Healing Times of Diabetic Foot Ulcers: Investigating the Influence of Infection and Peripheral Arterial Disease

Authors: Tamara E. Milne[1*], Deborah E. Schoen[2], Virginia M. Bower[3], Sally A. Burrows[4], Cara Westphal[1], Joel M. Gurr[1]

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Abstract:

Objective – To calculate healing times of diabetic foot ulcers (DFU) treated in a tertiary hospital podiatry department, and investigate the influence of infection [soft tissue infection (STI) and osteomyelitis (OM)] and peripheral arterial disease (PAD).

Methods – Data was collected for the period between October 2004 and September 2008. All DFUs that presented to the Royal Perth Hospital (RPH) podiatry department were included. Data was collected for the following variables: date of birth, sex, Aboriginal status, type of diabetes, DFU presentation date and healing date (if applicable), DFU location, presence of peripheral neuropathy (PN), PAD, and infection (STI or OM), and attendance at the Multidisciplinary Foot Ulcer Clinic.

Results – A total of 682 DFUs from 261 patients were analyzed (67% male, mean age 62 +/-12 years) of which 607 (89%) healed. The median healing time for all DFUs was 49 days. PAD and infection was diagnosed in approximately 35% and 48% (30% STI and 18% OM) of DFUs, respectively. Non-infected DFUs had a median healing time of 34 days (Interquartile Range [IQR]=56) compared with 83 days (IQR=121; Incident Rate Ratio [IRR]=1.94; 95% CI: 1.58-2.38; p=<0.001) and 115 days (IQR=173; IRR=2.88; 95% CI: 2.18-3.79; p=<0.001) for those complicated by STI and OM respectively. The median healing time for DFUs with no PAD was 46 days (IQR=93) compared to those complicated by PAD at 59 days (IQR=111; IRR 1.23; 95% CI: 0.98-1.55; p=0.08).

Conclusion – This study quantifies the negative impact that infection has on DFU healing times. While strict infection control procedures in the hospital setting are paramount, the authors propose that there may be a greater role for patient education in an effort to reduce infection rates in DFUs.

Key words: Diabetic foot ulcers, wound healing, healing times, diabetic foot infection, peripheral arterial disease

Corresponding author

*Tamara E. Milne
Ipswich Hospital, Diabetes Service, PO Box 878
Ipswich, Queensland, Australia, 4305
Phone: +617-3817-2475 Fax: +617-3413-5768

Email: *tamara_milne@health.qld.gov.au*

Affiliations

[1] Department of Podiatry, Royal Perth Hospital, Perth, Australia
[2] Combined Universities Centre for Rural Health, University of Western Australia, Perth, Australia
[3] School of Surgery, University of Western Australia, Perth, Australia
[4] School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

INTRODUCTION

Diabetic foot ulcers (DFU) are among the most severe complications of diabetes[1] and often require substantial human and financial resources to manage effectively[2-3]. It is estimated that 7% of the world's population now has diabetes[1] and the lifetime risk that a patient with diabetes will develop a DFU is estimated between 15 - 25%[4-7]. International studies clearly illustrate that DFUs are a common precursor to the development of infection, gangrene and amputation[1-3, 5, 8]. It is therefore vital that DFUs are healed in the most expeditious manner to reduce the risk of these complications developing.

The predominant focus in previous studies on wound healing has been on healing rates (i.e. percentage of wounds healed within a given time) and outcomes, (i.e. healed versus amputation) as opposed to the length of time to heal from intervention. Moreover, most available studies have also limited their research to DFUs of neuropathic origin. This excludes significant influencing variables such as the presence of infection and PAD, both of which are reported to be critical in affecting the healing times of DFUs[7, 9].

Given the paucity of data on standard healing times for DFUs against which to benchmark, the objective of this study was to calculate healing times of DFUs from intervention treated in a teaching hospital podiatry department and to investigate the influence of infection (STI and OM) and PAD on healing times.

METHODS

This study was conducted at the Royal Perth Hospital (RPH) podiatry department in Western Australia. RPH is an 850-bed teaching hospital. The podiatry department predominately manages high-risk foot complications in patients with diabetes. The podiatrists working in the department have longstanding expertise in the management of diabetic foot disease.

