OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE

Reconstructive

Complex Lower Extremity Wound in the Complex Host: Results From a Multicenter Registry

Paul J. Kim, DPM, MS*†
Christopher E. Attinger, MD*†
Dennis Orgill, MD‡
Robert D. Galiano, MD§
John S. Steinberg, DPM*†
Karen K. Evans, MD*†
Lawrence A. Lavery, DPM, MPH¶

Background: The complex diabetic lower extremity wound has not been well studied. There are a variety of new technologies now being applied with a paucity of evidence in evaluating their outcomes. The aim of this study is to describe clinical outcomes in the complex lower extremity wound in the comorbid host. We hypothesized that treatment choice would have minimal impact on healing outcomes in this compromised population.

Methods: A multicenter retrospective registry of patients with diabetes and lower extremity wounds was created to compare treatment modalities of collagen–glycosaminoglycan scaffold, negative-pressure wound therapy, local tissue flap, and free tissue transfer. Statistical analyses included descriptive, proportional comparisons and Cox regression.

Results: There were no statistical differences in age, hemoglobin A1c, or body mass index between groups. Study patients had a history of amputation (40.5%), peripheral vascular disease (54.6%), peripheral neuropathy (64.8%), end-stage renal disease (13.9%), renal/hepatic disease (40.4%), and hypertension (85%). The most common wound etiologies were surgical dehiscence (69%), diabetic neuropathic wounds (39%), and ischemic wounds (28%), most commonly located on the foot or at a prior amputation site (30%). Mean wound area was 57.9 cm^2 and almost half with exposed bone. There were no statistical differences between treatment groups in proportion or time to healing, recurrence, or time to return to baseline function.

Conclusions: Commonly used treatment modalities employed for this population of patients resulted in similar outcomes. This is the first study to describe the complex diabetic lower extremity wound in a complex host. *(Plast Reconstr Surg Glob Open 2019;7:e2129; doi: 10.1097/GOX.0000000000002129; Published online 11 April 2019.)*

INTRODUCTION

There are many multicenter studies that describe the diabetic lower extremity wound and its treatment options. However, the vast majority of studies include noncomplex patients and wounds managed in an outpatient clinic setting with only a selective patient population.[1–6] A more complex environment is created when considering that diabetics with lower extremity wounds also commonly present with additional layers of complexity, such as soft-tissue infection, osteomyelitis, immune compromise, peripheral vascular disease, history of amputation, and end-stage renal disease. Thus, although the traditional studies may offer internal validity to support the treatment of diabetic lower extremity wounds in the outpatient clinical setting, they do not include the growing population of more acutely complex wounds in an aging and comorbid

*From the *Georgetown University School of Medicine, Washington, D.C.; †Department of Plastic Surgery, MedStar Georgetown University Hospital, Washington, D.C.; ‡Division of Plastic Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, Mass.; §Department of Plastic Surgery, Northwestern University, Chicago, Ill.; and ¶Department of Plastic Surgery, University of Texas Southwestern, Dallas, Tex.*

Received for publication October 5, 2018; accepted December 12, 2018.

Supported by Integra LifeSciences Inc. (Plainsboro, NJ).

This study was approved by the Institutional Review Board Georgetown University Medical Center (Washington, D.C.), Partners Human Research Committee (Boston, Mass.), University of Texas Southwestern (Dallas, Tex.), and Northwestern University (Chicago, Ill.). All study data material on file with Integra LifeSciences Inc. Clinical Trials.gov: Retrospective Study Evaluating Outcomes for Integra Skin Sheets in Lower Extremity Complex Wounds; NCT01947387; Date Registered: August 12, 2013.

Copyright © 2019 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000002129

Disclosure: *Paul J. Kim, Christopher E. Attinger, Dennis Orgill, Robert D. Galiano, John S. Steinberg, and Lawrence A. Lavery have all received past research and consulting funding from Integra LifeSciences Inc. and Acelity Inc., the manufacturers of the devices discussed in this article. The remaining authors have no financial information to disclose.*

population with larger, deeper wounds that may have recent history of infection.[7] These wounds may benefit from a more intensive surgical approach.

A variety of strategies are employed for the treatment of these complex wounds in the complex host. However, because traditional wound studies exclude these patients, little is understood about the clinical challenges and outcomes of their management. For example, a functional amputation is a viable option for some patients; however, an attempt at limb salvage is often the preferred option from the patient perspective.[8,9] If limb preservation is the goal, there are available options including the use of Integra (Integra Life Sciences, Plainsboro, N.J.), negative-pressure wound therapy (NPWT), local tissue flaps (LTFs), and free tissue transfer (FTT). Largely, the available evidence for the efficacy or effectiveness of these treatment options is restricted to noncomparative, case studies, case series, smaller retrospective, or underpowered comparative studies.[10–16]

The aim of this study is to describe clinical outcomes in the complex lower extremity wound in the comorbid host. We hypothesize that using Integra versus NPWT, LTF, or FTT will not result in significant differences in healing outcomes.

