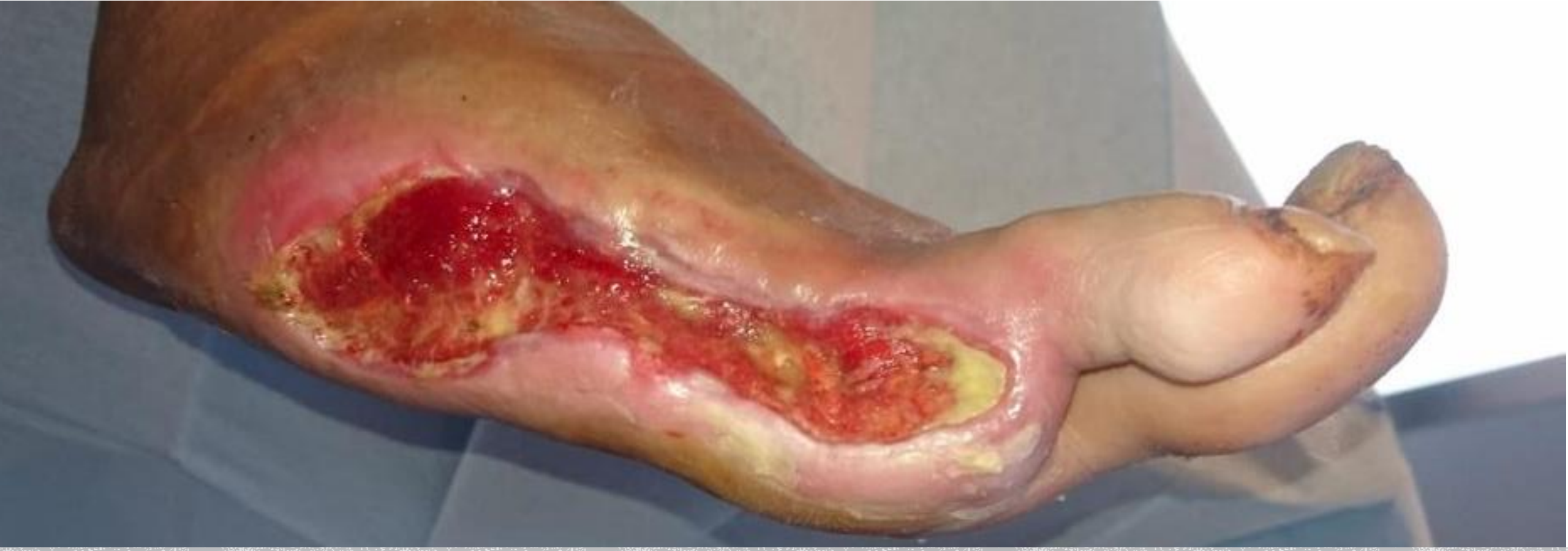


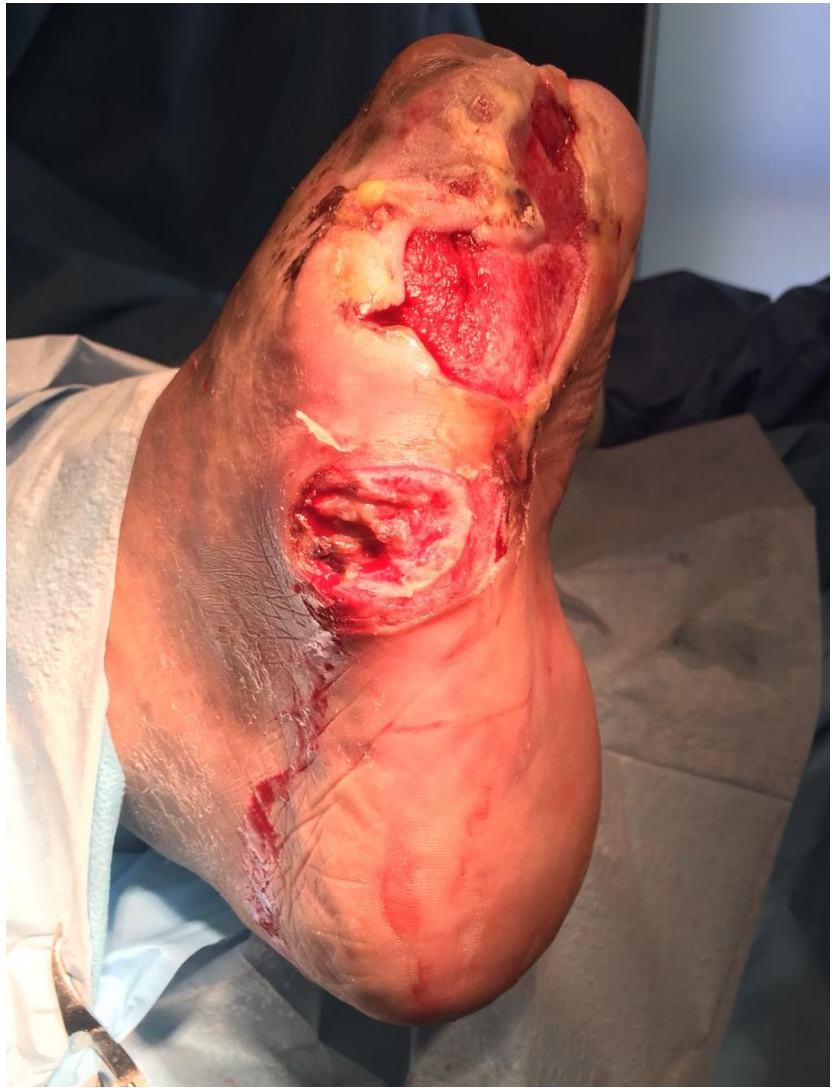
Wound Healing in Diabetic Foot Ulcer

Prof. Dr. José Luis Lázaro Martínez

Head Diabetic Foot Unit. Universidad Complutense de Madrid
Chairman Diabetic Foot Research Group IdISSC
Scientific Secretary Diabetic Foot Study Group on behalf EASD
President elect D-Foot Internation

Integral Assessment of DFU

- Patient's history
- Aetiology of Diabetic Foot Ulcer
- Vascular Status
- Location, foot deformities and joint mobility
- Size/Depth
- Exposed Bone
- Discard Infection
- Wound bed assesment
- Edge and Periwound Skin



STANDARD OF CARE DFU

- **PVD assessment**
  - If PVD is present: poor prognosis of the ulceration (close 70% DFU are neuroischemic)
  - If Critical Limb Ischemia is present: Revascularization is mandatory
- **Discard infection**
  - If Soft Tissue are getting infected: consider surgical debridement
  - Necrotizing Soft Tissue Infection: Emergency Approach (Aggressive Surgery and ATB I/V)
  - If Bone is infected: To define when surgery or medical therapy is the first step for managing
- **Offloading**
  - To evaluate location, BMI, LJM, Oedema, Hyperkeratosis y previous offloading devices
- **Wound management**
  - To define objectives in wound care

Diabetologia (2008) 51:747–755
DOI 10.1007/s00125-008-0940-0

OpenAccess

ARTICLE

Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study

L. Prompers · N. Schaper · J. Apelqvist · M. Edmonds · E. Jude · D. Mauricio · L. Uccioli · V. Urbancic · K. Bakker · P. Holstein · A. Jirkovska · A. Piaggesi · G. Ragnarson-Tennvall · H. Reike · M. Spraul · K. Van Acker · J. Van Baal · F. Van Merode · I. Ferreira · M. Huijberts