The RPH podiatry department comprises of two specialist outpatient clinics – the High Risk Foot Clinic and the Multidisciplinary Foot Ulcer Clinic. In the High Risk Foot Clinic, the podiatrist primarily manages patients with DFUs, with intermittent input from the patient's medical or surgical specialist as required. Alternatively, the Multidisciplinary Foot Ulcer Clinic is reserved for patients with particularly complex or chronic DFUs who are managed by an interdisciplinary team of medical, surgical, nursing, and allied health staff. This type of clinic is considered internationally to have the best practice in the management of diabetic foot complications[10-12].

The inclusion criteria for this study consisted of all patients diagnosed with diabetes (type 1 and type 2) who presented to the RPH podiatry department with a DFU between October 2004 and September 2008.

Data was collected for the following variables: presentation date, location of the DFU, date of birth, sex, Aboriginal status, and type of diabetes. The presence or absence of PN, PAD and infection (at any stage during DFU management) were also noted. Multiple DFUs on the same patient were recorded separately, making the DFU the unit of measure, not the patient. The presentation date of the DFU was defined as the date in which the patient first attended the clinic for treatment. This distinction was made for two reasons. Firstly, the date of onset is often difficult to estimate given the neuropathic nature of the majority of DFUs and is therefore an unreliable indicator. Secondly, the focus of this study is on the healing times from intervention by the department, which was implemented at initial presentation.

The healing date, where applicable, was recorded as the date of the clinical review where the DFU had epithelialized and was deemed healed by the treating podiatrist. The presentation date was then subtracted from the healing date in order to calculate the overall healing time in days. Other outcome measures including amputation, non-healing, transfer to another clinic, refusal of treatment, and failure to attend were documented. Lastly, it was recorded if the DFU had been managed through the Multidisciplinary Foot Ulcer Clinic (MDFUC) at any stage.

Approval for the study was received from the RPH Human Research Ethics Committee.

Definitions and Variables

For the purpose of this study we defined DFUs according to the International Working Group on the Diabetic Foot (IWGDF) description: a full-thickness break in the skin occurring below the malleoli in a patient with diabetes[13]. The type of diabetes was recorded based on the medical diagnosis of the patient's treating physician. The Neuropathy Disability Score and Neuropathy Symptom Score was used to assess PN[14]. PAD was diagnosed by an Ankle Brachial Index (ABI) of < 0.8 or a digital systolic pressure (hallux) < 45mmHg for cases where calcification (ABI > 1.3) was present[15]. STI was defined using the clinical criteria consistent with the Infectious Disease Society of America guidelines: a purulent discharge and/or ≥2 clinical signs of infection[16].

OM was diagnosed when the DFU probed to bone and was accompanied by associated underlying diagnostic imaging changes (including plain radiographs, MRI, and/or dual bone and white blood cell scan), and/or a positive bone culture or histological finding via percutaneous or intra-operative biopsy[17].

Four ulcer locations were identified for the purpose of this study: dorsal foot (excluding the digits), forefoot (including digits), midfoot, and rearfoot. Additionally, amputation site, regardless of location, was also recorded. All cases were managed according to the general treatment principles for DFUs. This includes off-loading, diagnosis and treatment of infection, assessment of neurovascular status, treatment of PAD, and regular wound debridement[7, 10, 18].

STATISTICAL ANALYSIS

Appropriate summary statistics describing the sample characteristics were undertaken for both the sample of patients and the sample of the DFU data. The potential sample bias due to loss of follow up was assessed using chi-square and student T tests. Logistic regressions were performed to investigate differences between patient and DFU characteristics of those who healed compared to those who did not. Negative binomial regression was performed on healing time to obtain Incident Rate Ratios (IRR) and 95% Confidence Intervals (CIs) for infection, PAD, and MDFUC. The negative binomial regression was chosen over Poisson regression due to over-dispersion (where the variance is greater than the mean) of our sample. A variance adjustment for the correlation of multiple ulcers within patients was applied to all regressions. Data was analysed using Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and significance was set at alpha = 0.05.