METHODS

Study Design

This was a retrospective, multicenter review of subject data from 4 participating sites (Georgetown University Hospital, Washington, D.C.; Brigham and Women's Hospital, Boston, Mass.; The University of Texas Southwestern Medical Center, Dallas, Tex.; and Northwestern University Feinberg School of Medicine, Chicago, Ill.). After Institutional Review Board approval, individual subject data were obtained from hospital medical records and physician clinical medical charts using relevant International Statistical Classification of Diseases, 9th revision and/Related Health Problems codes for diabetes and Current Procedural Technology codes for surgical cases that involved Integra, NPWT, LTF, and FTT for complex soft-tissue reconstruction of a diabetic lower extremity. Subject records were limited to retrospective data, and records within 5 years of the study initiation visit date were reviewed and included a time period of data from August 2008 to February 2014. This observational registry design prohibits a priori power analysis.

Subject Selection

A total of 686 cases were identified as being treated with Integra, NPWT, LTF, and/or FTT and were assigned to one of the defined treatment groups. Within each of the treatment groups, a total of 80 cases were randomly selected with as equal of a distribution across the treatment groups as possible, for a total of 320 cases. Two hundred eighty cases were identified for further screening.

Inclusion/Exclusion

Eligibility criteria included diabetics (type I or type II), >18 years of age, with a lower extremity wound, that required operative application of Integra, NPWT, LTF, or FTT. This initial operation was referred to as the index surgery (time of therapy). The wound was defined as complex if it involved exposed deep tissue (eg, bone, tendon, fascia, and/or ligament). Additionally, only cases with a minimum of 1 year follow-up from the index surgery were eligible for inclusion in the analysis (Fig. 1).

Index Surgery and Postoperative Care

Because this was a retrospective study, the surgical technique for the application of Integra, NPWT, LTF, or FTT and the postoperative care of these treatments were not standardized. Therefore, the data that were collected reflect the standard of care and individual technique for a particular investigative site.

Data Collection

Information collected and analyzed included age, gender, race/ethnicity, body mass index (BMI), ambulatory status, smoking status, vascularity assessment, and concomitant medical conditions. Additionally, information regarding wound etiology, size, chronicity, complexities, location, and clinical assessment of infection was collected and used for analysis. Data regarding healing outcomes, recurrence rates, and functional status were collected. All assessments of wound healing, wound recurrence, and return to ambulation were based on the judgment of the clinicians at each investigative site.

Statistical Analyses

All statistical tests were performed using SAS 9.2 (SAS Institutes Inc., Cary, NC). For statistical purposes, NPWT, LTF, and FTT were considered the control treatments, and Integra was considered the investigational treatment. Missing data were not imputed. Categorical variables are reported as percentages, and the chi-square test or Fischer exact test was used. Continuous data summaries include the mean, SD, median, and range. A nonparametric method was applied to the continuous variable comparison between the median for Integra and the other treatment groups (Wilcoxon signed-rank test). Kaplan–Meier wound healing survival curves were plotted to evaluate time to wound healing. Statistical analyses were performed using log-rank test, and a Cox proportional hazard model was used to estimate the adjusted effect of variables of interest on time to wound healing. Variables of interest included age, gender, BMI, history of smoking, history of amputation, peripheral vascular disease, transplant (immunosuppressive therapy), connective tissue disease, osteoporosis, hematologic disorder, end-stage renal disease, and wound on plantar foot.

RESULTS

Two hundred seventy-four of the 280 cases were eligible for inclusion in the final data set. Three subjects received 3 of the treatments simultaneously, 2 subjects received immediate split thickness skin grafts without the use of any of the treatments, and 1 subject received Integra and an split thickness skin graft. With these 6 subjects

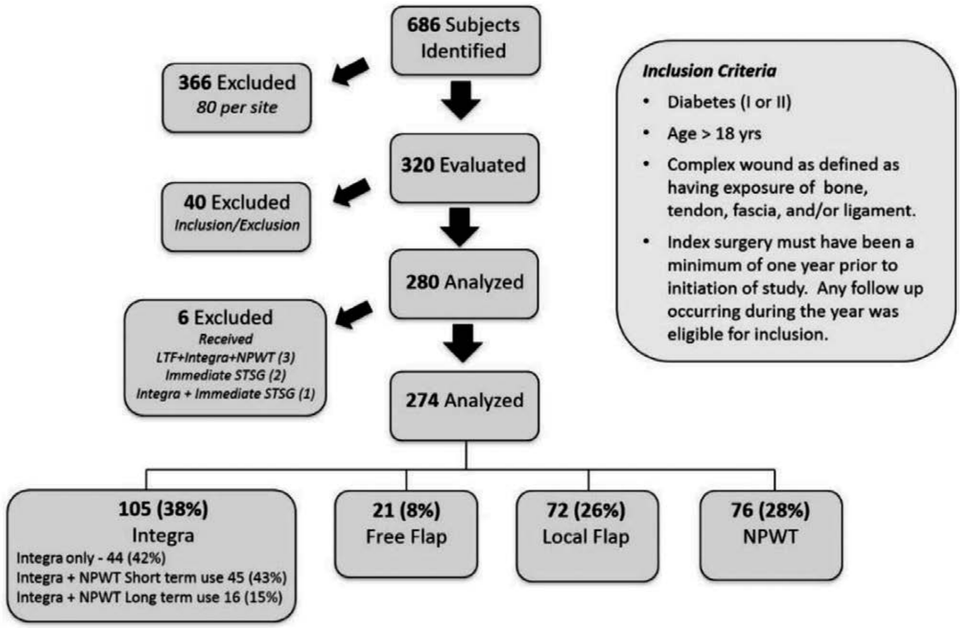

Fig. 1. Subject enrollment. Cases from 4 sites were identified for inclusion in the study. Based on inclusion criteria and treatment modality, 274 subjects were eligible and analyzed. Although aimed to equally distribute subjects across all 4 groups, varying numbers of patients were included with 105 wounds being managed with Integra, 21 wounds with a free flap, 72 wounds with a LTF, and 76 with NPWT. STSG indicates split thickness skin graft.

