

Focus on limb salvage in the diabetic foot

Authors:

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This article is based on an advisory board meeting, which was held in London on 27th June 2018, and sponsored by Integra LifeSciences. The expert group was convened to discuss the use of the Integra LifeSciences product portfolio in the diabetic foot, with a focus on limb salvage and creating an appropriate pathway of care that can guide management and be used in practice.

Diabetes is a growing worldwide issue: it is estimated that more than 422 million (8.5%) of the global adult population has diabetes (World Health Organization [WHO], 2016). It is further calculated that these patients have a one-in-four risk of developing a diabetic foot ulcer (DFU) over their lifetime (Armstrong et al, 2017).

Not only are all DFUs complex and costly wounds to treat from the outset, they are a marker of serious disease and comorbidities (Jupiter et al, 2016) and adversely affect patients' health, mobility and overall quality of life (Bradbury and Price, 2011).

The risk of complications in DFUs is high, as is the risk of recurrence. Potential complications include infection, delayed healing and amputation (Armstrong et al, 2017). Around 50% of DFUs become infected and, in approximately 20% of these patients, infection will lead to amputation (Wu et al, 2007). Half of patients with a DFU who undergo amputation will die within the following 5 years (Brennan et al, 2017). Furthermore, a patient with a healed DFU has a risk of recurrence estimated at anywhere between 17 and 60% within the following 3 years (Armstrong et al, 2017).

With this in mind, the expert group agreed that a concerted multidisciplinary approach, as well as optimised use of advanced therapies, is required when managing DFUs and their risk of complications.

The scale of the problem

Putting the global issue into perspective, overall diabetes prevalence is estimated at 6.8% across the European population (with the

highest being 14.9% in Turkey and the lowest rate being 2.4% in Moldova); this is currently estimated to translate into 2.8 million DFUs (5.1%) across Europe (Zhang, 2017).

Plantar ulcers have traditionally been considered the most common — however, toe ulcers are now found to be more prevalent (55% versus 45%, respectively). Foot deformity rates were found to be high (57%), as were rates of peripheral arterial disease (PAD) at 49%, and neuropathy (86%). Infection was frequent and found to be a significant problem at 58% (Prompers et al, 2007). Infection control was agreed to be an area of key importance that should be treated as a priority.

On assessing overall outcomes, the healing rate for DFUs was found to be 77%, with the odds ratio for non-healing higher in the presence of infection. Amputation and mortality rates were also elevated in the presence of infection, signifying that infection is a major issue affecting the outcomes of DFUs (Prompers et al, 2007).

From a US perspective, it is estimated that 30.3 million people have diabetes, which equates to approximately 1 in 10 of the population, with 1 in 4 undiagnosed or unaware of their condition (Centers for Disease Control and Prevention [CDC], 2018). The median rate across the general population is 9.1%, with this rising to 21.8% over the age of 75, with comorbidities and, in particular, obesity, also common.

Healing rates for DFUs were found to be 48% at 12 weeks and 66% at 6 months, with recurrence common (NHS Digital, 2017). Diabetes-related complications represent the

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seventh leading cause of death, with overall risk of death elevated by double in people with diabetes.

A US-wide study by Margolis et al (2011) found that 23% of new DFUs in people with diabetes led to immediate leg amputation.

The expert group noted that much of the data available on DFUs may be out of date and not necessarily representative of all geographic areas, but that in the majority of cases, the landscape has not changed, although levels continue to rise.

In tackling the problem, the expert group agreed that early intervention was key, with focus on: offloading; vascular assessment and optimisation; treatment of infection.

It is vital that management strategies involve a multidisciplinary-focused approach to care, and the adoption of advanced therapies where appropriate.

Multidisciplinary approach

It was agreed that a multidisciplinary team-focused approach is ideal in managing DFUs, but is often not the reality. The pathway of care is often led by the initial primary health care professional. Rapid referral for advancement of care is important and represents a huge opportunity for early intervention and potentially improved outcomes.

In many regions, geography is an issue. The levels of service vary across areas and differing care systems.

Ideally, a multidisciplinary approach should encompass:

- Strategy of care
- Team of care
- Pathway of care
- Focus on care.

To achieve this in practice, the multidisciplinary team should include:

- Podiatrist
- Diabetologist
- Orthotist
- Nurse/Diabetes Nurse Specialist
- Surgeons (Vascular, Orthopaedic, Plastic)
- Radiologists (Musculoskeletal, Interventional)
- Microbiologist/Infectious Diseases.