RESULTS

Patient and DFU Characteristics

A total of 287 patients with 747 DFUs were recorded in the period of the study. Aboriginal people represented 3.13% of the study population. A total of 65 DFUs from 44 patients were lost prior to healing due to patient death (25 DFU, 11 patients), transfer to another clinic (18 DFU, 14 patients), refusal of treatment (6 DFU, 3 patients) and failure to attend (16 DFU, 16 patients). Of these 44 patients, 18 were retained in the study due to healing in at least one DFU during the study period, resulting in a sample of 261 patients with 682 DFUs. These results are summarized in **Figure 1**.

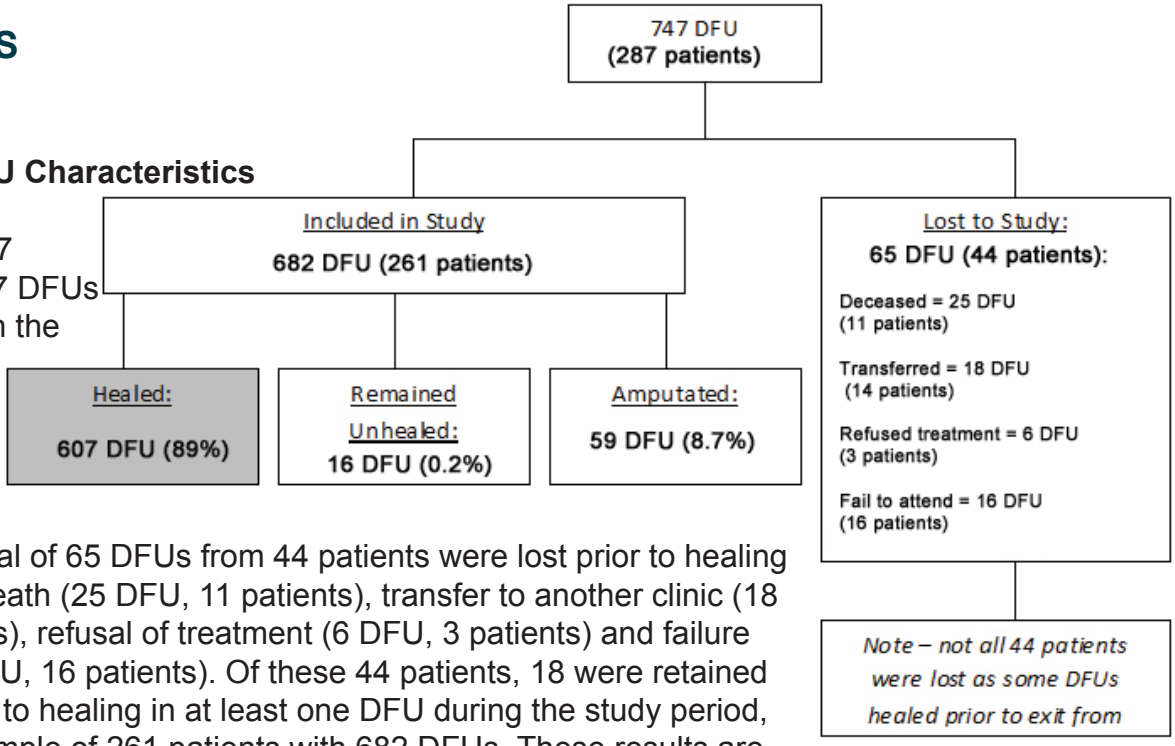

Figure 1. Patient and DFU Sample (n = 747)

Comparison of the patient characteristics for those lost prior to healing for at least one DFU, and those retained for the entire treatment period on all DFUs provided no statistical evidence of differences in sex, PAD, type of diabetes, age or PN. There were, however, a slightly higher proportion of patients treated by the Multidisciplinary Foot Ulcer Clinic who did not complete treatment on all DFUs. These results are summarised in **Table 1a.**

Mean age (+/-SD) was 62 +/-12 years and the male to female ratio was 2:1. The prevalence of type 1 diabetes among patients was 13%, PN 92% and PAD 35% **(Table 1a)**. Infection was present in approximately 48% of DFU cases respectively **(Table 1b)**. STI was a precursor in all cases where OM was diagnosed. DFU location is summarized in **Table 1b**.