Table 1. Subject Characteristics

Characteristic	Statistic	Integra N = 105	NPWT N = 76	LTF N = 72	FTT N = 21	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
Age	Mean ± SD	61.8±10.9	59.4±12.9	66±12.3	59.9±13.2	—	—	—
	Median	57.7	59.1	66.9	59.8	0.818	0.003	0.525
	Minimum–Maximum	42–82	33.1–86.3	33.3–93.2	32.2–90.8	—	—	—
Gender, n (%)	Female	39 (37)	33 (43)	28 (39)	8 (38)	0.394	0.814	0.934
	Male	66 (63)	43 (57)	44 (61)	13 (62)	—	—	—
Race, n (%)	White	45 (43)	47 (62)	43 (60)	11 (52)	0.030	0.165	0.416
	African American	32 (30)	17 (22)	13 (18)	7 (33)	—	—	—
	Latino, Hispanic	24 (23)	9 (12)	13 (18)	2 (10)	—	—	—
	Asian	1 (1)	2 (3)	1 (1)	0	—	—	—
	Other or unknown	3 (3)	1 (1)	2 (2)	1 (5)	—	—	—
BMI (kg/m^2)	Mean ± SD*	31.3±7.7	33.8±9.2	30.8±9.2	29.3±7.1	—	—	—
	Median	30.2	33.0	29.8	28.7	0.051	0.732	0.250
	Minimum–Maximum	15.8–67.3	15.5–62.2	18.1–46.6	13.7–48.4	—	—	—
HbA1c	Mean ± SD†	10.3±1.8	10.1±1.8	10.2±1.5	9.9±1.7	—	—	—
	Median	9.8	9.7	10.1	9.6	0.362	0.869	0.308
	Minimum–Maximum	7.6–16.9	6.8–15.0	7.9–14.7	7.5–15.3	—	—	—
Smoking status	Yes, n (%)‡	46 (45)	27 (36)	24 (33)	9 (43)	0.262	0.161	0.936
History of amputation	Yes, n (%)	35 (33)	31 (41)	35 (49)	10 (48)	0.304	0.041	0.212
Revascularization of affected limb	Yes, n (%)	16 (15)	9(12%)	11 (15)	3 (14)	0.513	0.994	1

*BMI missing 4 for NPWT, 3 for LTF, and 2 for FTT.
†HbA1c (hemoglobin A1c) missing for 5 Integra, 1 NPWT, and 8 LTF.
‡Smoking status missing for 2 Integra and 1 NPWT.

excluded, 274 were further analyzed with 105 (38%) receiving Integra, 76 (28%) NPWT, 72 (26%) LTF, and 21 (8%) FTT (Fig. 1).

In the Integra group, 3 different subsets of treatment options included were Integra use alone (n = 44; 42%), Integra + NPWT (short-term use) (n = 45; 43%), and Integra + NPWT (long-term use) (n = 16; 15%). For those who received Integra + NPWT (short-term use), NPWT was used during their index surgery inpatient admission period. For the cohort Integra + NPWT (long-term use), NPWT was used during inpatient treatment and continued through outpatient treatment after discharge.

The mean age of all subjects was 61.5±13.0, BMI 31.7±8.1, hemoglobin A1c (HbA1c) 10.2±1.7, smoking status 39.1%, revascularization of the limb with the target wound 14.2%, and history of amputation of 40.5% (Table 1).

Table 2. Concomitant Medical Conditions

	Integra N = 105	NPWT N = 76	LTF N = 72	FTT N = 21	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
	n (%)	n (%)	n (%)	n (%)			
Diabetes type 1*	9 (9)	14 (18)	11 (15)	4 (20)	0.056	0.159	0.223
Diabetes type 2*	94 (91)	62 (82)	59 (82)	16 (80)	—	—	—
Peripheral vascular disease	46 (44)	44 (58)	43 (60)	16 (76.2)	0.061	0.038	0.007
Peripheral neuropathy	65 (62)	50 (66)	47 (65)	15 (71.4)	0.592	0.648	0.408
End-stage renal disease on dialysis	14 (13)	13 (17)	10 (14)	1 (5)	0.482	0.916	0.463
Renal/hepatic	38 (36)	34 (45)	30 (42)	8 (38)	0.246	0.462	0.869
Hypertension	90 (86)	61 (80)	63 (88)	19 (90.5)	0.330	0.733	0.736
Immunosuppressive therapy	2 (2)	4 (5)	13 (18)	2 (10)	0.234	<0.001	0.129
Connective tissue disorder	1 (1.0)	0 (0)	3 (4.2)	0 (0)	1	0.305	1
Transplant	4 (4)	6 (8)	10 (14)	4 (19)	0.325	0.022	0.026
HIV	0 (0)	0 (0)	2 (3)	0 (0)	NA	0.164	NA

*Diabetes type not indicated for 2 subjects treated with Integra, 2 subjects receiving LTF, and 1 subject receiving a FTT.
HIV, human immunodeficiency virus; NA, not available.

