Chronic Wound Management

Addressing the Challenge of Diabetic Foot Ulcers

Faculty

Paul J. Kim, DPM, MS

Associate Professor, Department of Plastic Surgery
Director of Research, Center for Wound Healing
Georgetown University School of Medicine
Washington, DC

Thomas Serena, MD, FACS, FACHM

CEO and Medical Director
Serena Group
Cambridge, Massachusetts

Robert J. Snyder, DPM, MSc, CWS

Professor and Director of Clinical Research
Director, Fellowship Program in Wound Healing and Clinical Research
Barry University SPM
Miami, Florida

Disclosures

- Dr. Kim: Grant/Research Supportï Acelity; Consultantï Acelity
- Dr. Serena: Grant/Research Supportï Celleration, KCI, MiMedix, Redress, Systagenix; Consultantï Cytomedix, KCI, MiMedix, Smith & Nephew; Board Memberï Association for the Advancement of Wound Care
- Dr. Snyder: Consultantï Acelity

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Learning Objectives

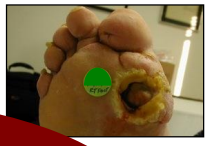
- Review relevant statistics and scope of diabetic foot ulcers (DFUS)
- Discuss science and evidence supporting current evaluation and management strategies for wound bed preparation in chronic diabetic foot ulcers including the role of silver, NPWT, Collagen ORC, instillation therapy and epidermal grafting
- Explore cases illustrating the role of advanced wound dressings in the management of diabetic foot ulcers

Overview of Foot Ulcers in Patients with Diabetes

Robert J. Snyder, DPM, MSc, CWS
Professor and Director of Clinical Research
Director, Fellowship Program in Wound Healing and Clinical Research
Barry University SPM
Miami, Florida

Diabetic Foot Ulcers

- One of the most common complications of diabetes
- Annual incidence 1% to 4%[1-2]
- Lifetime ris
- ~15%
- ~85%
- Peripheral neuropath



1 million amputations globally in patients with diabetes (every 30 seconds) In the US; 1200 amputations weekly

ation[3,5]

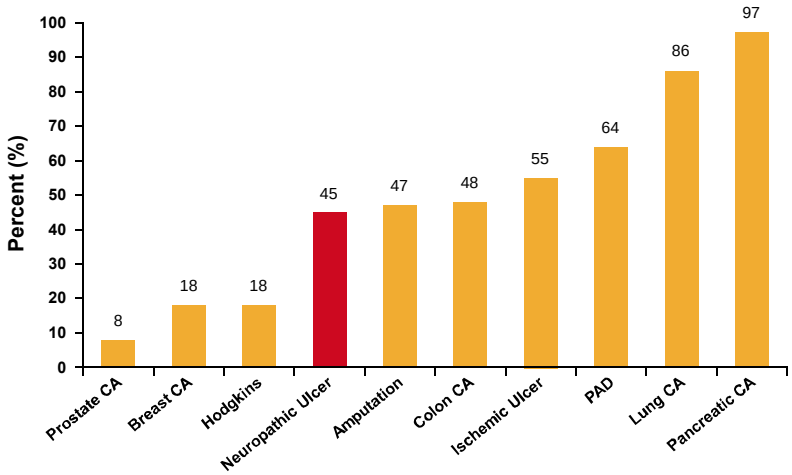
e

factor in diabetic foot ulcers[1-7]

  - Other factors: foot deformity, callus, trauma, infection, and peripheral vascular disease

1. Reiber GE, Ledoux WR. Epidemiology of diabetic foot ulcers and amputations: evidence for prevention. In: Wiliams R, et al, eds. *The Evidence Base for Diabetes Care.* Hoboken, NJ: John Wiley & Sons; 2002:641–665. 2. Boulton AJ, et al. *N Engl J Med.* 2004;351(1):48-55. 3. Sanders LJ. *J Am Podiatry Med Assoc.* 1994;84(7):322328. 4. Boulton AJ, et al. *Lancet.* 2005;366(9498):1719-1724. 5. Ramsey SD, et al. *Diabetes Care.* 1999;22(3):382-387. 6. Pecoraro RE, et al. *Diabetes Care.* 1990;13(5):513-521. 7. Apelqvist J, Larsson J. *Diabetes Metab Res Rev.* 2000:16(Suppl 1):S75-S83.

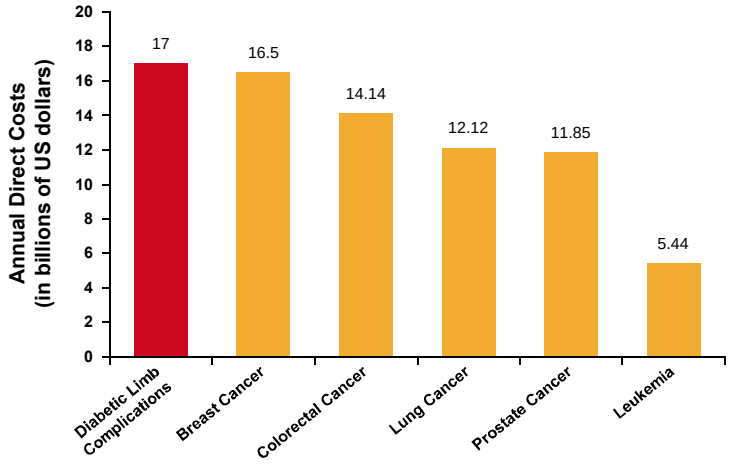
5 Year Mortality vs Cancer



CA = cancer; PAD = peripheral arterial disease.
Armstrong DG, et al. *Int Wound J.* 2007;4(4):286-287.

Cost vs Cancer

Cost of Diabetic Foot Compared with 5 Most Costly Cancers



Barshes NR, et al. *Diabet Foot Ankle.* 2013;4.

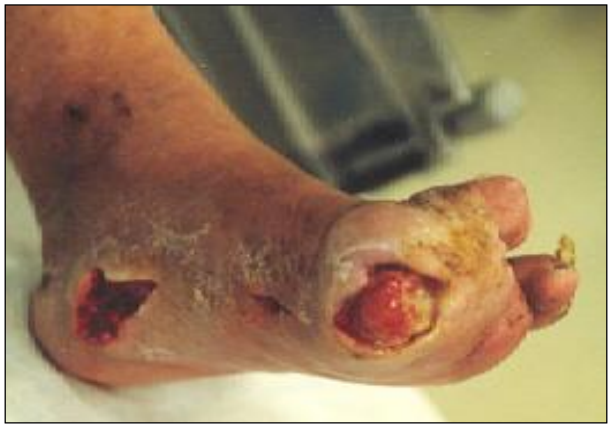
History of Foot Ulcer Increases Mortality among Individuals with Diabetes

10-Year Follow-up of the Nord-Trøndelag Health Study, Norway

- A large population based study examined the association between foot ulcers in patients with diabetes and mortality risk while controlling for disease factors
- Foot ulcers were independently associated with increased mortality risk
  - Patients with diabetes and a foot ulcer had an increased mortality risk of 2.3-fold (229%) compared to non-diabetic persons
  - In patients with diabetes, presence of a foot ulcer alone increased mortality risk by 47%

Iversen MM, et al. *Diabetes Care.* 2009;32(12):2193-2199.

Just Having a Neuropathic Foot Ulcer Is a Marker for Death!



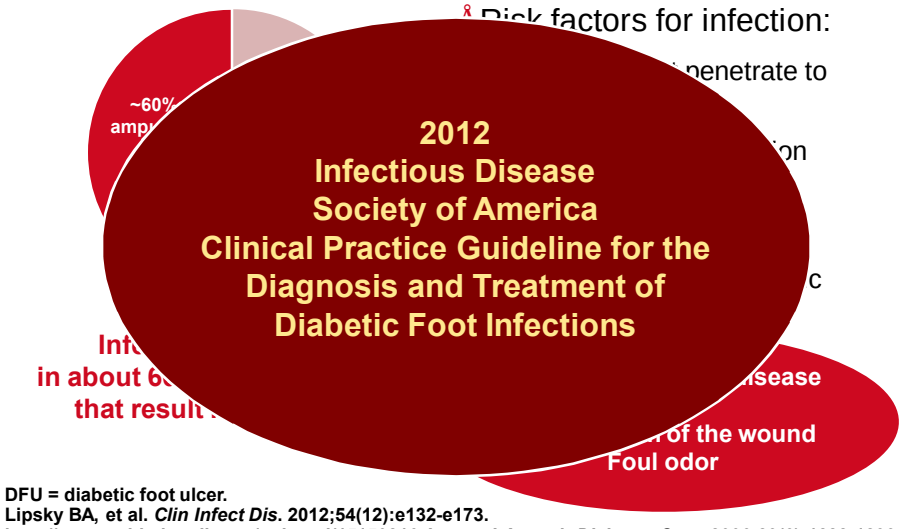
Snyder RJ. *Podiatry Management*. 2010.

The Extent of the Problem of ñProblem Woundsòé Diabetic Foot Ulcers

- In Denmark a multidisciplinary wound management program integrating vascular intervention and wound care has reduced LEA rate by 75%

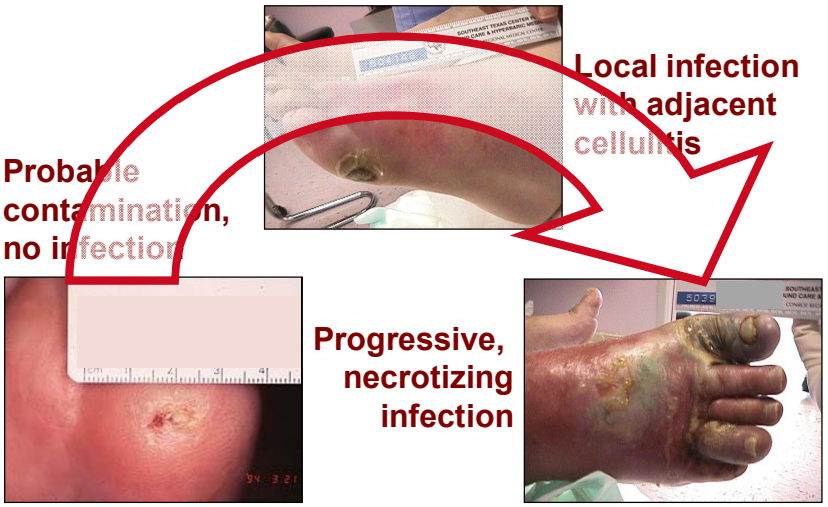
Gottrupp, F, et al. *Arch Surg*. 2001; 136: 765-772. Holstein P, et al. *Diabetologia*. 2000;43(7):844-847.

Infection Contributes to Various Complications Including Amputation

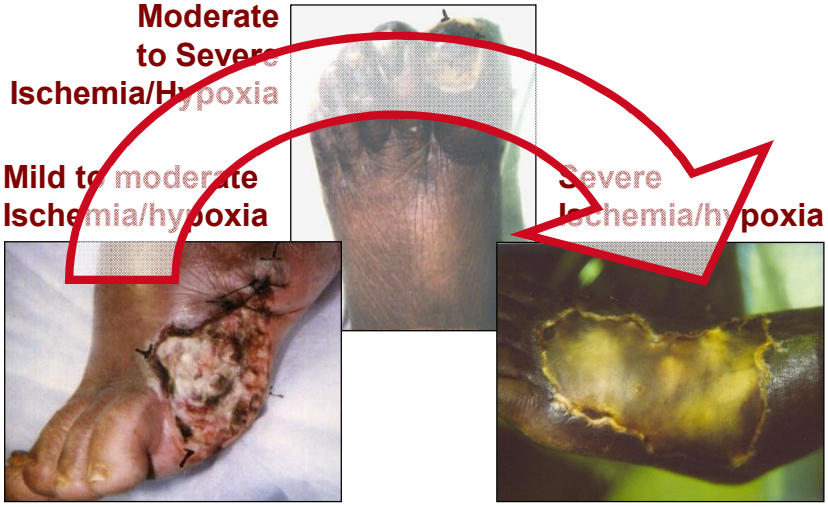


DFU = diabetic foot ulcer.
Lipsky BA, et al. *Clin Infect Dis*. 2012;54(12):e132-e173.
http://www.ncbi.nlm.nih.gov/pubmed/15150816. Lavery LA, et al. *Diabetes Care*. 2006;29(6):1288-1293.