Table 1a. Patient Characteristics (n=287)

	Lost or Partial Loss (44) % (n)	Not Lost (243) % (n)	P value	Retained (261) % (n)
Male	**61% (27)**	**67% (164)**	**0.43**	**67% (175)**
PAD	**49% (21)**	**36% (86)**	**0.11**	**35% (92)**
Type 1 Diabetes	18% (6)	13% (28)	0.7	13% (30)
Age (mean +/- SD)	64 +/-15	63 +/-12	0.7	62 +/-12
MDFUC*	54% (23)	37% (90)	0.04	38% (99)
PN	93% (41)	92% (222)	0.74	92% (239)
Aboriginal status	2% (1)	3% (8)	1.0	3% (8)

*** Multidisciplinary Foot Ulcer Clinic**

Table 1b. DFU Characteristics (n=747)

	Lost n=65 % (n)	Retained n=682 % (n)	P value
Infection:			**<0.001**
No	**19% (11)**	**52% (354)**	
Yes (STI only)	**58% (34)**	**30% (202)**	
Yes (OM)	**23% (14)**	**18% (124)**	
Location:			**0.014**
Dorsal	**38% (24)**	**23% (152)**	
Forefoot	**41% (26)**	**61% (411)**	
Midfoot	**6% (4)**	**5% (34)**	
Rearfoot	**13% (8)**	**7% (50)**	
Amputation Site	**3% (2)**	**3% (22)**	

Outcomes

Over the four-year period of the research study, 89% (607) of DFUs healed, 0.2% (16) remained unhealed, and 8.7% (59) led to amputation (**Figure 1**). The healed DFUs form the basis of the analysis on healing times in this paper. No statistically significant associations were detected between sex or type of diabetes and whether a DFU had healed. Differences were detected, however, in age, PAD and OM. The odds of healing decreases by 70% for DFUs with PAD (p<0.001, OR=0.30, 95% CI: 0.16-0.56) compared to DFUs without PAD. The odds of healing also decrease by 84% for those DFUs complicated by OM, compared to DFUs with no infection (p<0.001, OR=0.16, 95% CI: 0.08-0.34). No difference in the odds of healing was detected between STI and no infection. These results are summarized in **Table 2**.

Table 2. Associations between characteristics and healing status

	Healed DFU	Unhealed DFU	P value	OR	95% CI
Number of DFU	**607**	**75**			
Mean (+/- SD) age	**60 (12)**	**64 (11)**	**0.019**		
% Male (n)	72% (439)	80% (60)	0.22		
% Type II Diabetes (n)	89% (493)	88% (61)	0.99		
% PAD (n)	28% (169)	56% (41)	<0.001	0.30	0.16-0.56
% STI (n)	31% (186)	22% (16)	0.58	0.77	0.30-1.95
% OM (n)	15% (88)	48% (36)	<0.001	0.16	0.08-0.34

Note: p values are based on standard errors adjusted for multiple DFUs on the one patient.

Healing Times

The median healing time of all DFUs that healed (n=607) within the time frame of the study was 49 days (IQR=95). The median healing time for DFUs that were not complicated by infection was 34 days (IQR=56). By comparison, DFUs diagnosed with STI took significantly longer to heal at 83 days (IQR=121, IRR=1.94, 95% CI: 1.58-2.38, p < 0.001). Similarly, the median healing time was again significantly longer in DFUs complicated by OM at 115 days (IQR=173, IRR=2.88, 95% CI: 2.18-3.79, p<0.001).

Longer median healing times were observed for DFUs complicated with PAD (59 days, IQR=111) compared to those without evidence of PAD (46 days, IQR=93), although this result was not statistically significant (IRR=1.23, 95% CI: 0.98-1.55, p = 0.08). DFUs that had been reviewed by the MDFUC during any stage of their management had longer median healing times at 83 days (IQR=141) compared to DFUs never reviewed on this specialized clinic at 39 days (IQR=75, IRR=1.83, 95% CI: 1.47-2.27, p<0.001). These results are summarized in **Table 3**.