Table 3. Wound Etiology and Location

	Integra N = 105 n (%)	NPWT N = 76 n (%)	LTF N = 72 n (%)	FTT N = 21 n (%)	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
Wound etiology							
Surgical	75 (71.4)	44 (58)	55 (76)	15 (71)	0.058	0.463	1
Traumatic	9 (8.6)	14 (18)	8 (11)	6 (29)	0.050	0.610	0.020
Ischemic	23 (21.9)	20 (26)	24 (33)	11 (52)	0.491	0.091	0.004
Venous	2 (1.9)	1 (1)	0 (0)	1 (5)	1	0.515	0.424
Diabetic neuropathic ulcer	45 (42.9)	31 (41)	22 (31)	8 (38)	0.781	0.097	0.687
Pressure ulcer	9 (8.6)	13 (17)	8 (11)	2 (10)	0.083	0.573	1
Deformity	0 (0)	0 (0)	0 (0)	1 (5)	NA	NA	0.167
Infection/gangrene	7 (6.7)	3 (3.9)	4 (5.6)	5 (23.8)	0.523	1	0.029
Other	5 (4.8)	2 (3)	1 (1)	1 (5)	0.701	0.403	1
Wound location*							
Dorsal foot	7 (6.7)	2 (2.8)	2 (4.8)	1 (4.8)	0.307	0.314	1
Plantar foot	23 (21.9)	12 (16.9)	5 (7.4)	5 (23.8)	0.304	0.011	0.782
Foot	34 (32.4)	13 (18.3)	16 (23.5)	6 (28.6)	0.021	0.140	0.732
Toes	15 (14.3)	11 (15.5)	9 (13.2)	1 (4.8)	0.972	0.733	0.470
Ankle	9 (8.6)	10 (14.1)	5 (7.4)	2 (9.5)	0.320	0.783	1
Heel	8 (7.6)	11 (15.5)	11 (16.2)	4 (19.0)	0.138	0.106	0.115
Leg	9 (8.6)	12 (16.9)	20 (29.4)	2 (9.5)	0.135	0.001	1
Amputation site wounds*							
Yes	38 (36.2)	19 (26.8)	22 (32.4)	4 (19)	0.110	0.437	0.204

*Wound location NPWT missing 5 and LTF missing 4.
NA, not available.

Based on the subject's medical record, as many medical conditions as applicable could be selected (Table 2). Peripheral vascular disease, hypertension, peripheral neuropathy, and cardiovascular disease were the most common comorbidities reported. Additional medical conditions affecting a smaller portion of the study population include renal disease requiring or not requiring dialysis, immunosuppressive therapy, connective tissue disorders, patients receiving a transplant organ, and human immunodeficiency virus. Peripheral vascular disease was present in more subjects receiving a LTF and FTT than Integra ($P = 0.007$ and $P = 0.038$, respectively), more subjects were immunosuppressed receiving a LTF than Integra ($P < 0.001$), and more subjects had received a transplant organ in the LTF and FTT groups than those treated with Integra ($P = 0.026$ and $P = 0.022$, respectively). The detected differences (covariates) in the subject populations were adjusted for in the wound healing regression analysis.

Wounds were of surgical, traumatic, ischemic, venous, diabetic neuropathic, pressure, deformity, infection/gangrene, or other etiology (Table 3). There were statistically less traumatic, ischemic, and infection/gangrene wounds treated with Integra compared with those treated with a FTT ($P = 0.020$, $P = 0.004$, $P = 0.029$, respectively) and more diabetic ulcers treated with Integra than treated with a LTF ($P = 0.097$).

Wound location was separated into 6 sections of the foot: dorsal foot, plantar foot, toes, ankle, heel, and leg. Wounds in which dorsal or plantar was not specified were classified as foot. Statistically more wounds were treated with Integra on the plantar foot than a LTF ($P = 0.011$) and less wounds treated with Integra on the leg than a LTF ($P = 0.001$). Integra was also found to be used statistically more on the foot than NPWT ($P = 0.021$).

All wounds in this study had at minimum 1 deep exposed structure, and no differences in the types

Table 4. Wound Complexities

	Integra	NPWT	LTF	FTT	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
Chronicity of wound (wk)	n = 79	n = 45	n = 37	n = 14			
Mean ± SD	13.70 ± 21.19	25.67 ± 91.28	12.98 ± 20.21	5.62 ± 7.46	—	—	—
Median	6	6	6	3	0.700	0.430	0.039
Minimum–Maximum	0–104	0–624	0–104	0–29	—	—	—
Area of wound (cm^2)	n = 68	n = 33	n = 25	n = 11			
Mean ± SD	58.2 ± 111.7	30.3 ± 44.6	70.8 ± 148.6	110.1 ± 60.8	—	—	—
Median	32.3	12	27.5	100	0.003	0.903	0.001
Minimum–Maximum	1.5–840	0.1–168	0.3–750	35–220	—	—	—
Exposed structures, n (%)	n = 105	n = 76	n = 72	n = 21	0.965	0.564	0.360
Fat/superficial fascia	3 (3)	4 (5)	4 (6)	0 (0)	—	—	—
Muscle/tendon/deep fascia	17 (17)	10 (13)	5 (7)	5 (24)	—	—	—
Ligament/bone/capsule	45 (43)	35 (46)	36 (50)	12 (57)	—	—	—
Unknown	40 (40)	27 (36)	27 (38)	4 (20)	—	—	—
Clinically diagnosed infection (investigator assessment), n (%)	n = 75	n = 56	n = 41	n = 10			
	14 (18.7)	40 (71.4)	19 (46.3)	4 (40)	<0.001	0.002	0.208