Account for Spectrum of DFU Presentation

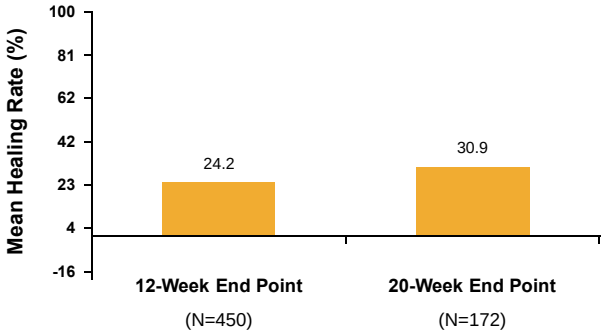


Account for Spectrum of DFU Presentation



Healing Neuropathic Ulcers: Results of a Meta-analysis

Weighted Mean Healing Rates

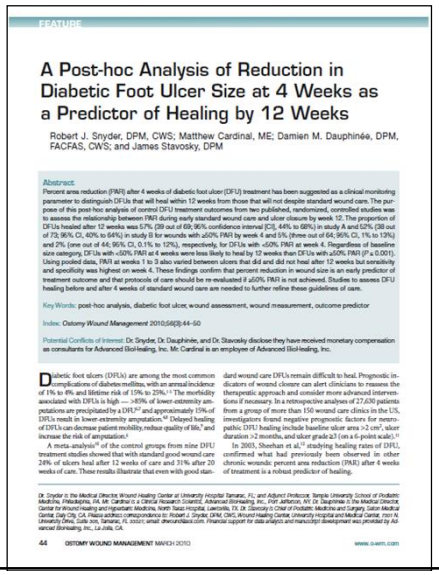


These data provide clinicians with a realistic assessment of their chances of healing neuropathic ulcers

Even with good, standard wound care, healing neuropathic ulcers in patients with diabetes continues to be a challenge

Margolis DJ, et al. *Diabetes Care.* 1999;22(5):692-695.

Post-hoc Analysis



FEATURE

A Post-hoc Analysis of Reduction in Diabetic Foot Ulcer Size at 4 Weeks as a Predictor of Healing by 12 Weeks

Robert J. Snyder, DPM, CWS; Matthew Cardinal, ME; Damien M. Dauphinée, DPM, FACFAS, CWS; and James Stavosky, DPM

Abstract

Percent area reduction (PAR) after 4 weeks of diabetic foot ulcer (DFU) treatment has been suggested as a clinical monitoring parameter to distinguish DFUs that will heal within 12 weeks from those that will not despite standard wound care. The purpose of this post-hoc analysis of control DFU treatment outcomes from two published, randomized, controlled studies was to assess the relationship between PAR during early standard wound care and ulcer closure by week 12. The proportion of DFUs healed after 12 weeks was 57% (39 out of 69; 95% confidence interval [CI], 44% to 68%) in study A and 52% (38 out of 73; 95% CI, 40% to 64%) in study B for wounds with ≥50% PAR by week 4 and 5% (three out of 64; 95% CI, 1% to 13%) and 2% (one out of 44; 95% CI, 0.1% to 12%), respectively, for DFUs with <50% PAR at week 4. Regardless of baseline size category, DFUs with <50% PAR at 4 weeks were less likely to heal by 12 weeks than DFUs with ≥50% PAR ($P \leq 0.001$). Using pooled data, PAR at weeks 1 to 3 also varied between ulcers that did and did not heal after 12 weeks but sensitivity and specificity was highest on week 4. These findings confirm that percent reduction in wound size is an early predictor of treatment outcome and that protocols of care should be re-evaluated if ≥50% PAR is not achieved. Studies to assess DFU healing before and after 4 weeks of standard wound care are needed to further refine these guidelines of care.

Key Words: post-hoc analysis, diabetic foot ulcer, wound assessment, wound measurement, outcome predictor

Index: *Ostomy Wound Management* 2010;56(3):44-50

Potential Conflicts of Interest: Dr. Snyder, Dr. Dauphinée, and Dr. Stavosky disclose they have received monetary compensation as consultants for Advanced BioHealing, Inc. Mr. Cardinal is an employee of Advanced BioHealing, Inc.

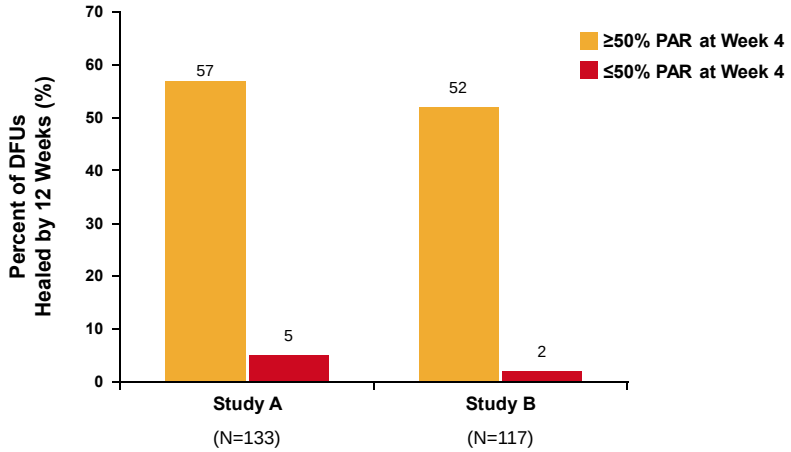
Diabetic foot ulcers (DFUs) are among the most common complications of diabetes mellitus, with an annual incidence of 1% to 4% and lifetime risk of 15% to 25%.[1-3] The morbidity associated with DFUs is high — >80% of lower-extremity amputations are precipitated by a DFU[4,5] and approximately 15% of DFUs result in lower-extremity amputation.[6] Delayed healing of DFUs can decrease patient mobility, reduce quality of life,[7] and increase the risk of amputation.[8]

A meta-analysis[9] of the control groups from nine DFU treatment studies showed that with standard good wound care 24% of ulcers heal after 12 weeks of care and 31% after 20 weeks of care. These results illustrate that even with good standard wound care DFUs remain difficult to heal. Prognostic indicators of wound closure can alert clinicians to reassess the therapeutic approach and consider more advanced interventions if necessary. In a retrospective analyses of 27,630 patients from a group of more than 150 wound care clinics in the US, investigators found negative prognostic factors for neuropathic DFU healing include baseline ulcer area >2 cm^2, ulcer duration >2 months, and ulcer grade ≥3 (on a 6-point scale).[11]

In 2003, Sheehan et al,[12] studying healing rates of DFU, confirmed what had previously been observed in other chronic wounds: percent area reduction (PAR) after 4 weeks of treatment is a robust predictor of healing.

Dr. Snyder is the Medical Director, Wound Healing Center at University Hospital Tamarac, FL, and Adjunct Professor, Temple University School of Podiatric Medicine, Philadelphia, PA. Mr. Cardinal is a Clinical Research Scientist, Advanced BioHealing, Inc., Fort Jefferson, NY. Dr. Dauphinée is the Medical Director, Center for Wound Healing and Hyperbaric Medicine, North Texas Hospital, Lewisville, TX. Dr. Stavosky is Chief of Podiatric Medicine and Surgery, Sutton Medical Center, Daly City, CA. Please address correspondence to: Robert J. Snyder, DPM, CWS, Wound Healing Center, University Hospital and Medical Center, 7201 N. University Drive, Suite 300, Tamarac, FL 33321; email: drwoundclass.com. Financial support for data analysis and manuscript development was provided by Advanced BioHealing, Inc., La Jolla, CA.

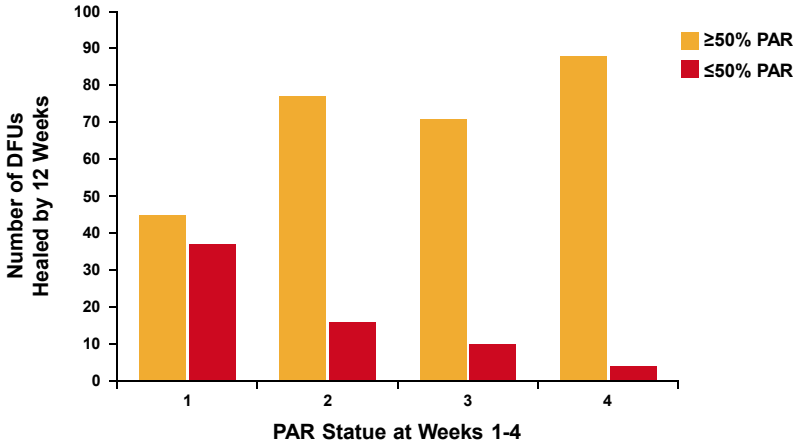
Association between PAR at Week 4 & DFU Closure at Week 12



Data was dichotomized by PAR of <50% or Ó50% by week 4 to assess the association of PAR with DFU closure by 12 weeks

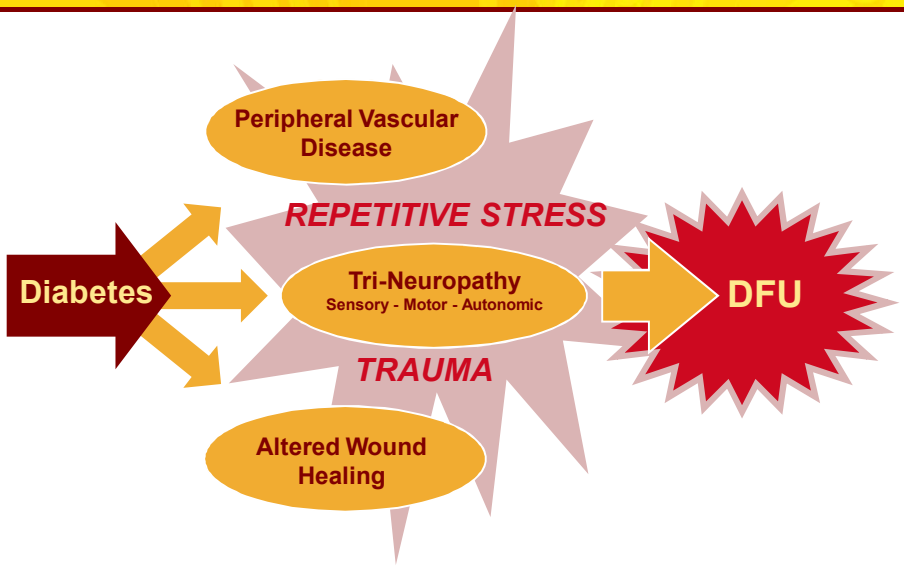
Snyder RJ, et al. *Ostomy Wound Manage.* 2010;56(3):44-50.

Number of DFUs that Healed by 12 Weeks

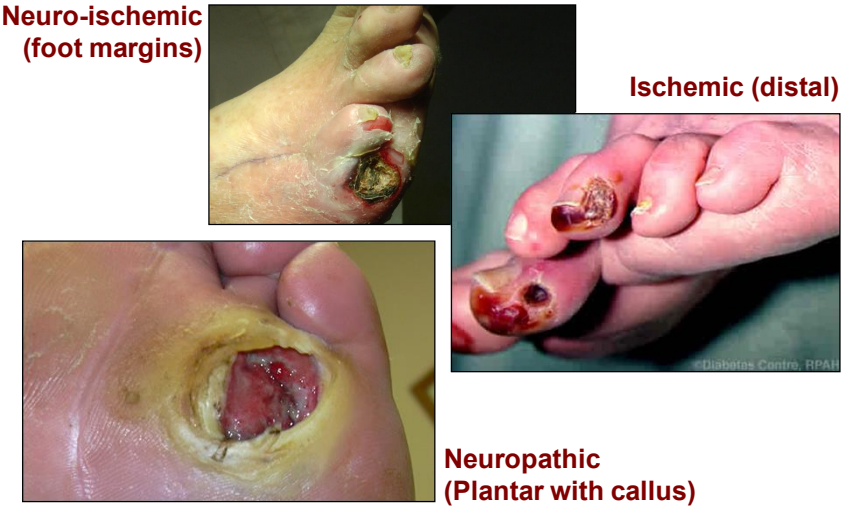


Results suggest that PAR at week 4 is the best prognostic indicator of healing by 12 weeks because it provides the highest specificity and sensitivity

Pathophysiology of DFU

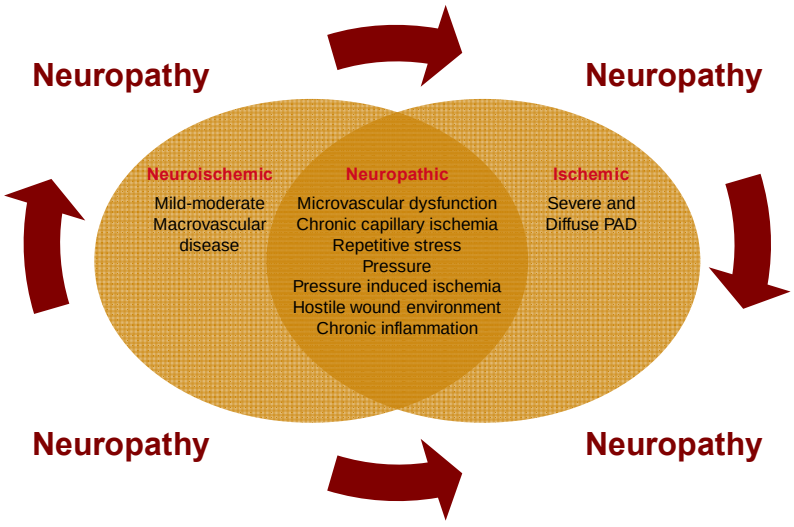


Foot ulcers in patients with diabetes can be classified as neuropathic, neuroischemic, or ischemic; however there is often an overlap between macro and microvascular disease that ñblurs the linesòbetween them



Snyder RJ, Cook R. *Textbook of Angiosomes*. 2013.