and those excluded (dropouts) from the present study

50% have some degree of PVD

	Included (n=1,088)	Dropouts (n=144)	p value
Age (years)	64.7±12.5	68.0±11.6	0.003
Male sex, n (%)[a]	703 (64.6)	85 (59.0)	0.189
Duration of diabetes, n (%)[a]			0.418
<5 years	148 (14.1)	19 (13.5)	
5–10 years	169 (16.1)	17 (12.1)	
>10 years	731 (69.8)	105 (74.5)	
Deep ulcer, n (%)[a]	476 (43.8)	80 (55.6)	0.007
Size of ulcer, n (%)[a]			0.843
<1 cm^2	403 (37.2)	50 (35.0)	
1–5 cm^2	563 (52.0)	76 (53.1)	
>5 cm^2	117 (10.8)	17 (11.9)	
Duration of ulcer, n (%)[a]			<0.001
<1 week	184 (17.0)	10 (7.0)	
1 week–3 months	627 (58.1)	68 (47.6)	
>3 months	269 (24.9)	65 (45.5)	
Plantar location, n (%)[a]	493 (48.2)	62 (46.3)	0.675
Pretibial oedema, n (%)[a]	197 (18.2)	29 (20.3)	0.538
Heart failure NYHA III–IV, n (%)[a]	117 (10.9)	23 (16.1)	0.065
Neurological disorder, n (%)[a]	70 (6.5)	9 (6.3)	0.918
Inability to stand or walk without help, n (%)[a]	107 (9.9)	15 (10.4)	0.843
Visual impairment, n (%)[a]	164 (15.3)	19 (13.2)	0.507
ESRD, n (%)[a]	63 (5.8)	7 (4.9)	0.639
Polyneuropathy, n (%)[a]	826 (78.5)	105 (76.1)	0.515
Infection, n (%)[a]	591 (57.2)	82 (61.2)	0.380
PAD, n (%)[a]	505 (47.5)	78 (56.1)	0.056

Unless otherwise stated, data are mean values±SD
[a] Percentages may not sum to 100 due to missing information

What Is the Clinical Utility of the Ankle-Brachial Index in Patients With Diabetic Foot Ulcers and Radiographic Arterial Calcification?

The International Journal of Lower Extremity Wounds
1–5

DOI: 10.1177/1534734615596906
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Francisco Javier Álvaro-Afonso, DPM, PhD[1,2], José Luis Lázaro-Martínez, DPM, PhD[1,2], Javier Aragón-Sánchez, MD, PhD[3], Esther García-Morales, DPM, PhD[1,2], Yolanda García-Álvarez, DPM, PhD[1,2], Raúl Juan Molines-Barroso, DPM, PhD[1,2]

Abstract

The purpose of this study was to analyze the influence interpretation of ankle-brachial index (ABI) values in patient database of 60 patients with diabetic foot ulcers from the between January 2012 and March 2014. For each patient, an brachial index (TBI) were assessed by an experienced clinici applied the Pearson correlation coefficient. Fifty percent (n < 0.7 associated with peripheral arterial disease (PAD). In pa was higher than in patients without RAC (52%, 11/21). TI patients with an ABI < 1.4 (n = 46) was lesser (r = .484, P (n = 21; r = .686, P = .001). ABI values between 0.9 and 1.4 v the prevalence of PAD, especially in patients with neuropat