Table 5. Cox Regression Time to Heal

Parameter	Pr > Chi-Square	Hazard Ratio (95% CI)
NPWT versus Integra	0.126	2.444 (0.779–7.667)
LTF versus Integra	0.607	0.648 (0.124–3.393)
FTT versus Integra	0.419	2.156 (0.335–13.882)
Age		
Older	0.043	0.952 (0.907–0.998)
Gender		
Female versus male	0.813	0.872 (0.281–2.709)
BMI	0.003	0.867 (0.789–0.953)
Smoker		
Yes versus no	0.027	3.566 (1.154–11.02)
Peripheral vascular disease		
Yes versus no	0.004	0.148 (0.041–0.537)
Transplant		
Yes versus no	0.331	3.847 (0.254–58.175)
End-stage renal disease		
Yes versus no	0.195	2.967 (0.572–15.392)
Wound on plantar surface		
Yes versus no	0.101	2.695 (0.826–8.796)
Surgical		
Yes versus no	0.744	1.197 (0.406–3.529)
Traumatic		
Yes versus no	0.004	0.168 (0.05–0.572)
Ischemic		
Yes versus no	0.383	2.043 (0.41–10.168)
History of amputation		
Yes versus no	0.007	0.194 (0.059–0.632)
Diabetic neuropathic ulcer		
Yes versus no	0.661	0.8 (0.295–2.17)
Pressure ulcer		
Yes versus no	0.840	1.24 (0.154–9.997)
Wound age	0.434	1.005 (0.992–1.018)
Wound area	0.997	1 (0.995–1.005)
Exposed structures		
Fat versus muscle/tendon	0.568	0.123 (0–163.994)
Fat versus ligament/bone	0.652	0.194 (0–244.336)
Fat versus other	0.603	0.155 (0–175.693)
Clinically diagnosed infection		
Yes versus no	0.233	2.316 (0.583–9.205)

*BMI, body mass index; Pr, probability.

of structures were detected among treatment groups (Tables 4–5). Mean wound chronicity was the greatest in wounds treated with NPWT; however, median chronicity was the same for wounds treated with Integra, NPWT, and LTF (6 weeks). Chronicity of wounds managed with Integra (median, 6 weeks) was greater than those treated with a FTT (median, 3 weeks) (P = 0.039). Area of the wound was also evaluated, and it was determined that the median was largest for FTT (100 cm^2) followed by Integra (32.2 cm^2), LTF (27.5 cm^2), and NPWT (12 cm^2). Statistical differences in median values were found between Integra and FTT and Integra and NPWT (P = 0.001 and P = 0.003, respectively).

Evidence of infection was assessed at the time of the index surgery, and it was most commonly observed in those treated with NPWT (71.4%) followed by LTF (46.3%), FTT (40%), and Integra (18.7%). Clinically diagnosed infection per the investigator's assessment was found to be statistically different between the Integra managed wounds and those managed with a LTF and NPWT (P = 0.002 and P < 0.001, respectively).

Complete healing was observed in 46.7% (49/105) of wounds managed with Integra, 47.4% (36/76) of wounds treated with NPWT, 61.1% (44/72) of wounds treated with a LTF, and 57.1% (12/21) of wounds treated with a FTT. No statistical differences were found between the treatment groups. Of the wounds that did not heal, a proportion was amputated, lost to follow-up, or had follow-up at 1 year indicating that the wound was still open (Fig. 2). After removing cases in which the healing status was unknown at 1 year (lost to follow-up category), the healing percentages for the groups were found to be in 65.3% (49/75) of wounds managed with Integra, 70.6% (36/51) of wounds treated with NPWT, 88.0% (44/50) of wounds treated with a LTF, and 70.6% (12/17) of wounds treated with a FTT.

Median time to wound healing (complete re-epithelialization) as assessed by the investigator for wounds managed with Integra was 142 days, NPWT was 118 days, LTF was 65 days, and FTT was 140 days. A statistical difference was found between the median time to wound healing for Integra and LTF (P < 0.001). At 1 year after index surgery, 66.2%, 72.1%, 73.2%, and 71.3% of wounds managed with Integra, NPWT, LTF, and FTT, respectively, were healed (Fig. 3).

To estimate the adjusted effect of variables of interest on time to healing with Integra, FTT, LTF, and NPWT, a