Snyder-Cook Circle of Overlapping Vascular Progression



Snyder RJ, Cook R. *Textbook of Angiosomes*. 2013.

DFUé Pathophysiology Final Common Pathways

- Infection
- Ischemia/hypoxia
- Cellular failure
- Pressure/trauma
- Inflammation
- Age

All final common pathways are implicated in DFU healing failure!!

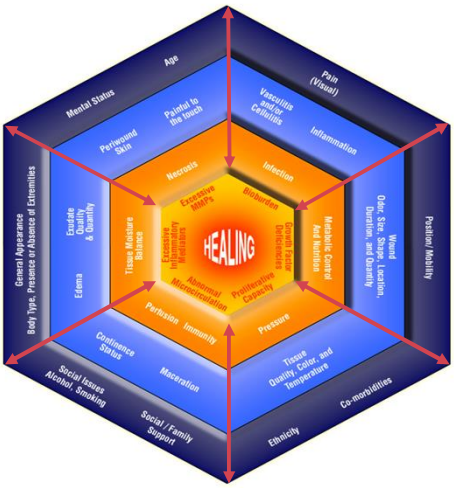
ñThink Like an Internist, Before You Act Like a Surgeonò

Wound management often requires a subtle balance between medical and surgical interventions

Wm. Ennis, DO 2009.

Core Healing Principles

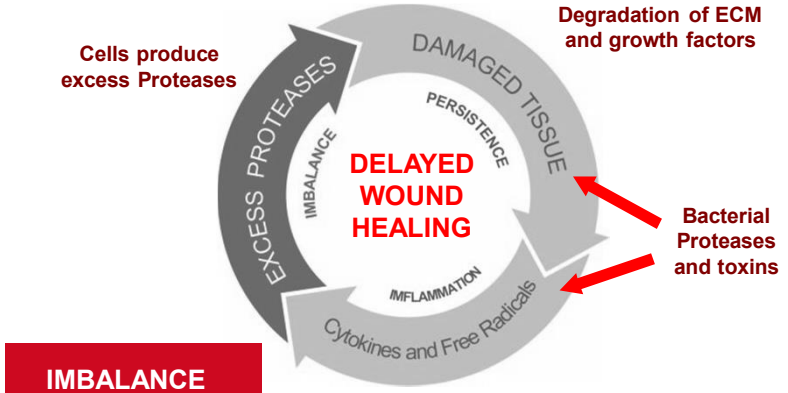
- Patient factors
- Physical aspects
- MACROscopic environment
- MICROscopic environment



Proposed Mechanisms for Chronicity in DFUs

Falanga V. *Blood Cells Mol Dis*. 2004;32(1):88-94. Kirsner R, Personal Communication 2010.

What Causes Delayed Healing?



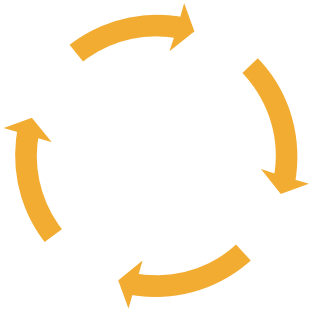
IMBALANCE causes delayed healing!

ECM = extracellular matrix.

Wysocki AB, et al. *J Invest Dermatol*. 1993;101(1):64-68. Harris IR, et al. *Exp Dermatol*. 1995;4(6):342-349.

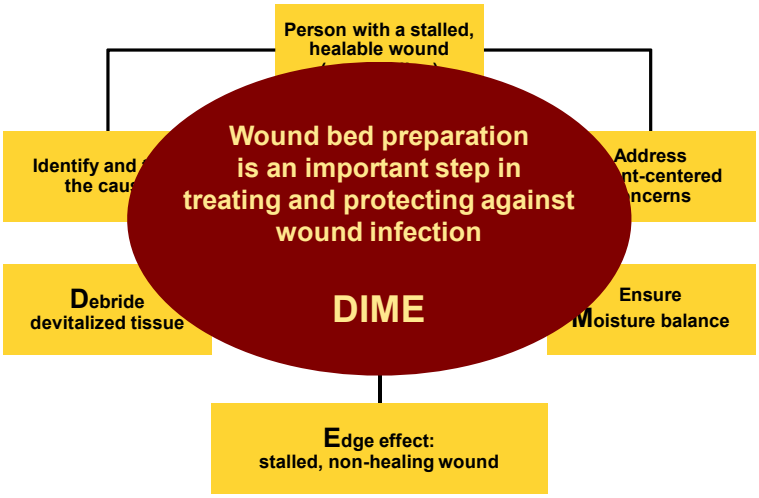
A Paradigm Shift in Wound Management Protocols:

Understanding the wound micro-environment may lead to better choices



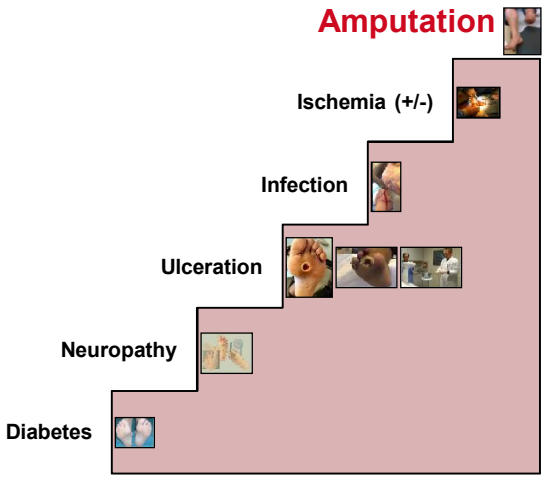
Snyder RJ. *Wounds*. 2005;(Suppl 1):S12-S17.

Wound Bed Preparation



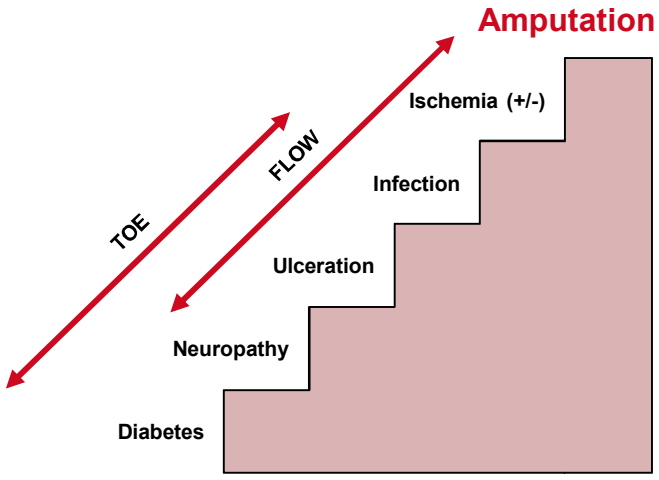
Sibbald RG, et al. Adv *Skin Wound Care*. 2011;24(9):415-436. Schultz GS, et al. *Wound Repair Regen*. 2003;11(Suppl 1):S1-S28.

Stairway to Amputation



Rogers LC, et al. *J Vasc Surg*. 2010;52(3 Suppl):23S-27S.

Stairway to Amputation



Rogers LC, et al. *J Vasc Surg*. 2010;52(3 Suppl):23S-27S.

Essential Questions

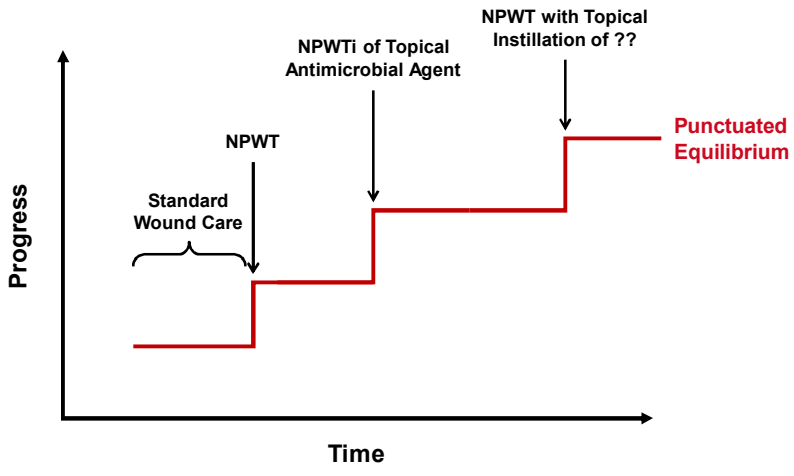
- What can we do to prepare the wound to support healing?
- What can we put on the wound to rebalance the wound micro-environment?
- What can we do to sustain ulcer healing?

Role of NPWT with Instillation in Diabetic Foot Ulcers

Paul J. Kim, DPM, MS
Associate Professor
Georgetown University School of Medicine
Director of Research
Department of Plastic Surgery
MedStar Georgetown University Hospital

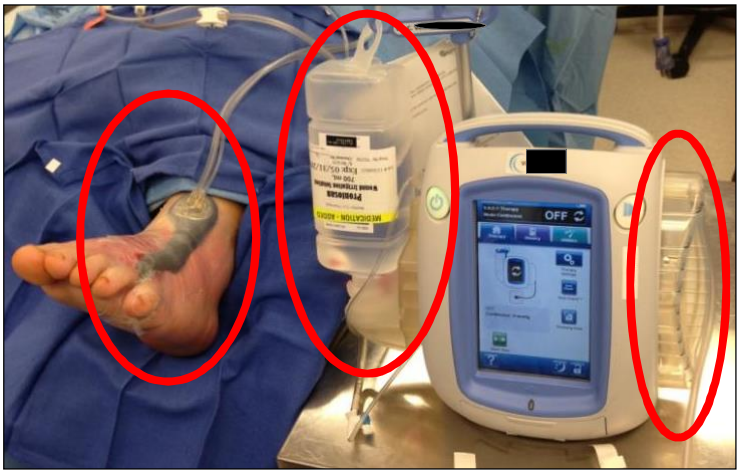
Georgetown University Hospital

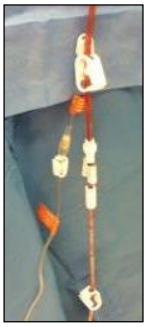
Evolution



NPWT = negative pressure wound therapy; NPWTi = negative pressure wound therapy with instillation.

NPWT with Instillation





Negative-Pressure Wound Therapy with Instillation: International Consensus Guidelines

Paul J. Kim, D.P.M., M.S.
Christopher E. Attinger, M.D.
John S. Steinberg, D.P.M.
Karen K. Evans, M.D.
Burkhard Lehner, M.D.
Christian Willy, M.D., Ph.D.
Larry Lavery, D.P.M., M.P.H.
Tom Wolvos, M.D., M.S.
Dennis Orgill, M.D., Ph.D.
William Ennis, D.O., M.B.A.
John Lantis, M.D.
Allen Gabriel, M.D.
Gregory Schultz, Ph.D.