There needs to be an emphasis on rapid access to care, with early interventions, multisource referral and the facility for emergency referrals to be seen the same/next day. The multidisciplinary team approach, while ideal, is often not the reality. The initial stage is the patient consulting a healthcare professional in primary care; delay at this stage

can represent a missed opportunity for early intervention and improved outcomes.

Geography within regions represents a further issue as levels of service can vary. It is agreed that structured pathways are required in which there is designated responsibility for care.

A single clinician should be responsible for coordinating the care pathway, to ensure that gaps do not occur — for instance, in the UK, this is usually the podiatrist. However, no area of care should be viewed in isolation and there needs to be increased cohesion and communication between primary/acute and community care.

Medical versus surgical approach?

It was agreed that considering the benefits and differences of a medical versus surgical approach, context is key, as the two approaches can result in 'radical differences' in care. In general, a 'more aggressive' surgical approach is taken in the US, while in other geographical areas, focus of treatment can vary.

Preventative care should always be viewed as the optimum approach, both in terms of patient wellbeing and in the resulting practical and economic benefits. This, again, relates to the emphasis on speed — dealing with smaller ulcers that can be healed via debridement and offloading, before this becomes an issue that affects deeper tissue and results in the need for surgery. The expert group agreed that the diabetic foot has traditionally been seen as a 'less attractive' area of care, and there has been a need for perspective to change. Limb salvage is seen as a priority, but it was also noted that function should be given equal consideration. It was suggested that treatment is often driven by risk, where there is a need to see the bigger overall picture.

Offloading was agreed to be the key first-line treatment, with total contact casting recognised as the 'gold standard' of care. The major obstacle to successful treatment with offloading was agreed to be patient concordance, which can be problematic. Patient education is required in order to aid concordance and, as a result, successful treatment. Coupled to this is a popular focus solely on healing, where education about the importance of function is also required. It was agreed that the clinician's primary goal should be a functional limb. Similarly, the patient's goal is often to retain independence via functional ambulation.

Clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine (adapted from Hingorani et al, 2016).

- Recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities or previous amputation
- In patients with plantar DFU, recommend offloading with a total contact cast or irremovable fixed ankle walking boot
- In patients with a new DFU, recommend probe to bone test and plain films to be followed by magnetic resonance imaging if a soft tissue abscess or osteomyelitis is suspected
- Recommend comprehensive wound care and various debridement methods
- For DFUs that fail to improve (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, recommend adjunctive wound therapy options
- In patients with DFU who have PAD, recommend revascularisation by either surgical bypass or endovascular therapy.

A total contact casting system, such as TCC-EZ® (Derma Sciences/Integra LifeSciences) has been found to decrease time to healing and, as such, is associated with reduced costs (Armstrong et al, 2001). The expert group agreed that reducing time and costs was of key importance and that making use of total contact casting provides an ideal option where possible.

Debridement also forms a key part of care. The group agreed that advances in debridement practice have been of significant benefit — while debridement is vital in the management of infection, there is a need to preserve tissue wherever possible to preserve reconstructive options and function, and this should be the emphasis.

Use of biologic scaffolds in DFU

There is a significant amount of published data on the use of biologic scaffolds for advanced wound care; initially, this was mainly focused on use in burns and reconstructive surgery. However, there is increasing evidence for the use of biologic scaffolds in the management of DFUs.

Despite the clearly documented benefits, the use of biologic scaffolds in practice remains