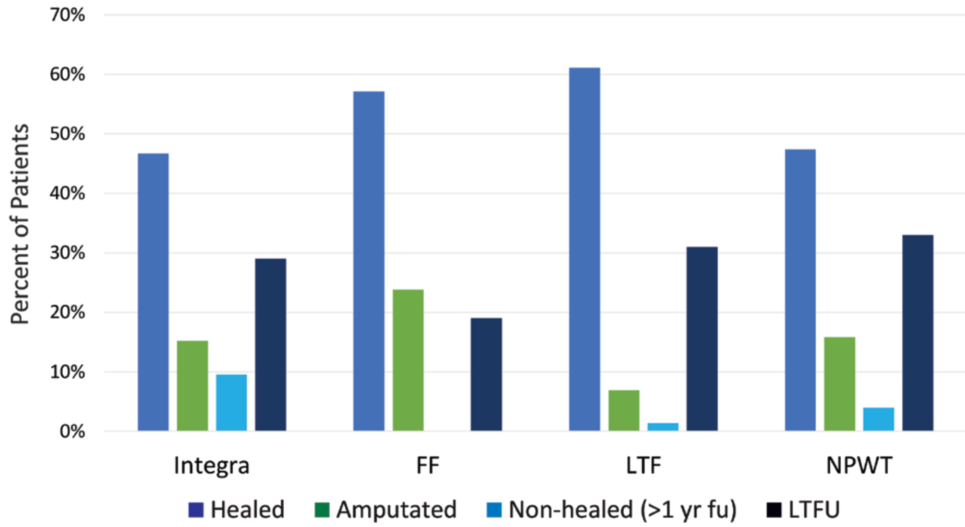

Fig. 2. Healing outcomes. Healing outcomes were assessed by the investigator during follow-up visits. Wound healing was observed for 46.7%, 57.1%, 61.1%, and 47.4% for wounds managed with Integra, FFs, LTF, and NPWT, respectively, with no statistical differences observed. When removing subjects in which the healing status was unknown at 1 year (ie, LTFU), the healing percentages increased to 65.3%, 70.6%, 88.0%, and 70.6% for Integra, FF, LTF, and NPWT (modified population). FF indicates free flap; LTFU, lost to follow-up.

Cox proportional hazard model was used with demographic, comorbidities, and wound characteristic included. The results of Cox proportional hazard model adjusted for demographic and other variables of interest showed no significant difference between Integra and other treatment modalities (Table 6). A significantly higher hazard ratio (HR) was found in subjects as age and BMI increased [P = 0.043, HR = 0.952 (0.907–0.998) and P = 0.003, HR = 0.867 (0.789–0.953), respectively]. Subjects with peripheral vascular disease and having a history of a previous amputation were found to have a significantly higher HR [P = 0.004, HR = 0.148 (0.041–0.537) and P = 0.007, HR = 0.194 (0.059–0.632)]. Additionally, wounds of traumatic origin were also found to have a significantly higher HR [P = 0.004, HR = 0.168 (0.05–0.572)]. No significant differences were detected between Integra and NPWT, LTT, or FTT on time to wound healing after adjusting the covariates.

Follow-up time posthealing was reported as a means: Integra 94.8 days, NPWT 91.9 days, LTF 94.3 days, and FTT 68 days; median: Integra 40.5 days, NPWT 63 days, LTF 42.5 days, and FTT 3.5 days. Although no statistical differences were detected, it was important to note that <50% of wounds that healed in all groups had >12-week follow-up posthealing, with Integra 49.0%, NPWT 47.2%, LTF 40.9%, and FTT 25.0%. The recurrence rates were as follows: Integra 26.5% (n = 49), NPWT 19.4% (n = 36), LTF healed 15.9% (n = 44), and FTT 8.3% (n = 12) (Integra versus FTT P = 0.264, Integra versus LTF P = 0.213, Integra versus NPWT P = 0.447). No statistical differences were observed between groups.

More than 60% returned to a minimum of their functional level recorded at the time of index surgery, with no statistical differences between the treatment groups (Table 7). Time to return to baseline function was a mean of Integra 108.1 days, NPWT 120.6 days, LTF 87.7 days, and FTT 127.1 days; and median of Integra 74, NPWT 76, LTF 39, and FTT 122 days with no statistical differences observed.

DISCUSSION

This is the most robust study to date attempting to define the complex diabetic lower extremity wound in a complex host and its relationship to outcomes when utilizing common treatment modalities. The data from this study suggest that Integra, NPWT, LTF, and FTT are all viable options showing similar healing outcomes for complex wounds in complex hosts. The information presented in this article represents the first in a series of articles analyzing data from this large multicenter registry which will include information on infection and wound bed preparation, resource utilization, and ultimately an article suggesting treatment recommendations and algorithms for care.

An objective of this study was to define the profile of these especially vulnerable patients with complex wounds. The patient population in this study was summarized as an obese (mean BMI, 31.7), uncontrolled diabetic (mean glycated hemoglobin, 10.2%) in their fifth decade of life (mean age, 61.5 years) with significant comorbidities including peripheral vascular disease (54.6%), end-stage renal disease (13.9%), and a history of amputation (40.5%). Many of the wounds were located on the plantar aspect of the foot, with large surface areas and exposed ligament, bone, or capsule. In the literature, the term "complex" has been inaccurate in describing wounds as complex. This includes the uninfected venous leg ulcers and the classic Wagner I or II neuropathic diabetic foot