Washington, D.C.; Heidelberg and Berlin, Germany; Dallas, Texas; Scottsdale, Ariz.; Boston, Mass.; Chicago, Ill.; New York, N.Y.; Vancouver, Wash.; Gainesville, Fla.

Background: Negative-pressure wound therapy with instillation is increasingly utilized as an adjunct therapy for a wide variety of wounds. Despite its growing popularity, there is a paucity of evidence and lack of guidance to provide effective use of this therapy.
Methods: A panel of experts was convened to provide guidance regarding the appropriate use of negative-pressure wound therapy with instillation. A face-to-face meeting was held where the available evidence was discussed and individual clinical experience with this therapy was shared. Follow-up communication among the panelists continued until consensus was achieved. The final consensus recommendations were derived through more than 80 percent agreement among the panelists.
Results: Nine consensus statements were generated that address the appropriate use of negative-pressure wound therapy with instillation. The question of clinical effectiveness of this therapy was not directly addressed by the consensus panel.
Conclusion: This document serves as preliminary guidelines until more robust evidence emerges that will support or modify these consensus recommendations. (*Plast. Reconstr. Surg.* 132: 1569, 2013.)

Kim PJ, et al. ***Plast Reconstr Surg*. 2013;132(6):1569-1579.**

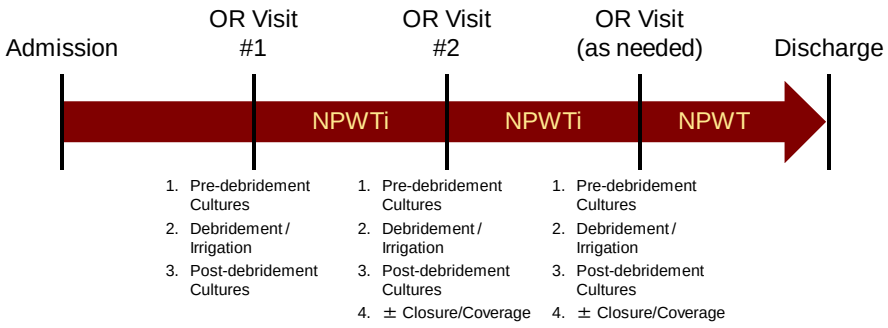
Consensus Statement #1

NPWTi can be used as an adjunct therapy after being appropriately treated and evaluated in the following wound types:

1. Acutely and chronically infected
2. Contaminated
3. **Diabetic**
4. Traumatic
5. Decubitus
6. Wounds with exposed bone
7. Wounds with underlying osteomyelitis
8. Infected wounds in the presence of orthopedic hardware or joint implants*
9. Painful
10. As a bridge between staged/delayed amputation
    - Appropriately treat and evaluate
    - Not a sole modality to treat infection

***no FDA indication.**
Kim PJ, et al. *Plast Reconstr Surg*. 2013;132(6):1569-1579.

Georgetown University Hospital Treatment Algorithm for Inpatient Care of the Infected Wound

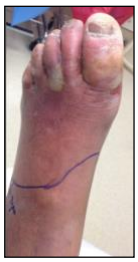
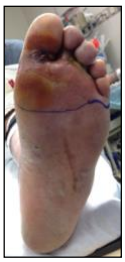
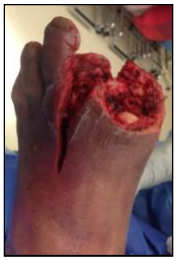
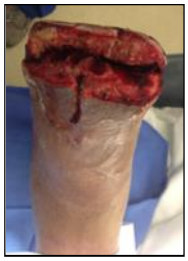
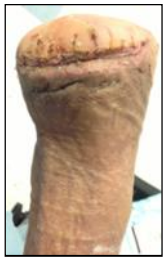
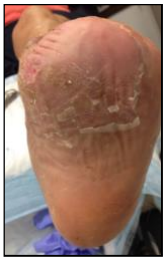


- Patients receive antibiotics per ID service at the time of admission
- Time elapsed between the first and second OR visit within 2 to 4 days
- Coverage or closure is dictated by the prior post-debridement culture results and clinical assessment

OR = operating room; ID = infectious diseases.

Case Study 1

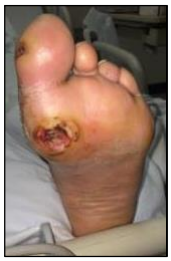
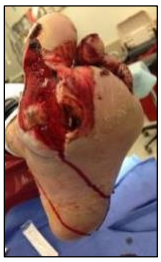
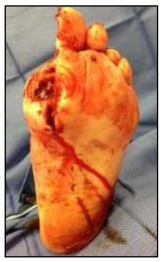
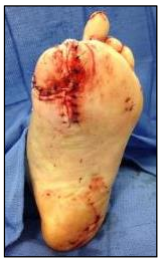
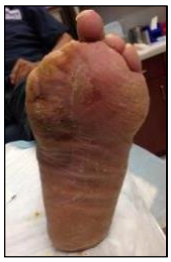
- **32-year-old male**
  - Type II DM, PVD, and peripheral neuropathy
  - Presented with cellulitis, abscess
- **Hospital course**
  - OR #1 I&D, NPWTi, post-debridement cultures + Strep B
  - OR #2 TMA + closure

DM = diabetes mellitus; PVD = peripheral vascular disease; I&D = incision and drainage; TMA = transmetatarsal amputation.

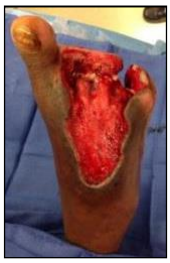
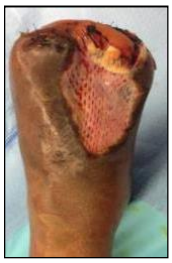
Case Study 2

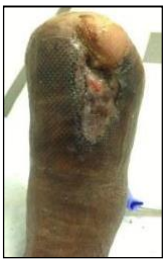
- **54-year-old male**
  - Type II DM, PVD, and peripheral neuropathy
  - Presented with cellulitis, abscess, osteomyelitis of the 1st metatarsal head, proximal phalanx of the hallux
- **Hospital course**
  - OR #1 I&D, 3 days of NPWTi, OR #2 filet of hallux closure
  - OR visit #1 post-debridement cultures positive methicillin-resistant *staphylococcus aureus*
  - OR visit #2 predebridement cultures no growth

Case Study 3

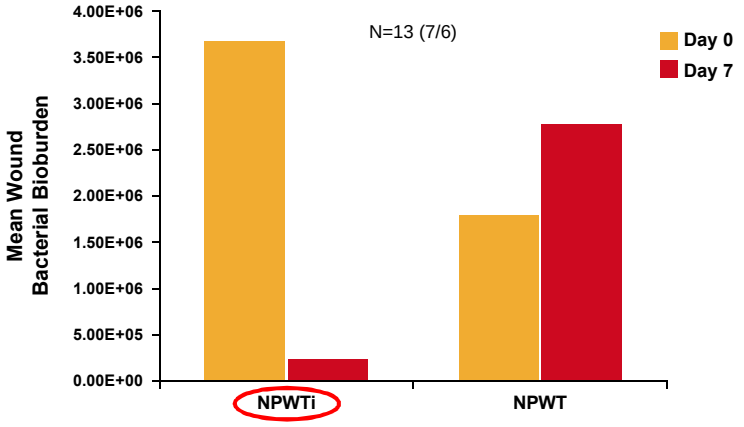
- **52-year-old female**
  - Poorly controlled DM
  - Hospital to hospital transfer with cellulitis, abscess, exposed tendon
- **Hospital Course**
  - OR #1 Initial I&D, 2 days with NPWTi, OR #2 Repeat I &D, 3 days of NPWTi, OR #3 filet of hallux, Integra
  - OR visit #1 post-debridement cultures positive strep, *Pseudomonas*
  - OR visit #2 post-debridement cultures positive strep
  - OR visit #3 predebridement cultures negative



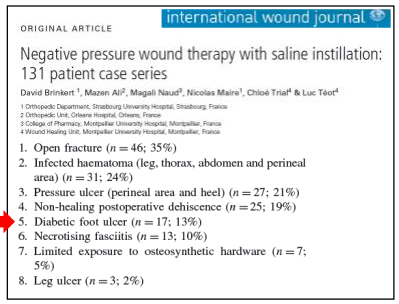
NPWTi with ¼ Strength (0.125%) Dakin's: Human

Bacterial Bioburden Change over Time with NPWTi vs NPWT



Goss SG, et al. *J Am Coll Clin Wound Spec.* 2014;4(4):74-80.

NPWTi with Normal Saline: Human



international wound journal

ORIGINAL ARTICLE

Negative pressure wound therapy with saline instillation: 131 patient case series

David Brinkert [1], Mazen Ali[2], Magali Naud[3], Nicolas Maire[1], Chloé Trial[4] & Luc Téot[4]

1 Orthopedic Department, Strasbourg University Hospital, Strasbourg, France
2 Orthopedic Unit, Orleans Hospital, Orleans, France
3 College of Pharmacy, Montpellier University Hospital, Montpellier, France
4 Wound Healing Unit, Montpellier University Hospital, Montpellier, France

1. Open fracture ($n = 46$; 35%)
2. Infected haematoma (leg, thorax, abdomen and perineal area) ($n = 31$; 24%)
3. Pressure ulcer (perineal area and heel) ($n = 27$; 21%)
4. Non-healing postoperative dehiscence ($n = 25$; 19%)
5. Diabetic foot ulcer ($n = 17$; 13%)
6. Necrotising fasciitis ($n = 13$; 10%)
7. Limited exposure to osteosynthetic hardware ($n = 7$; 5%)
8. Leg ulcer ($n = 3$; 2%)

Percentage of Patients Receiving Conventional NPWT *BEFORE* NPWTi

	Patients (%)
Centre 1 (Orléans)	42
Centre 2 (Montpellier)	37
Centre 3 (Strasbourg)	35
Mean	35

Percentage of Patients Receiving Conventional NPWT *AFTER* NPWTi

	Patients (%)
Centre 1 (Orléans)	51
Centre 2 (Montpellier)	72
Centre 3 (Strasbourg)	23
Mean	48.8

Percentage of Patients for Each Closure Method

	Skin Graft (%)	Flap (%)	Primary Suture (%)
Centre 1 (Orléans)	70	1	29
Centre 2 (Montpellier)	59	31	10
Centre 3 (Strasbourg)	44.30	20	35.50
Mean	57.76	17.33	24.83

Wound closure was achieved in 128 of 131 wounds

Brinkert D, et al. *Int Wound J.* 2013;10(suppl 1):56-60.

The Impact of Negative-Pressure Wound Therapy with Instillation Compared with Standard Negative-Pressure Wound Therapy: A Retrospective, Historical, Cohort, Controlled Study

Paul J. Kim, D.P.M., M.S.
Christopher E. Attinger, M.D.
John S. Steinberg, D.P.M.
Karen K. Evans, M.D.
Kelly A. Powers, D.P.M., M.S.
Rex W. Hung, M.D.
Jesse R. Smith, B.A., M.S.
Zinnia M. Rocha, B.S.
Larry Lavery, D.P.M., M.P.H.