41,6% Arterial Calcification

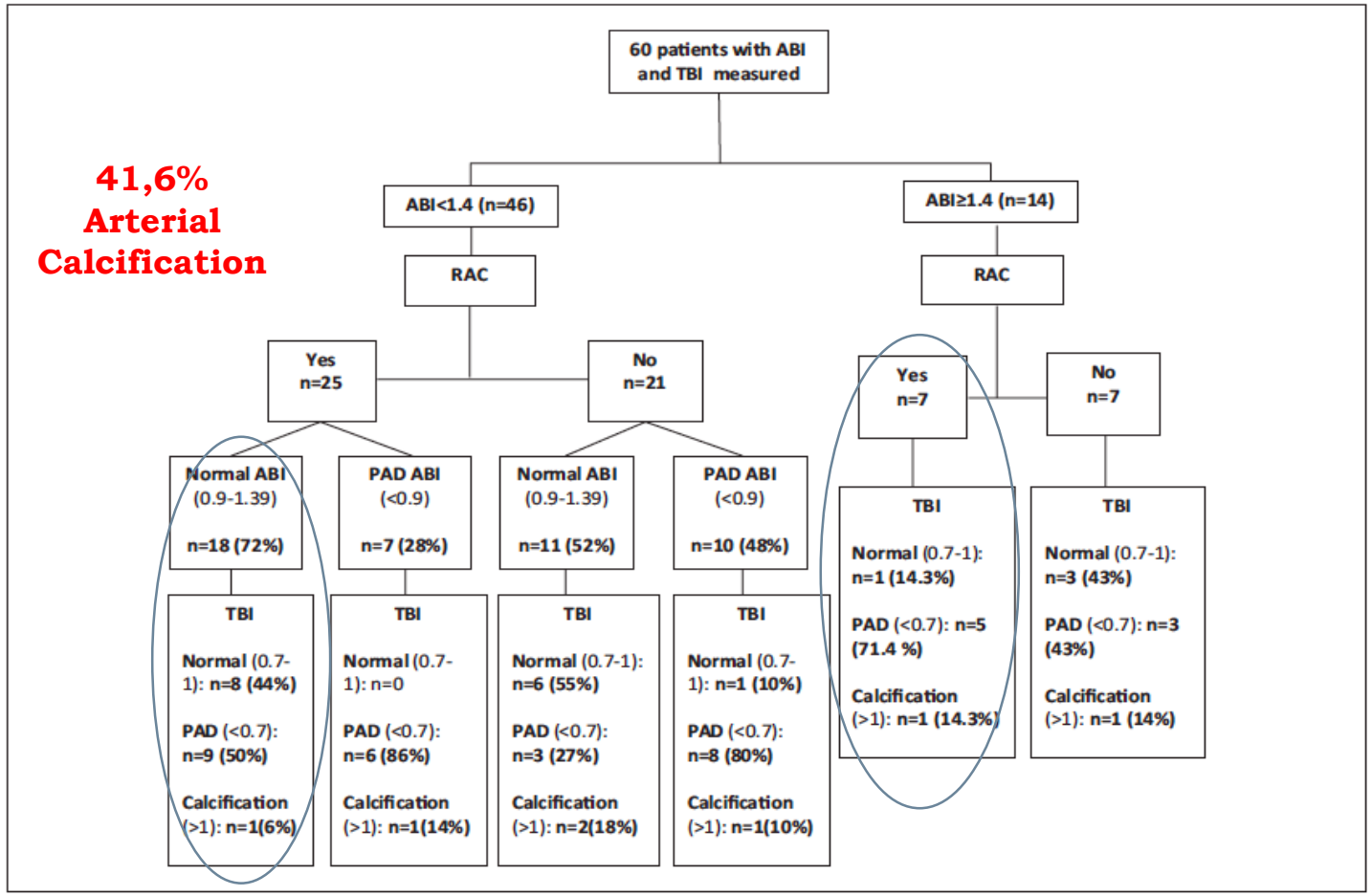
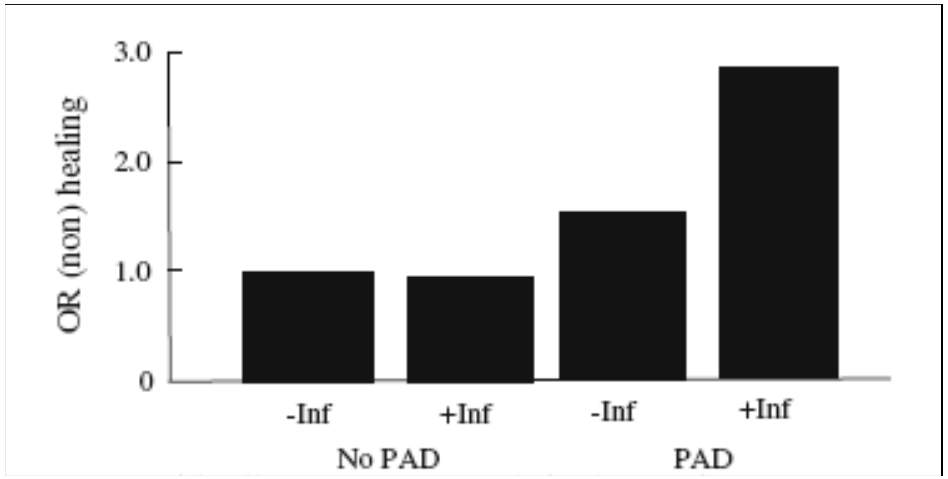


Figure 2. Flow chart of patients of the study.
Abbreviations: ABI, ankle-brachial index; TBI, toe-brachial index; PAD, peripheral arterial disease; RAC, radiographic arterial calcification.