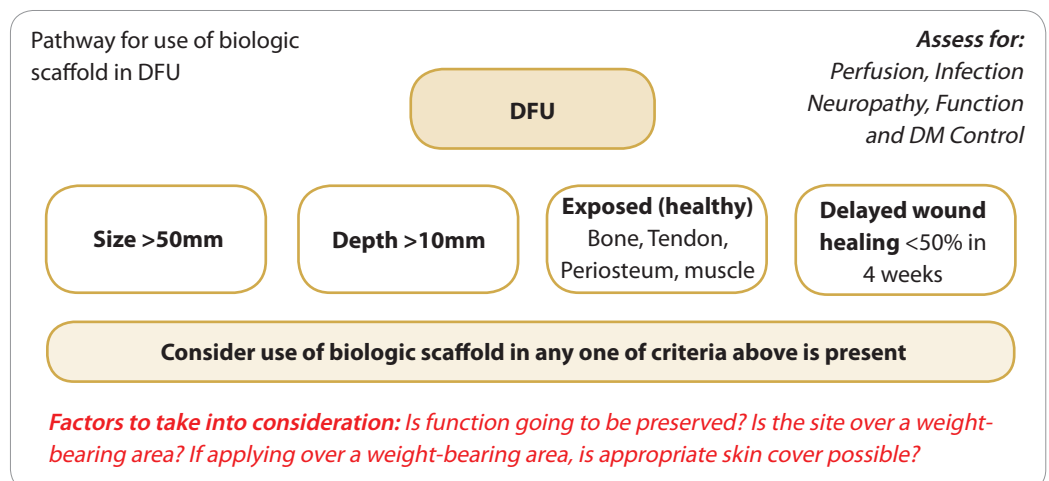
limited. In order for the practice to become more widely used, knowledge of the benefits needs to be broadly disseminated and promoted.

The Integra Dermal Regeneration Template (IDRT) biologic scaffold/dermal substitute has been the subject of more than 500 published articles. IDRT was used in the FOUNDER (Foot Ulcer New Dermal Replacement) study to treat chronic, hard-to-heal DFUs in the US (Driver et al, 2015).

The multicentre, randomised controlled trial (RCT) involving 32 sites and 307 patients, found that healing rates were significantly improved, thus demonstrating scope for the use of IDRT in DFU treatment. Complete DFU closure during the treatment phase was significantly greater with the use of the IDRT (51%) than in the control group (32%; $P=0.001$) at 16 weeks. The median time to complete DFU closure was 43 days for the IDRT group and 78 days for the control group in wounds that healed.

The time to complete wound closure was found to be decreased, with increased rates of wound closure, improvements in patient quality of life and fewer adverse events compared with standard of care treatment. The IDRT was found overall to be safe and effective

Figure 1. Pathway for use of IDRT in DFU.



Further information on the Integra Dermal Regeneration Template.

- Dermal regeneration product for the treatment of severe wounds
- Traditionally used for severe burns treatment and scar contractures repair; now indicated for the treatment of DFUs
- Portfolio of options includes:
 - Bi-layer matrix
 - Bi-layer meshed matrix
 - Single layer
 - Single layer thin
- Integra Flowable Wound Matrix available for use in deep soft tissue or tunnelling wounds.

Agreed potential benefits of using Integra Dermal Regeneration Template in DFU management (compared with standard care).

- More robust healed tissue and potential reduced recurrence
- Better long-term function
- Enhanced healing rates
- Closure in large wounds, which may help to avoid secondary infection
- Reduced risk of infection
- More flexible, for use in shear areas
- Lower rate of adverse events
- Improved patient quality of life.

in the treatment of chronic, hard-to-heal DFUs compared to standard of care.

Pathway for use of IDRT in DFU

Further to the scope of use demonstrated by the FOUNDER study (Driver et al, 2015), the expert group agreed upon a structured pathway for the use of the IDRT in DFU treatment [Figure 1].

The group reached a consensus that using IDRT in these clinical scenarios (and with the listed considerations taken into account) is beneficial to healing and should be considered if any one of the criteria are present.

The group agreed on the 4-week healing window for standard of care: after 4 weeks, if sufficient improvement is not seen, advanced therapies should be introduced. It should be noted that, if the wound is not healing, other factors should be considered in order to optimise the opportunity for a successful outcome: e.g. consider potential ischaemia, soft tissue infection, osteomyelitis, patient concordance to offloading.

The need for infection control — given the high levels of infection and associated complications in DFUs — was also emphasised. Increased time to wound closure increases the risk of infection, which is another potential advantage to IDRT use in DFU management, given the results regarding speed to healing in the FOUNDER study (Driver et al, 2015).

The group noted the potential use of negative pressure wound therapy (NPWT) in conjunction with IDRT use as an area that may see promising results and decrease time to healing. This requires further research and evidence.

Ongoing care

Particularly considering the risk of recurrence, it was agreed that ongoing maintenance therapy is required, which again should have a focus on continuity of care.

Following surgery, protection and offloading were agreed to be key to success. The benefits of surgery/treatment may be lost if maintenance offloading is not put in place. As noted, patient concordance is an ongoing issue, and patient education is key to setting expectations, aiding concordance and optimising successful outcomes.

