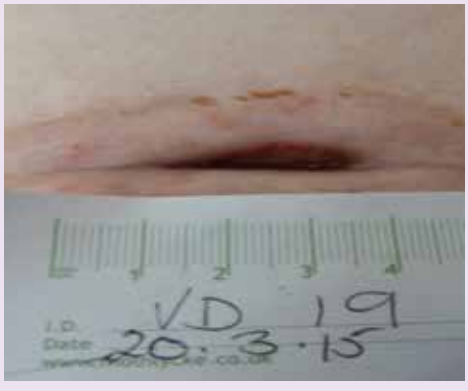

Figure 4e. Kidney wound after 3 weeks of Nanogen Aktiv treatment, while undergoing chemotherapy

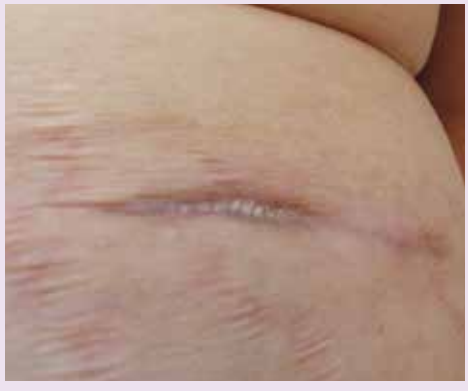

Figure 4f. Kidney wound healed after 5 weeks with Nanogen Aktiv

Table 5. Case study 2. Cost to maintain breast wound

	Prior cost
Weeks	16
Appointment	2224
Breast mesh (materials)	80
Kidney (materials)	30
Cost to maintain	**2334**

Table 6. Case study 2. Cost to maintain suture line

	Prior cost
Weeks	6
Appointment	504
Breast mesh (materials)	397.2
Kidney (materials)	162.6
Cost to heal	**1063.8**

needed to get patient to undergo chemotherapy immediately (6 weeks postoperatively). It was deemed more important than the wound, as delaying the chemotherapy would have life-threatening consequences. Pre-chemotherapy screening identified cancer in the patient's kidney. The kidney was removed, but the suture line leaked heavily and was not healing. The prognosis for both wounds during chemotherapy was poor. Chemotherapeutic regimens target proliferating cells by interfering with specific components of the cell cycle. Although rapidly dividing tumour cells is the primary target, any tissues or cell types with high turnover rates—macrophages and fibroblasts involved in wound healing, for example—are susceptible to the effects of systemic or locally administered agents. The expected time to healing for these wounds, while the patient underwent chemotherapy, was 6-9 months. The wound care team had previously experience with Nanogen Aktiv and persuaded the MDT to implement treatment with Nanogen Aktiv and Aktigel. Both wounds were successfully healed, while the patient continued to undergoing chemotherapy, within 6 weeks.

Challenges

Two wounds, once the nanogen treatment had been stopped, immediately regressed. In these cases, another membrane was

applied and the wounds went on to close by continuing the application of the Nanogen Aktigel until the wound healed. It was decided that from that point on, all wounds would carry on with Aktigel only to healing once the Nanogen Aktiv membrane treatment had finished.

One wound was removed from the trial; a clinician seeing a wound in week 2 noticed a significant change in colour, to a dark red. The principal investigators were made aware that this was likely to happen, but were not present in clinic at this time. The nurse removed the patient from the trial.

Unfortunately, one patient had to be removed, owing to concordance issues, when nearly healed.

Limitations

While documentation throughout was robust, in wound assessment, and measurement, pain documentation was limited to faces scales (Wong and Baker, 1988). In hindsight, a descriptive rating may have given a better indication on whether the biotechnology dressing improved pain in relation to chronic wounds.

A wide variety of secondary dressings, and medical devices were used in addition to the primary biotechnology dressing. It was impossible to establish if the secondary dressings had impacted on the outcomes. This was thought to be unlikely as the majority of secondary dressing chosen had been used in the previous 6 months on all of the patients.

Conclusion

In this evaluation Nanogen Aktiv had a significant effect on kick starting hard-to-heal (non-healing) wounds, that previously had a history of only being maintained. In practice the authors found that a 2-week course of Nanogen Activ followed by the Nanogen Aktigel proved most effective for healing, with the added benefits of a better cosmetic result. It improved patient concordance by reducing pain and providing hope to patients who had endured these chronic wounds for excessive periods of time. This had a significant positive impact on the quality of life of these patients.

Nanogen healed 18 out of 20 (80%) of previously unhealed wounds. One of the excluded patients went on to heal with Nanogen and the other patient was non-concordant. It was proven to be unambiguously cost effective compared to the cost on maintaining wounds only. It appears to have a place in the toolkit of wound care specialists, who often see these unhealed and/or static wounds. The wound care team are now extending this study to include more patients, using an in-depth pain analysis that will include numerical, descriptive elements of pain along with the use of prescribed or over-the-counter analgesia and monitoring sleep patterns. BJN

KEY POINTS

- Twenty patients with chronic wounds were treated with a new biotechnology dressing that is provided in a mesh and gel combination
- The aim of the evaluation was to test the proposition that the revolutionary nanogen range of bio-cellulose products heal previously unhealed chronic and complex wounds cost effectively
- Nanogen healed 18 out of 20 previously unhealed wounds

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Bainbridge P (2013) Wound healing and the role of fibroblasts (2013) *J Wound Care* **22**(8): 407-12

Bliss M (2003) The importance of accurate terminology in wound care. *J Tissue Viability* **13**(4): 180

Demling RH (2010) The difficult to heal and chronic wound (A review of a matrix deficiency state) The potential role of a matrix replacement therapy. Eplasty. http://tinyurl.com/o2xdb4j (accessed 21 October 2015)

European Wound Management Association (2008) *Position document: hard-to-heal wounds: a holistic approach*. http://tinyurl.com/lc772d6 (accessed 21 October 2015)

Fletcher J (2008) Optimising Wound Care in the UK and Ireland: a best practice statement. *Wounds UK* **4**(4): 73- 81

Forrest L (1985) Current concepts in soft connective tissue wound healing. *Br J Surg* **70**(3)**:** 133–40

Leaper DJ, Harding KG (eds) (1998) *Wounds: biology and management*. Oxford University Press, Oxford

Mast BA, Schultz GS (1996) Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. *Wound Repair Regen* **4**(4): 411–20. doi: 10.1046/j.1524-475X.1996.40404.x

NHS Choices (2015) Doncaster and Bassetlaw Hospitals NHS Foundation Trust. http://tinyurl.com/o6l6f8p (accessed 21 October 2015)

Schultz GS, Davidson JM, Kirsner RS (2011). Dynamic reciprocity in the wound microenvironment. *Wound Repair Regen* **19**(2): 134–48. doi: 10.1111/j.1524-475X.2011.00673.x.

Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H (2010) Topical silver for preventing wound infection. *Cochrane Database Syst Rev* (3): CD006478. doi: 10.1002/14651858.CD006478.pub2

Posnett J, Franks PJ (2007) The costs of skin breakdown and ulceration in the UK. In: *Skin Breakdown: the silent epidemic*. Smith & Nephew Foundation, Hull: 6-12

Posnett J, Franks PJ (2008) The burden of chronic wounds in the UK. *Nurs Times* **104**(3): 44–5

Personal Social Services Research Unit (2014) Unit Costs of Health and Social Care 2014. http://tinyurl.com/o3l9538 (accessed 21 October 2015)

Winter GD (1962) Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature* **193**: 293–4

Wong DL, Baker CM (1988) Pain in children: comparison of assessment scales. *Pediatr Nurs* **14**(1): 9–17