Table 3. Healing Times in Days (n=607)

Variable	Mean (SD)	Median (IQR)	IRR*	95% CI	P-value
All DFU	**98 (131)**	**49 (95)**			
No PAD	**93 (123)**	**46 (93)**			
PAD	113 (152)	59 (111)	1.23	0.98-1.55	0.08
No Infection	63 (83)	34 (56)			
STI	122 (136)	83 (121)	1.94	1.58-2.38	<0.001
OM	181 (205)	115 (173)	2.88	2.18-3.79	<0.001
No MDFUC	76 (97)	39 (75)			
MDFUC	139 (173)	83 (141)	1.83	1.47-2.27	<0.001

*** Incident Rate Ratio (IRR) is the ratio of average healing times between two groups.**

DISCUSSION

Most published papers report on the estimated healing rate and clinical outcome of DFUs. This approach does not provide a clinically relevant estimate of the time needed to achieve wound healing for DFUs from the time of intervention.[9] This study provides preliminary data on healing times for DFUs and not only identifies key variables that impede wound healing, but also quantifies the impact of these variables. The results of this study can provide an internal benchmark for the institution against which to measure ongoing performance.

The DFU variables reported in this study are comparable to those commonly cited in the medical literature[2]. It should be noted, however, that more recent studies have shown an upward trend in the prevalence of DFUs complicated by PAD at approximately 50%.[7, 19-20]

The 3.13% of the study population identified as Aboriginal people mirrors the Western Australian (WA) population, however, high rates of amputation amongst Aboriginal people in WA have been reported and Aboriginality in this study may be under-reported.[21] The use of a single Aboriginal status identifier as used in this study is weak, albeit improved since 2000.[22-23] Under-identification of Aboriginality in administrative health data collections has been shown to be high both in death records and mortality and morbidity in cardiovascular health records when data linkage systems are utilized in WA.[24-25]

Previous studies have also reported comparable healing outcomes to those reported in our study, with approximately 65-77% of DFUs healing, 11-12% still undergoing treatment, 5-24% resulting in amputation and 3-6% being lost to the study[7, 19, 20, 26-28].

Infection complicated approximately half of all DFUs included in this study. While the rate of infection was surprisingly high to the authors, it is consistent with other published studies. STI has been reported to complicate between 40-80.8% of all DFUs, with a rate of 40-50% being most commonly cited[2, 20, 29-31]. Varied rates of DFUs complicated by OM have been detailed in the medical literature (12-66%); however, an incidence of approximately 20% is most frequently reported, which is equivalent to the results from this study[4, 28-32].

The unfavorable impact of infection was clearly highlighted in this study with significantly increased healing times for DFUs complicated by either STI or OM. Importantly, the results of this study quantify the negative consequences that infection has on DFU healing time. As noted earlier, most available studies on healing times of DFUs have excluded DFUs complicated by infection and therefore only limited evidence was available for comparison. Oyibo et al., 2001 described a median healing time for infected ulcers of 84 days compared to DFUs that were not complicated by infection, 56 days (p= 0.05, n=194)[2]. Unfortunately, the Oyibo study did not define infection or differentiate between STI and OM. Lavery et al., 2007 further reported an increase in the mean healing times for DFUs complicated by OM (267 +/- 284 days) compared to DFUs without underlying OM (169 +/- 268 days, n=247)[30].

Prolonged healing time has a direct impact on the human and financial resources required to manage DFUs. While STI can be managed in the outpatient setting, OM may require admission to the hospital, and potentially require surgery that contributes to the exponentially increased costs associated with DFUs. The personal and institutional impact of diabetic foot infection clearly demonstrates the importance of minimizing the risk of infection in DFUs, as this will ultimately have dramatic flow-on benefits in reducing healthcare costs. While health services continually strive to maintain strict infection control policies and procedures, the authors propose that there may also be a role for enhanced patient education on patient-regulated infection control in the home. Between clinic appointments patients are responsible for their own care and, in some instances, may even be involved in redressing their wounds. During these times, well away from a sanitized clinical environment, may lay the potential risk of suboptimal self-care practices contributing to the DFU becoming infected. With this in mind, applied education needs to be provided to the patient in an effort to reduce the overall infection rate in DFUs.

There was weak evidence of an association between PAD and DFU healing times in the present study. However, previous studies on wound healing support an association between PAD and healing time. Gul et al. (2006) reported significantly higher median healing times in the presence of PAD compared to no underlying PAD ($p < 0.004$).[19] Similarly, Oyibo et al. (2001) reported that neuroischaemic DFUs have a median healing time of 140 days compared to neuropathic ulcers at 63 days ($p = 0.03$)[2]. Zimny et al. (2002) reported that neuropathic DFUs have the shortest mean healing time of 77.7 days (95% CI 62-93) compared to neuroischaemic and ischaemic DFU healing times of 123.4 (95% CI 101-145) and 133 (95% CI 116-149) days respectively[9]. Most recently Prompers et al. (2008) suggested that the significantly worse healing rates observed in DFUs with PAD compared to those without PAD (69% versus 84%; $p<0.001$) require that they be defined as two separate disease states[7].