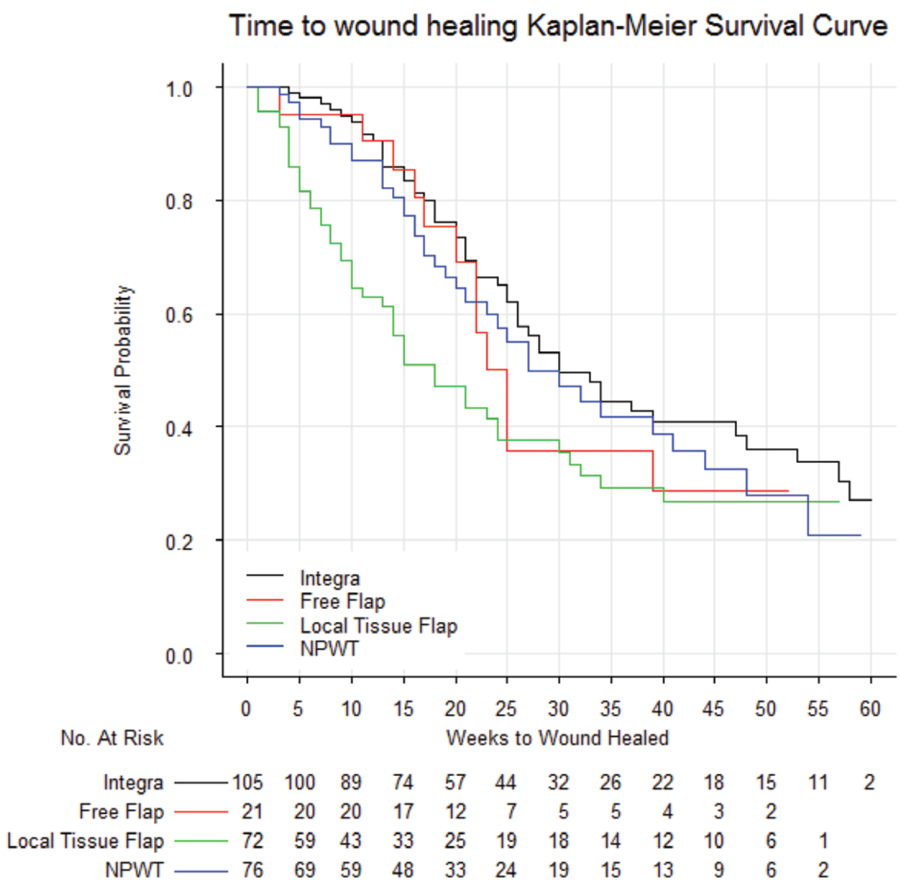

Fig. 3. Time to wound healing Kaplan–Meier survival curve. Time to complete wound healing is shown using Kaplan–Meier curves. At 1 year after index surgery, 66.2%, 71.3%, 73.2%, and 72.1% of wounds managed with Integra, free flap, local tissue flaps, and NPWT, respectively, were healed.

Table 6. Wound Recurrence

	Integra	NPWT	LTF	FTT	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
Wounds that healed	n = 49	n = 12	n = 44	n = 36			
Percentage recurrence	13 (26.5%)	1 (8.3%)	7 (15.9%)	7 (19.4%)	0.264*	0.213†	0.447†
Mean time of follow-up ± SD	94.8 ± 107.5	68 ± 122.6	94.3 ± 111.3	91.9 ± 92.1	—	—	—
Median time of follow-up	40.5	3.5	42.5	63	—	—	—
Minimum–Maximum	0–343	0–329	0–381	0–277	—	—	—

*Fisher exact test.
†Chi-square test.

Table 7. Return to Baseline Function

Statistic n	Integra n = 37	NPWT n = 40	LTF n = 49	FTT n = 13	Integra Versus NPWT	Integra Versus LTF	Integra Versus FTT
Return to baseline function	23 (62.2%)	30 (75.0%)	38 (77.6%)	9 (69.2%)	0.224	0.120	0.746
Mean ± SD (d)	108.1 ± 112.2	120.6 ± 119.6	87.7 ± 99.0	127.1 ± 99.0	—	—	—
Median (d)	74	76	39	122	0.605	0.233	0.164
Minimum–Maximum (d)	5–400	6–377	1–350	22–328	—	—	—

ulcer (DFU) that can be managed effectively with a variety of methods in an outpatient setting.[17,18] We propose that a complex wound is one in which there is a high risk of limb loss due to exposed deep tissue, ischemia, and infection that requires hospitalization with surgical intervention.

The overall healing rate across the surgical treatment strategies evaluated in this study is 51%. This rate of healing is similar and/or slightly less than what is reported for clinic-based DFU trials.[1–6] Additionally, "healing" a complex wound requires vascularized tissue coverage and re-epithelialization although the classic outpatient DFU trial only measures closure. Considering the chronicity, size, and depth of these wounds in a compromised host, these results are surprisingly good. Considering the alternative of a major amputation, limb preservation utilizing Integra, NPWT, LTF, or FTT seems to be viable options. Importantly, these treatment modalities did not negatively impact return to baseline function (74.1%). Whereas as a major amputation would impact return to function.

In the environment of the complex wound in the complex host, wound recurrence in this study was <20%. This may reflect the durability of the treatments despite the lack of a standardized postoperative care. Major amputation has reported stump complication rates of 9%–13%,[19,20] and annual reulceration of full thickness foot ulcers was as high as 60%.[21,22] Thus, the recurrence rates after limb salvage attempt were acceptable with the advantage of retaining the limb.