Washington, D.C.; and Dallas, Texas

Background: Negative-pressure wound therapy with instillation is a novel wound therapy that combines negative pressure with instillation of a topical solution. **Methods:** This retrospective, historical, cohort-control study examined the impact of negative-pressure wound therapy with and without instillation. **Results:** One hundred forty-two patients (negative-pressure wound therapy, $n = 74$; therapy with instillation, 6-minute dwell time, $n = 34$; and therapy with instillation, 20-minute dwell time, $n = 34$) were included in the analysis. Number of operative visits was significantly lower for the 6- and 20-minute dwell time groups (2.4 ± 0.9 and 2.6 ± 0.9, respectively) compared with the no-instillation group (3.0 ± 0.9) ($p \leq 0.05$). Hospital stay was significantly shorter for the 20-minute dwell time group (11.4 ± 5.1 days) compared with the no-instillation group (14.92 ± 9.23 days) ($p \leq 0.05$). Time to final surgical procedure was significantly shorter for the 6- and 20-minute dwell time groups (7.8 ± 5.2 and 7.5 ± 3.1 days, respectively) compared with the no-instillation group (9.23 ± 5.2 days) ($p \leq 0.05$). Percentage of wounds closed before discharge and culture improvement for Gram-positive bacteria was significantly higher for the 6-minute dwell time group (94 and 90 percent, respectively) compared with the no-instillation group (62 and 63 percent, respectively) ($p \leq 0.05$). **Conclusion:** The authors' results suggest that negative-pressure wound therapy with instillation (6- or 20-minute dwell time) is more beneficial than standard negative-pressure wound therapy for the adjunctive treatment of acutely and chronically infected wounds that require hospital admission. (*Plast. Reconstr. Surg.* 133: 709, 2014.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Kim PJ, et al. *Plast Reconstr Surg.* 2014;133(3):709-716

Demographics

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*P**	Value (%)	*P*†
Age, yr Mean ± SD	58 ± 13	63 ± 16		55 ± 17	
Range	18-95	20-88	.11	18-90	.43
Male sex	38 (51)	20 (59)	.54	22 (65)	.22
Race					
African American	21 (28)	17 (50)	.03	15 (44)	.13
Caucasian	39 (53)	16 (47)	.68	14 (41)	.30
Hispanic	2 (6)	1 (3)	1.0	0 (0)	1.0
Asian	1 (3)	1 (1)	1.0	1 (3)	.72
Other	6 (8)	5 (15)	.32	4 (12)	
BMI, kg/m^2	32 ± 9.14	29.6 ± 6.77	.17	32.9 ± 8.89	.63
Current smoker	7 (9)	2 (6)	.72	1 (3)	.74
Comorbitities					
Diabetes type 1	7 (9)	2 (6)	.72	4 (12)	.74
Diabetes type 2	35 (47)	18 (53)	.54	16 (47)	1.0
ESRD	22 (30)	12 (35)	.66	4 (12)	.05
PVD	27 (36)	10 (29)	.52	11 (32)	.83
Autoimmune disease	4 (5)	4 (12)	.26	3 (9)	.68
Hemiparalysis	1 (1)	2 (6)	.23	1 (3)	.53
History of cancer	6 (8)	2 (6)	1.0	3 (9)	1.0
Kidney/pancreas transplant	3 (4)	1 (3)	1.0	1 (3)	1.0

NPWTi 6 = negative-pressure with instillation 6-minute dwell time; NPWTi 20 = negative-pressure with instillation 20-minute dwell time; BMI = body mass index; ESRD = end-stage renal disease.
***Comparison of NPWT and NPWT 6. †Comparison of NPWT and NPWTi 20.**
Kim PJ, et al. *Plast Reconstr Surg*. 2014;133(3):709-716.

Wound Cause and Anatomical Location

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*P**	Value (%)	*P*†
Primary Cause					
Ischemic wound	17 (23)	7 (21)	1.0	8 (24)	1.0
Neuropathic wound	16 (22)	6 (18)	.80	7 (21)	1.0
Decubitus wound	16 (22)	6 (18)	.80	4 (12)	.29
Surgical wound	17 (23)	9 (26)	.81	10 (29)	.48
Venous	3 (4)	2 (6)	05	1 (3)	1.0
Traumatic	4 (5)	2 (6)	1.0	1 (3)	1.0
Other (unclear)	3 (4)	2 (6)	.65	3 (9)	.38
Anatomical Location					
Forefoot	12 (16)	6 (18)	1.0	12 (35)	.04
Midfoot	12 (16)	3 (9)	.38	3 (9)	.38
Hindfoot / heel	22 (30)	6 (18)	.24	3 (9)	.03
Transmetatarsal amputation site	1 (1)	2 (6)	.23	2 (6)	.23
Ankle	7 (9)	4 (12)	.74	3 (9)	1.0
Leg	7 (9)	4 (12)	.74	6 (18)	.40
Below-knee amputation site	1 (1)	2 (6)	.23	0 (0)	
Knee	1 (1)	1 (3)	.53	2 (6)	.23
Thigh	3 (4)	1 (3)	1.0	0 (0)	
Back / buttock	2 (3)	2 (6)	.59	3 (9)	.32
Abdomen	5 (7)	3 (9)	.71	0 (0)	
Arm	1 (1)	0 (0)	1.0	0 (0)	

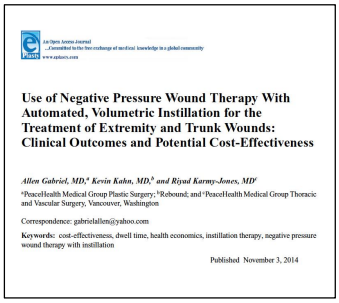
***Comparison of NPWT and NPWT 6. †Comparison of NPWT and NPWTi 20.**
Kim PJ, et al. *Plast Reconstr Surg*. 2014;133(3):709-716.

Results: Outcomes

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*P**	Value (%)	*P*†
No. of OR visits	3.0 ± 0.9	2.4 ± 0.9	.04	2.6 ± 0.9	.003
Length of hospital stay	14.92 ± 9.2	11.9 ± 7.8	.10	11.4 ± 5.1	.03
Time to final surgical procedure	9.23 ± 5.2	7.8 ± 5.2	.04	7.5 ± 3.1	.002
Closed	46 (62)	32 (94)	.0004	27 (80)	.08
Remained closed at 1 mo	28 (61)	24 (75)	.23	14 (52)	.47
Overall culture improvement	28 (38)	20 (59)	.06	17 (50)	.30
Culture improvement with Gram-negative, *Corynebacterium*, and yeast excluded	17 (63)	19 (90)	.0001	13 (65)	.77

*Comparison of NPWT and NPWT 6. †Comparison of NPWT and NPWTi 20.
Kim PJ, et al. *Plast Reconstr Surg*. 2014;133(3):709-716.

NPWTi with Saline or Polyhexanide: Human



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Use of Negative Pressure Wound Therapy With Automated, Volumetric Instillation for the Treatment of Extremity and Trunk Wounds: Clinical Outcomes and Potential Cost-Effectiveness

Allen Gabriel, MD,[a] Kevin Kahn, MD,[b] and Riyad Karmy-Jones, MD[c]

[a]PeaceHealth Medical Group Plastic Surgery; [b]Rebound; and [c]PeaceHealth Medical Group Thoracic and Vascular Surgery, Vancouver, Washington

Correspondence: gabrielallen@yahoo.com

Keywords: cost-effectiveness, dwell time, health economics, instillation therapy, negative pressure wound therapy with instillation

Published November 3, 2014

Comparative Outcomes between NPWTi-d and NPWT Patients

	NPWTi-d	NPWT	*P*
Patients, n	48	34	
Mean hospital stay, d	8.1	27.4	<.0001
Mean time to wound closure, d	4.1	20.9	<.0001
Mean surgical debridements in the OR	2	4.4	<.0001
LOT, d	4.1	20.9	<.0001

Potential Cost-Effectiveness of NPWTi-d

	NPWTi-d	NPWT	Difference
Patients, n	48	34	
Trips to OR for debridement	2.0	4.4	2.4
Mean cost of an OR debridement	$3393	$3393	ð
Total OR debridement cost	$6786	$14,929	$8143
Length of NPWTi-d, d	ð	20.9	20.9
Daily cost of therapy	$194.80	$106.08	$88.72
Total therapy costs	$799	$2217	$1418

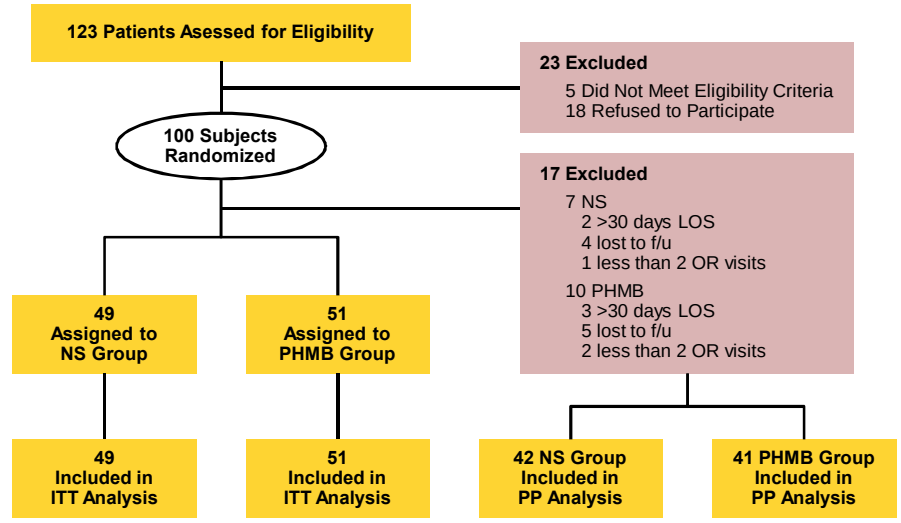
d = days; LOT = length of therapy.
Gabriel A, et al. *Eplasty*. 2014;14:328-338.

Saline vs 0.1% Polihexanide + 0.1% Betaine

- Prospective, randomized, comparative effectiveness study
  - NPWTi (V.A.C. Ulta System with Veraflo®, Acelity Inc.)
  - Normal saline vs 0.1% polihexanide + 0.1% betaine (PHMB) (Prontosan®, B. Braun Medical Inc.)
- 4 surgeons, single institution
- Device settings
  - 20 minute dwell, 2 hours of negative pressure
- Eligibility criteria
  - Admission for infected wounds that require OR debridement
  - All wound types
- Both ITT and PP analysis

PHMB = polyhexamethylene biguanide; ITT = intention-to-treat; PP = per protocol.
Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Analysis



LOS = length of stay; f/u = follow-up; NS = normal saline.
Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Demographics and Comorbidities ITT and PP

ITT				PP		
NS (%)	PHMB (%)	*P*		NS (%)	PHMB (%)	*P*
28 (57.14)	43 (84.31)	.004*	Male	27 (64)	34 (83)	081
21 (42.86)	8 (15.69)	.004*	Female	15 (36)	7 (17)	.082
59.64 ± 15.36	55.94 ± 13.86	.208	Age	60.66 ± 15.13	58.24 ± 12.42	.430
29.39 ± 7.86	29.46 ± 13.86	.977	BMI	29.10 ± 8.19	29.80 ± 6.99	.680
21 (42.9)	21 (41.2)	1	AA	19 (51.4)	15 (38.4)	.505
22 (44.9)	23 (45.1)	1	Caucasian	17 (45.9)	19 (48.7)	.661
1 (2.0)	5 (9.8)	.205	Asian	1 (2.7)	5 (12.8)	.109
18 (36.7)	21 (41.2)	.686	Amp Hx	16 (38.1)	17 (41.5)	.824
8 (16.3)	5 (9.8)	.384	CA Hx	6 (14.3)	5 (12.2)	1
26 (53.1)	29 (56.9)	.841	DM	22 (52.4)	24 (58.5)	.661
6 (12.2)	5 (9.8)	.758	ESRD	4 (9.5)	3 (7.3)	1
1 (2.0)	4 (7.8)	.363	CAD	1 (2.4)	3 (7.3)	.360
3 (6.1)	4 (7.8)	1	CVA Hx	2 (4.8)	4 (9.8)	.433
6 (12.2)	3 (5.9)	.313	HEP	3 (7.1)	2 (4.9)	1
2 (4.1)	2 (3.9)	1	RA	1 (2.4)	2 (4.9)	.616
9 (18.4)	12 (23.5)	.626	PVD	9 (21.4)	9 (22.0)	1
2 (4.1)	3 (5.9)	1	Transplant Hx	1 (2.4)	2 (4.9)	.616
21 (42.9)	19 (37.3)	.684	Smoking Hx	17 (40.5)	16 (39.0)	1

Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Wound Etiology ITT and PP

ITT				PP		
NS (%)	PHMB (%)	*P*		NS (%)	PHMB (%)	*P*
14 (28.6)	17 (33.3)	.669	Neuropathic	14 (33.3)	13 (31.7)	1
16 (32.7)	20 (39.2)	.537	Surgical	13 (31.0)	16 (39)	.495
3 (6.1)	2 (3.9)	.675	Venous	2 (4.8)	2 (4.9)	1
6 (12.2)	6 (11.8)	1	Ischemic	6 (14.3)	5 (12.2)	1
7 (14.3)	4 (7.8)	.352	Decubitus	4 (9.5)	4 (9.8)	1
1 (2.1)	1 (2.0)	1	Trauma	1 (2.4)	0	-
2 (4.1)	1 (2.0)	.614	Other	1 (4.8)	1 (2.4)	1

Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Wound Location ITT and PP

ITT				PP		
NS (%)	PHMB (%)	*P*		NS (%)	PHMB (%)	*P*
10 (20.4)	15 (29.4)	.359	Forefoot	10 (23.8)	13 (31.7)	.469
3 (6.1)	5 (9.8)	.716	Midfoot	2 (4.8)	3 (7.3)	.676
5 (10.2)	6 (11.8)	1	Hindfoot / heel	3 (7.1)	5 (12.2)	.483
5 (10.2)	1 (2)	.108	TMA site	6 (14.3)	1 (2.4)	.109
9 (18.4)	10 (19.6)	1	Ankle	7 (16.7)	9 (22)	.588
5 (10.2)	2 (3.9)	.264	Lower Leg	5 (11.9)	1 (2.4)	.202
1 (2.0)	5 (9.8)	.205	BKA, AKA site	1 (2.4)	4 (9.8)	.202
3 (6.1)	3 (5.9)	1	Knee	3 (7.1)	1 (2.4)	.616
1 (2)	1 (2)	1	Thigh	0	1 (2.4)	-
4 (8.2)	0	-	Back / buttock	3 (7.1)	0	-
3 (6.1)	3 (5.9)	1	Abdomen	2 (4.8)	3 (7.3)	.676

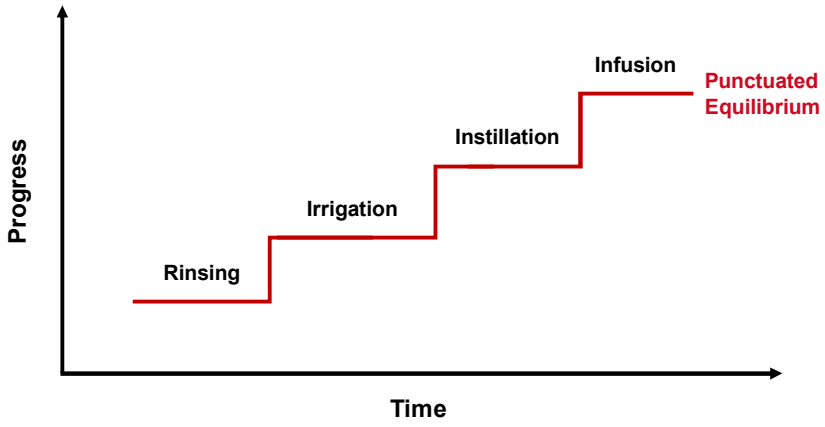
Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Outcomes ITT and PP

ITT				PP		
NS (%)	PHMB (%)	*P*		NS (%)	PHMB (%)	*P*
2.51 ± 0.89	2.75 ± 0.87	.185	NO	2.52 ± 0.92	2.76 ± 0.69	.193
13.63 ± 11.74	14.51 ± 8.98	.675	LOS	11.74 ± 6.01	14.19 ± 6.54	.079
5.73 ± 3.75	7.73 ± 5.49	.038*	Time to FSP	5.57 ± 3.61	7.46 ± 4.42	.035*
42 (85.7)	47 (92.2)	.352	CC	39 (92.9)	39 (95.1)	1
34 (69)	33 (65)	.832	F/U CC	32 (82.1)	30 (76.9)	.895

NO = Number of Operations; FSP = Final Surgical Procedure (Days); CC = Closed, Covered.
*Statistically significant, *P*<.04.
Kim, PJ. Presented at: Diabetic Limb Salvage Conference; October 2014; Washington, DC.

Evolution



Conclusions

- NPWTi has a role in diabetic foot ulcer treatment
- Currently
  - Adjunct for infection/biofilm clearance
- Future
  - Directly potentiate healing

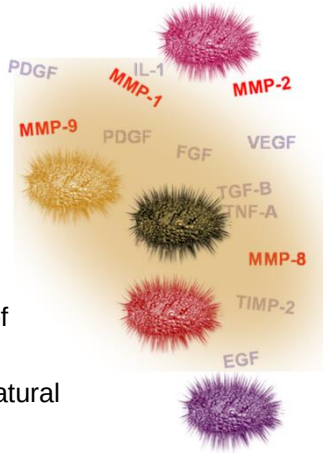
From Beginning to End: Orc/Collagen Silver and Epidermal Grafting in Managing DFUs

Thomas E. Serena, MD, FACS, FACHM MAPWCA
Founder & Chief Executive Officer SerenaGroupÊ
Cambridge, MA

SerenaGroup

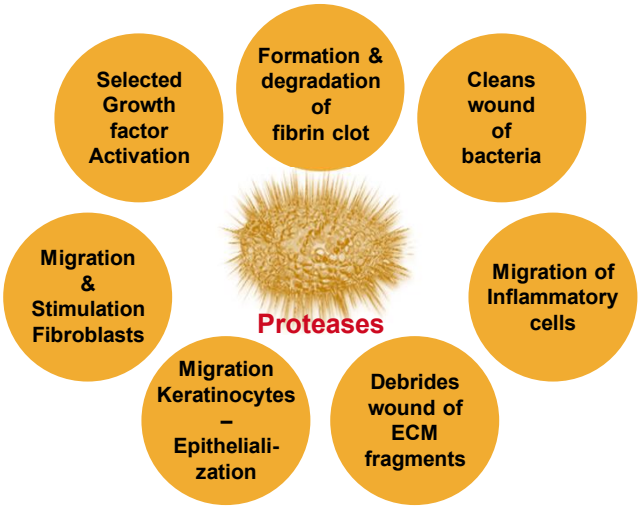
Proteases in Wound Healing

- Proteases are protein-degrading enzymes
- **2 categories of proteases**
  - Serine proteases eg. Elastase
  - Matrix metalloproteases eg. MMPs
- Function optimally under physiological conditions
- Proteases are required for wound healing
- Collectively, can degrade all components of the extracellular matrix
- Normally controlled at the tissue level by natural inhibitors eg, TIMPs, AAT
- Synthesised and stored as inactive pro-enzymes



Armstrong DG, Jude EB. *J Am Podiatr Med Assoc*. 2002;92(1):12-18. Ovington LG. *Ostomy Wound Manage*. 2002;48(6 Suppl):3-7. Nwomeh BC, et al. *Clin Plast Surg*. 1998;25(3):341-356.

Proteases in Normal Wound Healing

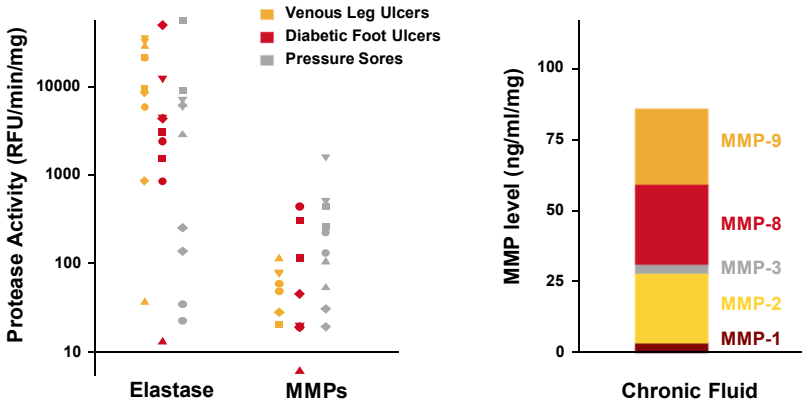


Nwomeh BC, et al. *Clin Plast Surg*. 1998;25(3):341-356.

Proteases in Chronic Wounds

Proteases are in excess in chronic wounds

Inflammatory Proteases Predominate

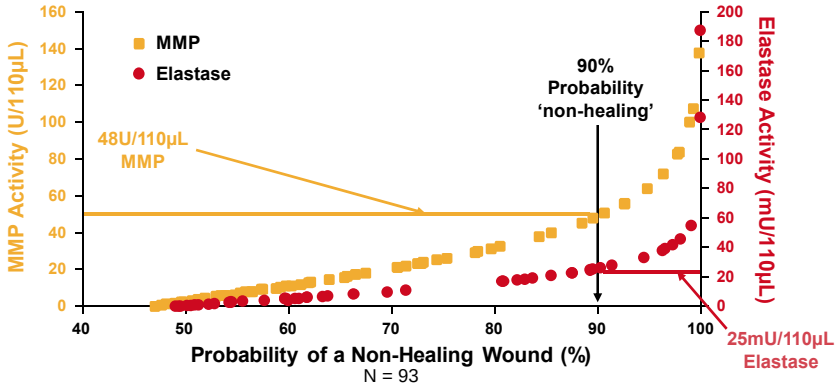


Published Data: Cullen B, et al. *Wound Repair Regen*. 2002;10(1):16-25.

Defining EPA Correlation to Healing Status

- Defining "elevated" in EPA through statistical analysis
- A chronic with EPA has a 90% probability it won't heal (without appropriate intervention)

Probability of a Non-Healing Wound vs Protease Activity Level



Serena T, et al. Protease activity levels associated with healing status of chronic wounds. Poster, Wounds UK 2011.

Excessive Proteases in Chronic Wounds

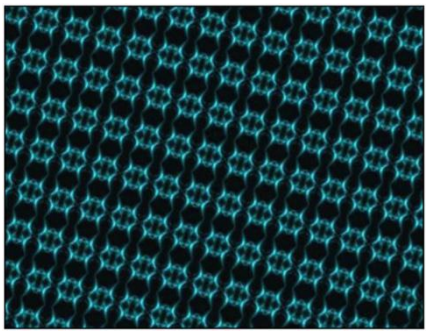
- Numerous studies have found elevated levels of MMPs in chronic wounds:

Venous Leg Ulcers *Wysocki, et al. J Invest Dermatol. 1993;101:64*	↑ ***Collagenase***
	↑ ***Gelatinase***
Diabetic Foot Ulcers *Cullen, et al. Wound Rep Reg. 2002;10:16*	↑ ***Elastase***
	↑ ***Plasmin***

Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. *J Invest Dermatol.* 1993 Jul;101(1):64-8. Cullen B, Smith R, McCullochE, Silcock D, Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. *Wound Rep Reg.* 2002;10:16-25.

ORC/Collagen

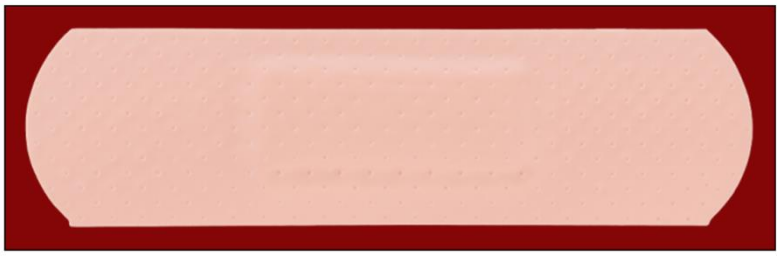
- 45% ORC
- 55% collagenð bovine
- Bioresorbable
- Open-pored matrix



Hall J. *Podiatry Today*. 2002;15(8):26-30.

Benefits of ORC/Collagen Combination

- Binds more MMPs than ORC or collagen alone



Cullen B. *Ostomy Wound Manage*. 2002;42(Suppl 6):8-13.

ORC/Collagen

- Acts by binding and inactivating MMPs
- ORC stimulates cell proliferation
- Protects growth factors
- With or without silver

Cullen B, et al. *Int J Biochem Cell Biol.* 2002;34(12):1544-1556. Cullen B, et al. *Wound Repair Regen.* 2002;10(1):16-25.