The expert group agreed that, in the case of IDRT use, tracking long-term results would be useful in order to gauge the success of the treatment in terms of tissue quality and associated recurrence rates.

Cost of care and drivers for change

DFU management is agreed to be a costly area

Figure 2. Estimated annual cost of DFU compared with other chronic conditions (adapted from Kerr, 2017).

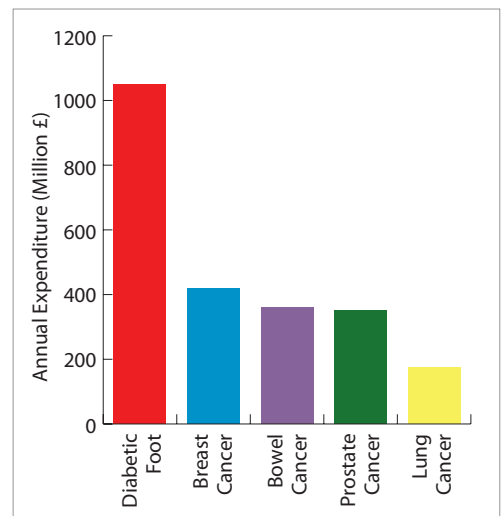
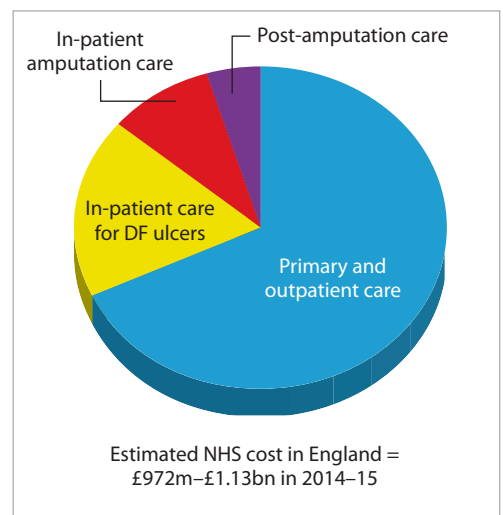


Figure 3. Cost of amputation and ulceration in the UK (adapted from Kerr, 2017).



of treatment; HES data suggest there are nearly 90,000 patients with DFUs, though there are no corresponding data for the actual cost of treatment. One source estimates the annual cost of DFUs to be around £1.2 billion ([Figure 2]; Kerr, 2017). Between 2014 and 2015, the cost of DFU-associated amputation in the UK was estimated at £1.13bn [Figure 3].

Furthermore, costs are not only variable, but can be very unclear in practice. This means that, as well as tracking real-world costs, it is also difficult to track and measure potential cost savings. It is difficult to collect data, as relevant treatment can occur across different 'pockets' of care — once again illustrating the need for a cohesive, multidisciplinary-driven approach.

In the US, insurance companies should have data tracking individual patients, but this does not translate into practice. It was also noted that

tracking concordance data is particularly unreliable, as it is self-reported and often overestimated. This makes it difficult to track costs accurately.

Evidence-based data is required in order to make the case for advanced therapies and novel products to be used in practice. However, it was agreed that, while RCTs are still seen as the recommended means of providing high-quality evidence, conducting RCTs in the field of wound care can be problematic.

There is a need to identify gaps in current care, to enable investment in a full, multidisciplinary-focused pathway. It was also agreed that 'clinical champions' are required, in order to promote use of advanced and novel new therapies. Raising awareness, publicising relevant statistics and general education are all of key importance.

Conclusions

It was agreed by the expert group that there is scope for use of biologic scaffolds in the treatment of DFUs and, as such, they should be incorporated as part of a structured, multidisciplinary care approach. This is demonstrated by the more than 500 published articles examining the role of IDRT in wound healing, and the results of the FOUNDER study that show IDRT can significantly increase complete DFU wound closure, compared to the control group. Further study and use in practice is needed, and it was suggested that a registry of specific use in DFUs (e.g. to include relevant data such as vascular information, etc) would be valuable, in order to increase targeted use in practice and, therefore, improve potential outcomes. Tracking of long-term follow-up, in order to assess quality of healing and reduction of recurrence rates, could also be beneficial. The need was also identified for drivers for change in practice — for new products to be adopted, as well as structured pathways followed to ensure early intervention and to prevent any missed opportunities for optimum care and improved patient outcomes.

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