There are several limitations of this study. The retrospective nature of this study makes it susceptible to patient selection bias, surgeon-preferred procedure bias, and thus has poor internal validity. Further, the uneven number of patients in each of the cohorts makes results interpretation challenging. This study is designed in a registry style that attempted to be *inclusive* to more accurately reflect a real-world perspective. However, the investigative sites included only academic institutions, whereas a true real-world design would include urban and rural community hospitals and Veteran Affairs Hospitals. On the other hand, it can be argued that the complexity of this population is more likely managed at academic institutions such as those that participated in this study. Thus, the external validity of this study may be applicable to facilities treating less-complex patients and wounds because the extreme of this patient population is represented here. In essence, the retrospective registry design is observational or descriptive at best and assumptions should be carefully considered. Furthermore, whereas covariates were adjusted in the healing outcomes analysis to account for differences in patient profiles across cohorts, it was observed that patients with a higher level of complexity received LTF or free flap more frequently. The covariate adjustment to the regression was performed with the intent to minimize this procedure selection bias.

Due to study design, the authors readily concede that a number of factors may have affected patient and procedure selection bias in the data presented. However, it is important that each investigative site had ready access to a reconstructive plastic surgeon with the training and ability to employ any of the treatment modalities studied. Surgeon preferences are impossible to delineate in surgical outcome studies unless in a prospective randomized design with rigid eligibility criteria and standardized surgical technique.

The original concept of the plastic reconstructive ladder or elevator has been recently challenged with technologies including dermal substitutes and NPWT.[23] The data in this article are the first published to support this novel treatment paradigm. Another important pragmatic consideration is that options that are technically simpler than a FTT and LTF, such as application of Integra or NPWT, can provide similar outcomes. This is especially important for patients who are not candidate for such surgeries and/or institutions that do not have access to a reconstructive plastic surgeon with an interest or expertise in the diabetic lower extremity.

CONCLUSIONS

The complex lower extremity wound in a compromised host is a challenging problem. This is the first study examining the outcomes of commonly utilized treatment modalities in a single study. The study results presented inform future design of prospective studies that may help us determine if defined treatment algorithms can result in improved clinical outcomes.

Paul Jeong Kim, DPN, MS
Associate Professor
Georgetown Un iversity
Department of Plastic Surgery, MedStar
Georgetown University Hospital
3800 Resevoir Rd, NW
Washington, DC
Email: paul.j.kim@gunet.georgetown.edu

REFERENCES

1. Lavery LA, Fulmer J, Shebetka KA, et al; Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J.* 2014;11:554–560.
2. Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. *Adv Skin Wound Care.* 2014;27:356–362.
3. Veves A, Falanga V, Armstrong DG, et al; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care.* 2001;24:290–295.
4. Marston WA, Hanft J, Norwood P, et al; Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care.* 2003;26:1701–1705.
5. Niezgoda JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care.* 2005;18(5 pt 1):258–266.
6. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. *Wound Repair Regen.* 2015;23:891–900.
7. Lee CS, Chien CV, Bidwell JT, et al. Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: an analysis of the U.S. Nationwide inpatient sample. *BMC Cardiovasc Disord.* 2014;14:73.
8. Brown BJ, Crone CG, Attinger CE. Amputation in the diabetic to maximize function. *Semin Vasc Surg.* 2012;25:115–121.
9. Attinger CE, Brown BJ. Amputation and ambulation in diabetic patients: function is the goal. *Diabetes Metab Res Rev.* 2012;28(suppl 1):93–96.
10. Shuck J, Nolan J, Kanuri A, et al. The effect of positive post-debridement cultures on local muscle flap reconstruction of the lower extremity. *Plast Reconstr Surg.* 2015;136:9–10.

11. Sinkin JC, Reilly M, Cralley A, et al. Multidisciplinary approach to soft-tissue reconstruction of the diabetic Charcot foot. *Plast Reconstr Surg*. 2015;135:611–616.
12. Kim PJ, Attinger CE, Steinberg JS, et al. Integra bilayer wound matrix application for complex lower extremity soft tissue reconstruction. *Surg Technol Int*. 2014;24:65–73.
13. Ducic I, Attinger CE. Foot and ankle reconstruction: pedicled muscle flaps versus free flaps and the role of diabetes. *Plast Reconstr Surg*. 2011;128:173–180.
14. Attinger CE, Ducic I, Hess CL, et al. Outcome of skin graft versus flap surgery in the salvage of the exposed achilles tendon in diabetics versus nondiabetics. *Plast Reconstr Surg*. 2006;117:2460–2467.
15. Iorio ML, Goldstein J, Adams M, et al. Functional limb salvage in the diabetic patient: the use of a collagen bilayer matrix and risk factors for amputation. *Plast Reconstr Surg*. 2011;127:260–267.
16. Kim PJ, Attinger CE, Steinberg JS, et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg*. 2014;133:709–716.
17. Vowden K. Complex wound or complex patient? Strategies for treatment. *Br J Community Nurs*. 2005;suppl:S6, S8, S10 passim.
18. Tricco AC, Cogo E, Isaranuwatchai W, et al. A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. *BMC Med*. 2015;13:90.
19. Belmont PJ, Jr, Davey S, Orr JD, et al. Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program. *J Am Coll Surg*. 2011;213:370–378.
20. Aulivola B, Hile CN, Hamdan AD, et al. Major lower extremity amputation: outcome of a modern series. *Arch Surg*. 2004;139:395–399; discussion 399.
21. Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. *Diabet Med*. 2003;20:665–669.
22. Uccioli L, Faglia E, Monticone G, et al. Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care*. 1995;18:1376–1378.
23. Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. *Plast Reconstr Surg*. 2011;127(suppl 1):205S–212S.