Collagen/ORC Clinical Evidence

Evidence – an overview:

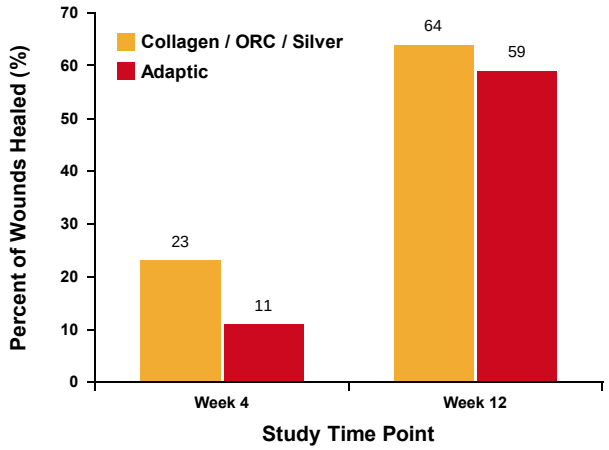
7 RCTs - 569 patients

DFUs 3 RCTs	VLUs 3 RCTs	PUs 1 RCT

Collagen / ORC:

Author	Wound Type	Endpoint
Wollina, U	VLU	Reduction in wound size Good / excellent healing response
Vin, F	VLU	Healing rate after 12wks (*P*<.0001)
Lâzaro-Martinez, J	DFU	Complete healing
Vevez, A	DFU	Complete wound closure Increased efficacy for <6 month-old wounds
Nisi, G	PU	Complete healing

ORC/Collagen/Silver

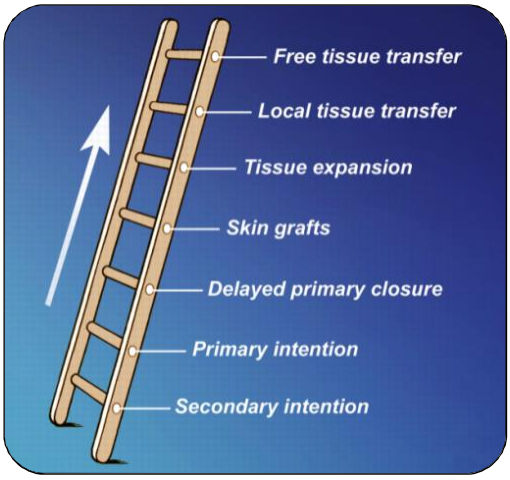


Serena, et al. Submitted to Advances in Skin and Wound Care 2015.

Suction Blister Epidermal Grafting

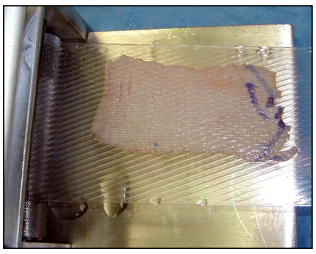
DSL# 13-0232.GMAAP.P2P14.O

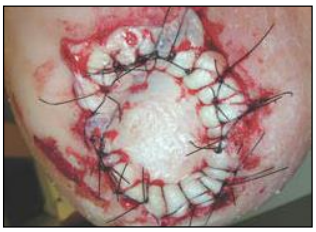
The Reconstructive Ladder



SmartMD. http://sackidmd.blogspot.com/2012/05/reconstructive-ladder-or-why-does.html. Accessed July 21, 2013.

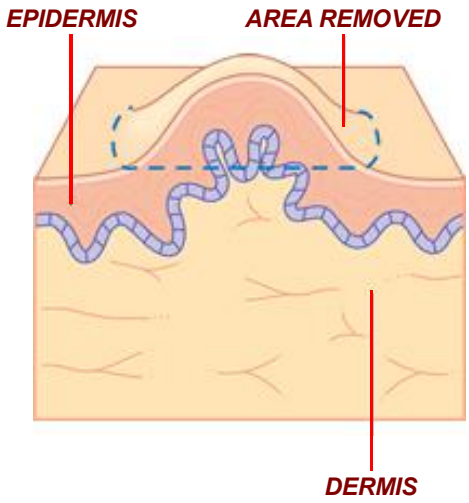
Definitions: Grafting





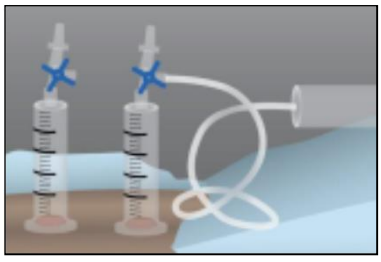
- **Autografts**
  - Transfer skin from one part of the body to another
- **Allografts**
  - Skin transplanted from a different body
- **Xenografts**
  - Grafts from animal sources
- **Biologic skin grafts**
  - Combinations of living cells and collagen matrix
- **Composite grafts**
  - Contain more than one type of tissue

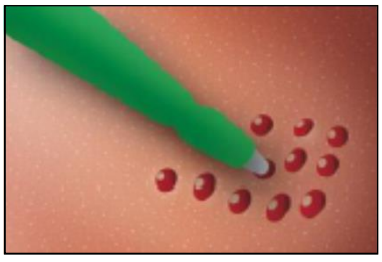
Epidermal Grafts (ñPinch Graftsò)



Epidermal Harvesting Techniques

- Miniature punch grafting
- Cultured epidermal autografts
- SBEG





Savant SS. *Indian J Dermatol Venereaol Leprol*. 1992;58(5):3130-31344. Gallico CG, et al. *N Engl J Med*. 1984;311(7): 448-451. Falabella R. *Dermatol Surg*. 2005;31(10):1277-1284.

Epidermal Graft Effectiveness Data

- Biswas A, et al. The Micrograft concept for wound healing: strategies and application. *J Diabetes Sci Technol*. 2010;4(4):808-819.
- Hsieh CS, et al. Five yearsô experience of the modified Meek technique in the management of extensive burns. *Burns*. 2008;34(3):350ï 354.
- Ichiki Y, Kitajima Y. Successful treatment of scleroderma-related cutaneous ulcer with suction blister grafting. *Rheumatol Int*. 2008;28(3):299ï 301.
- Costanzo U, et al. Autologous suction blister grafting for chronic leg ulcers. *J Eur Acad Dermatol Venereol*. 2008;22(1):7ï 10.
- Njoo MD, et al. A Systematic review of autologous transplantation methods in vitiligo. *Arch Dermatol*. 1998;134(12):1543-1549.
- Patel NS, Paghdal KV, Cohen GF. Advanced treatment modalities for vitiligo. *Dermatol Surg*. 2012;38(3):381-391.
- Li J, et al. Suction blister epidermal grafting using a modified suction method in the treatment of stable vitiligo: a retrospective study. *Dermatol Surg*. 2011;37(7):999-1006.

Rapid Healing of Intractable DFUs with Exposed Bones following a Novel Therapy of Exposing Bone Marrow Cells and Then Grafting Epidermal Sheets

- A prospective study of 38 patients designed to assess the effectiveness of bone marrow cell exposure and subsequent epidermal grafting in accelerating healing and reducing the need for amputation
- Intractable DFUs
  - 18 patients without exposed bone
    - 10 patients received epidermal grafts
    - 8 patients received standard of care alone
  - 20 patients with exposed bone
    - 11 patients received epidermal grafts
    - 9 patients received standard of care alone
- **Procedure:** Suction blister grafts were harvested from the thigh or abdomen
- **Results**
  - Patients with DFUs without exposed bone who received epidermal grafts had shorter healing times compared with the standard of care arm
  - Patients with DFUs with exposed bone who received epidermal grafts did not require any amputations

DFUs = diabetic foot ulcers.
Yamaguchi Y, et al. *Br J Dermatol*. 2004;151(5):1019-1028.

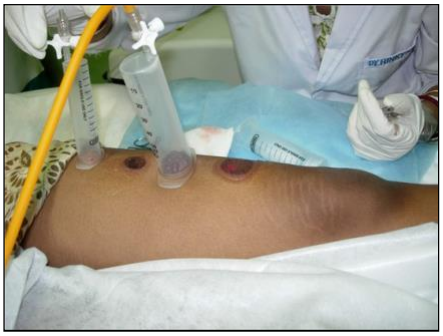
Results

	SBEG	Standard of Care	*P* Value
	Time to Healing	Time to Healing	
Patients without Exposed Bone	4.3 ± 0.6 weeks	11.6 ± 3.4 weeks	.42
	Amputations	Amputations	
Patients with Exposed Bone	0 / 11	8 / 9	<.0001

Yamaguchi Y, et al. *Br J Dermatol.* 2004;151(5):1019-1028.

Until 2012é .

- Epidermal grafting was considered an effective therapy for hypopigmented skin disorders and chronic wounds
- Harvesting techniques, however, were cumbersome and required considerable time and skill to perform.



http://www.skindoctorindia.com/treatments.aspx. DSL# 13-0232.GMAAP.P2P14.O.

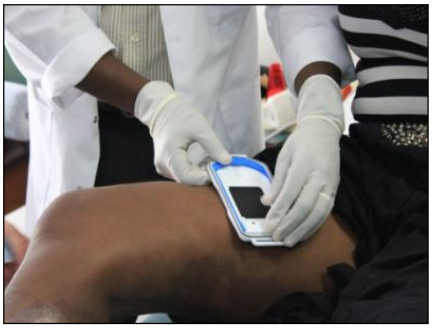
Epidermal Harvesting System Development

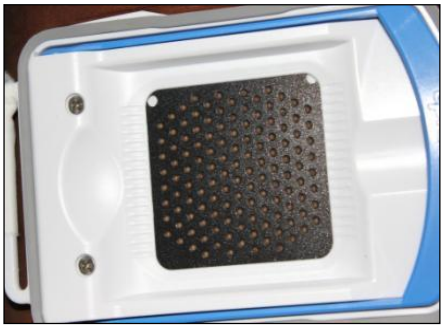
The Wound Clinic at Bernard Mevs Hospital August 2012

Port au Prince, February 2010

DSL# 13-0232.GMAAP.P2P14.O.

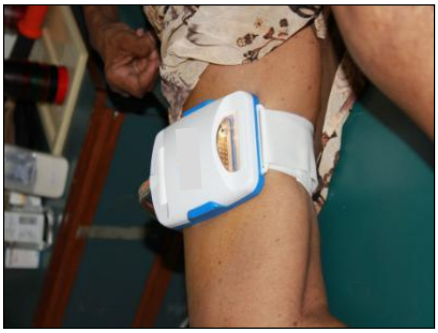
Epidermal Harvesting System Procedure





DSL# 13-0232.GMAAP.P2P14.O.

Device in Place: Skin Heated to 40° C and Negative Pressure Applied



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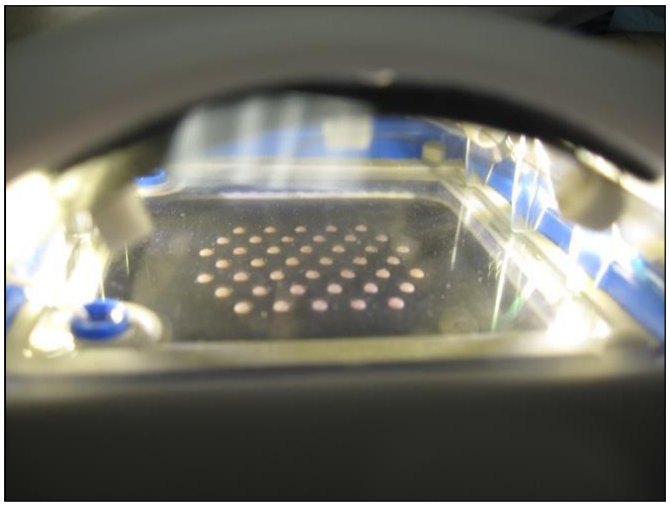
Epidermal Grafts Rising



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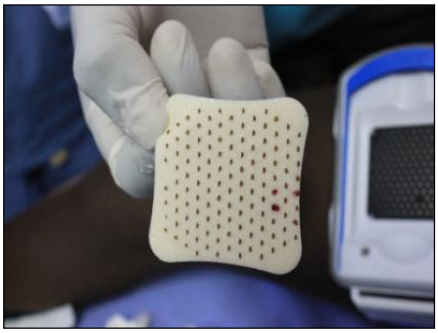
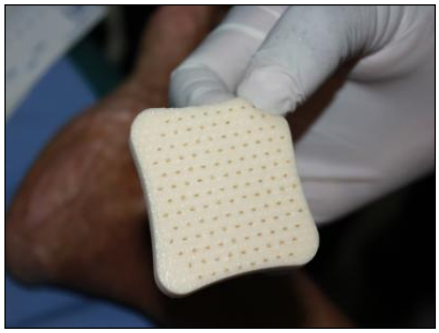
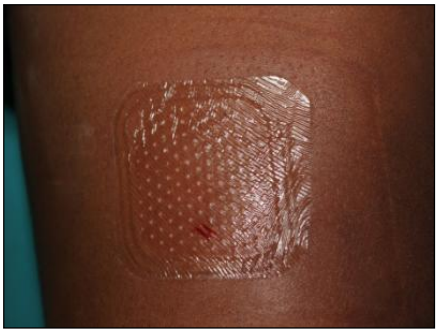
Epidermal Grafts on Adhesive Foam

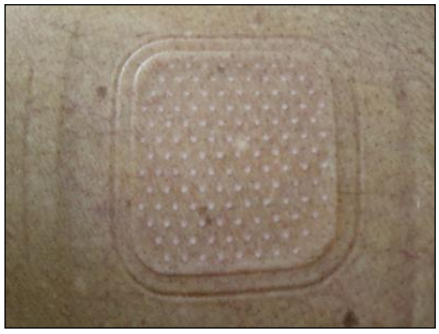




DSL# 13-0232.GMAAP.P2P14.O.