It is well accepted that vascular disease hinders the healing process by decreasing the supply of oxygen and other critical nutrients required by the tissues[33]. The healing time for DFUs complicated with PAD was included in this study, however, it not longer from a statistically significant perspective. When commencing this study in 2004, PAD was defined as an ABI < 0.8, or by using a digital systolic toe pressure of <45mmHg in cases where arterial calcification (ABI > 1.3) was present[15]. At this time, the authors noted that there was not a large consensus in the medical literature for the criteria to diagnose PAD using a digital systolic toe pressure. It should be highlighted, however, that the more recent literature has lowered the threshold for PAD (ABI < 0.9), and that a digital systolic toe pressure of < 30-50mmHg in fact indicates critical limb ischemia[34-36]. Utilizing these updated guidelines would influence the number of DFUs with PAD included in the study and may have led to statistically significant findings.

Over one-third of DFUs in the study were reviewed at MDFUC at some stage in their management. The MDFUC at RPH is typically reserved for the most complex and/or chronic DFU. Although there are no formal guidelines as to which DFU will be referred to the MDFUC, they are generally those DFUs that are non-healing despite following the appropriate treatment guidelines. In addition, they are commonly complicated by persistent STI or diagnosed with OM. Our results report that DFUs reviewed by MDFUC take almost twice as long to heal as those never reviewed in that specific clinic. This can be explained by the fact that the DFUs were not randomly assigned into the High Risk Foot Clinic or MDFUC. Instead, complex and chronic DFUs are deliberately selected to attend the latter, which would naturally lead to DFUs with comparatively lengthy healing times. Therefore, the significantly prolonged healing times of DFUs managed through the MDFUC in comparison to the High Risk Foot Clinic suggests not that the clinic has a negative impact on the healing time of DFUs, but rather that the appropriate cases are being referred to the MDFUC. This is important as given the limited time period when all of the medical, surgical, nursing and allied health staff are available together for the MDFUC, their combined efforts should be directed towards those particularly challenging cases that require diverse interdisciplinary input.

Limitations

There are two key limitations to this study that the authors have identified. The most significant of these is that wound depth was not recorded in the present study. Previous research has demonstrated that severity of the DFU (including wound depth) affects and predicts healing times and outcomes[19, 37]. As acknowledged in the recently released *National Evidence Based Guidelines: Prevention, Identification and Management of Foot Complications in Diabetes (2011)* foot ulcer severity is graded on wound depth, presence of infection and presence of PAD. In this study, only two of these three key variables were recorded[38].

To address this limitation the RPH podiatry department will undertake a retrospective follow-up study that will include a number of additional variables, including wound depth. Including this supplementary information will allow the authors to grade the DFU severity using the University of Texas wound classification system and then compare the new data with healing time[39].

The second key limitation is that the present study relied on staff diligence and compliance to record the data. Given the clinical pressures in a busy hospital environment, potentially a number of DFUs were not recorded at all.

A quantity of missing data was identified during preliminary analysis that can likely be attributed to staff compliance. Where missing data was identified, a retrospective review of patient's medical records was required in order to retrieve missing data for the study. This process is likely to have had a negative, albeit small effect on the validity of the data.

CONCLUSION

This research shifts the focus away from healing rates to provide preliminary data on healing times for DFUs. The advantage of this approach is that it provides a clinically relevant estimate of the time required to achieve wound healing for DFUs from the time of intervention. This information is useful for both the patient and clinician as it enables both parties to identify realistic treatment goals and expectations. The information can also act as an internal benchmark for the institution against which to measure their performance.

The negative impact that infection has on DFU healing times is quantified in this study. Longer healing times equate to increased utilization of scarce health service resources, which increases exponentially if the patient requires hospital admission. While strict infection control procedures in the hospital setting are paramount, the authors propose that there may be an additional role for patient education in an effort to reduce the overall infection rate in DFUs within our institution.

Declaration of Competing Interests: Nothing to Declare

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