Donor Sites





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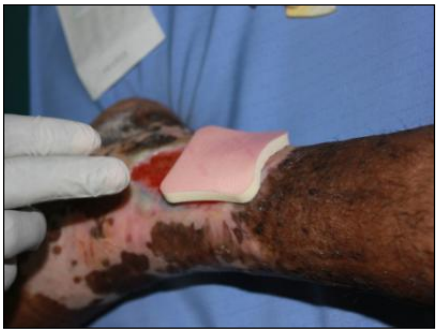
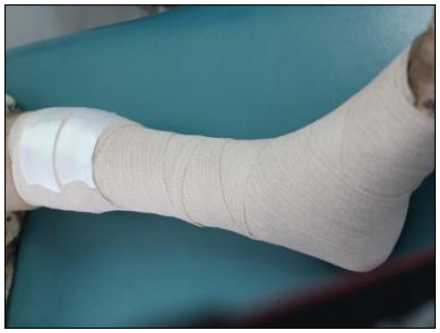
Placing and Securing the Dressing on the Wound





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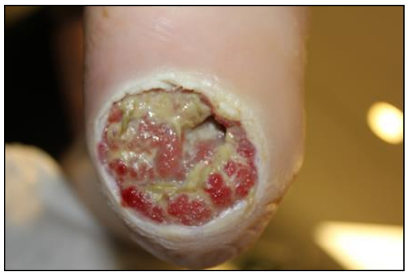
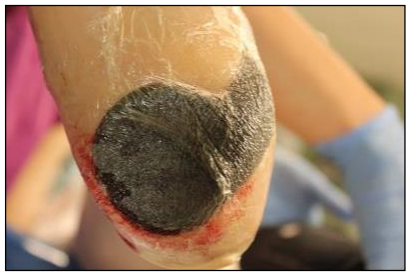
Case Studies

Case Study 1: Diabetic Heel Ulcer

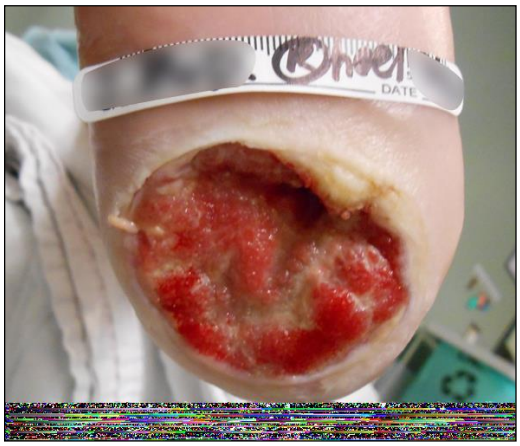


Initial photo

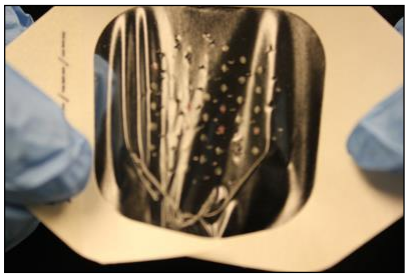


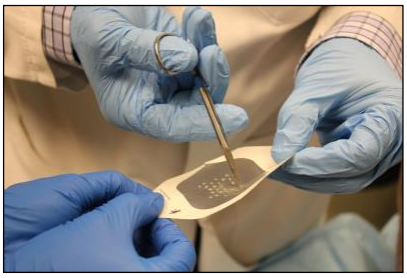
NPWT therapy in place

Wound Bed at Day 4

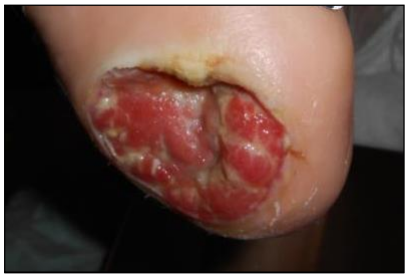


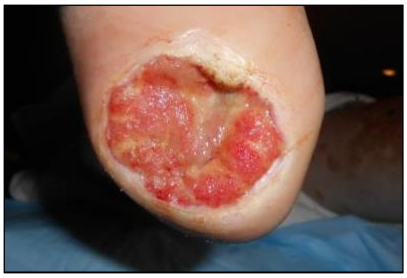
Using Transparent Dressing for Microdome Acquisition



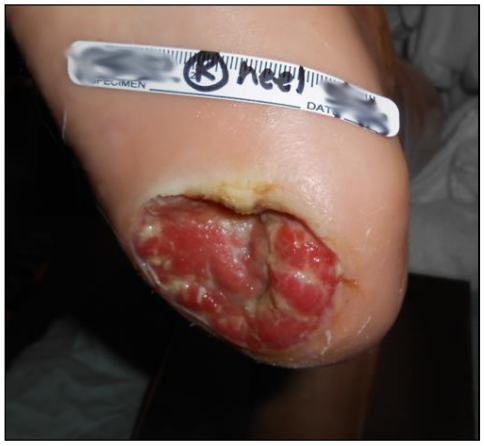


Days 15 and 18 Post-Grafting

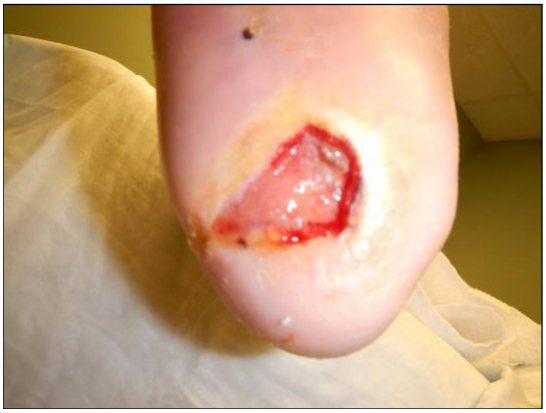




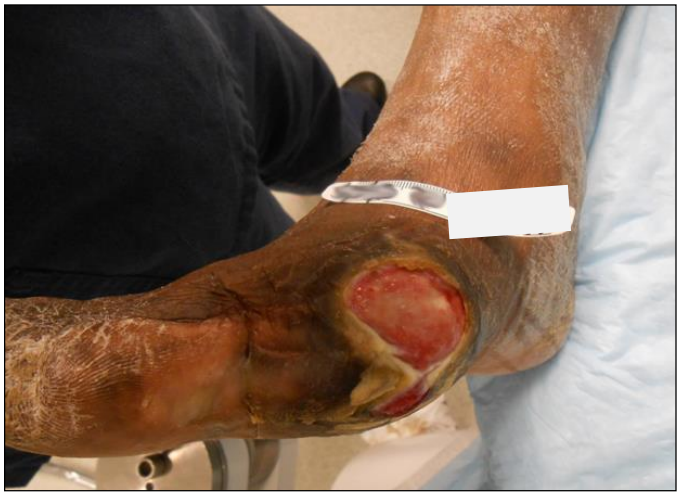
3-Week Follow-Up Postepidermal Graft, NPWT Therapy, and Hyperbaric Oxygen Therapy



8 Week Follow-up



Case Study 2 ï Chronic Foot Wound
Photo prior to epidermal graft placement



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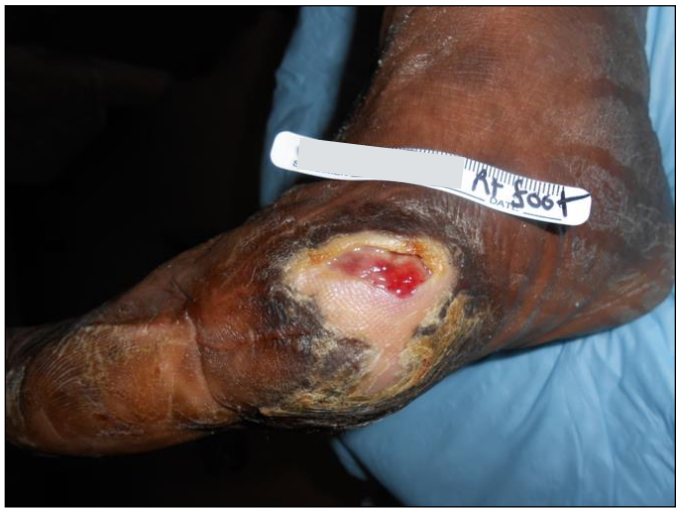
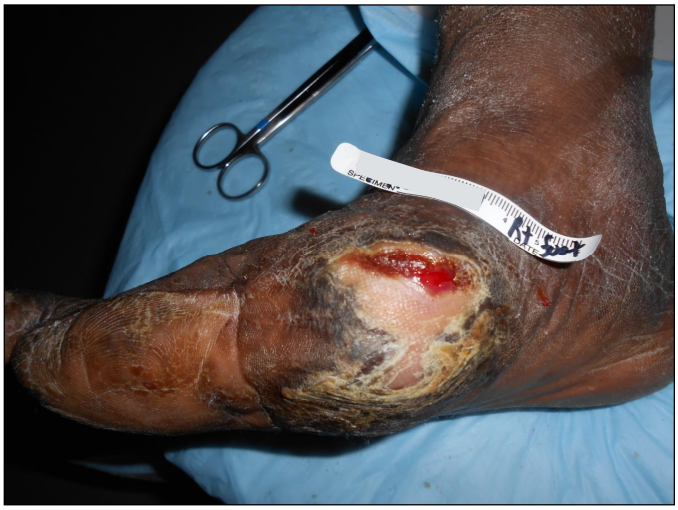
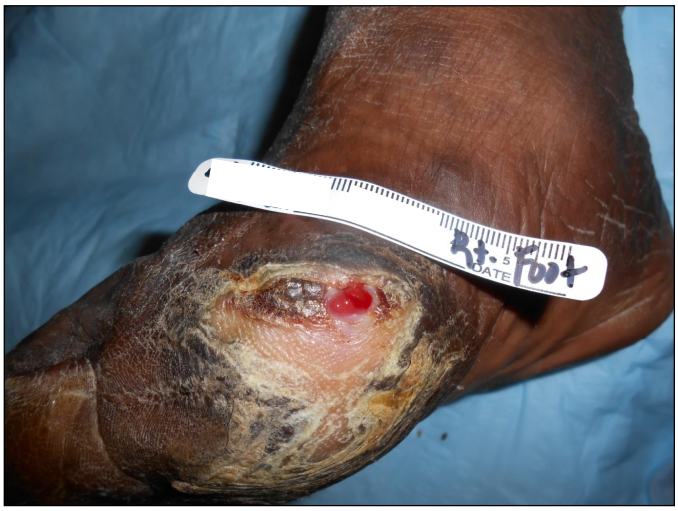
Follow-up Post Application of Epidermal Graft



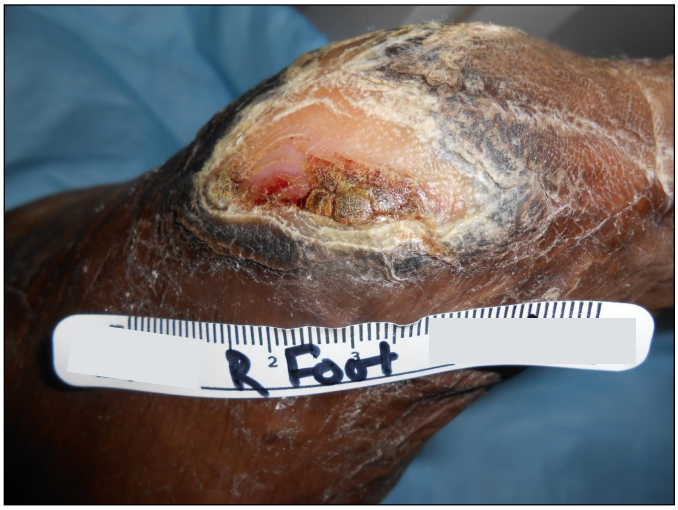
Weekly Follow-up



Weekly Follow-up



Follow-up



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