PVD and healing

	Inf - / PAD –	Inf + / PAD -	Inf - / PAD +	Inf + / PAD +
	A	B	C	D
Prevalence	24%	27%	18%	31%
Healing	90%	89%	69%	36%
Costs	4.514€	9.273 €	9.851 €	16.835 €

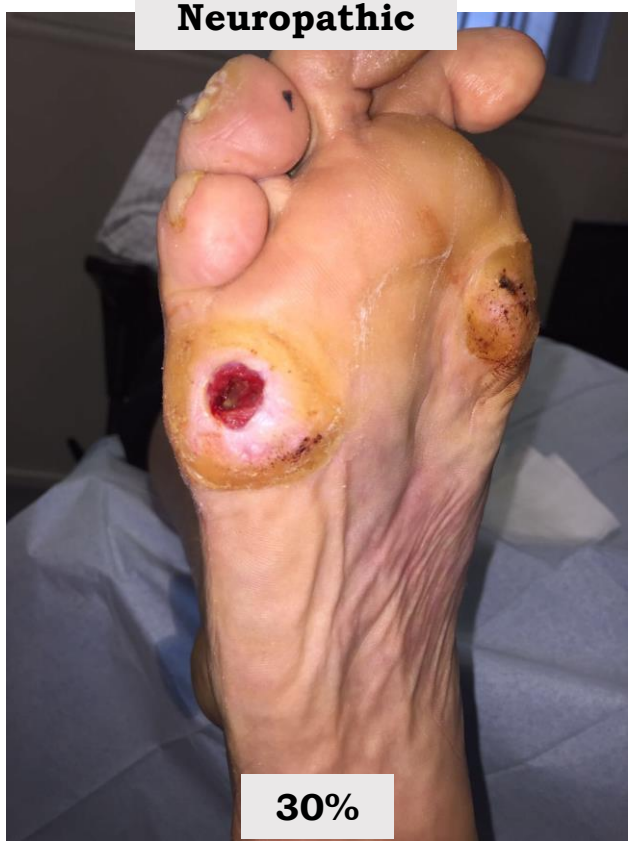


OR 2.82 (1.82-4.22, p<.001)

Prompers L. Eurodiale Study. Diabetologia 2007
Naburs-Franssen MH. Diabetes Care 2005
Prompers L. Eurodiale Study . Diabetologia 2008 (Febr)
Prompers L. Eurodiale Study. Diabetologia 2008 (May)

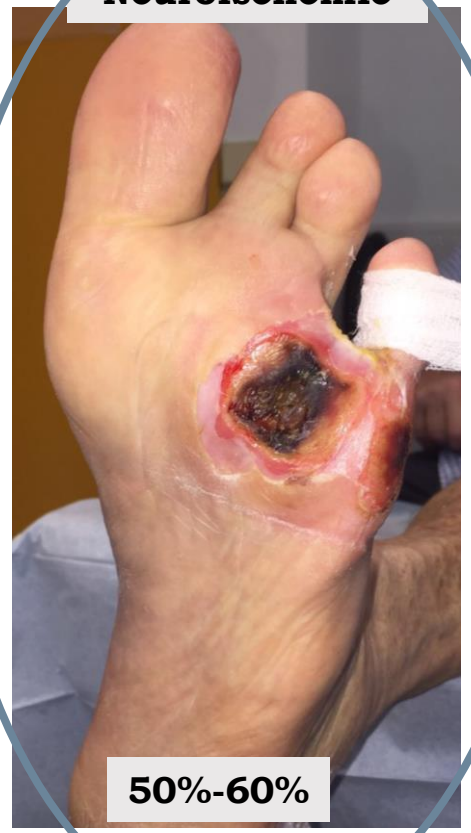
Aetiology of the Ulcer

Neuropathic



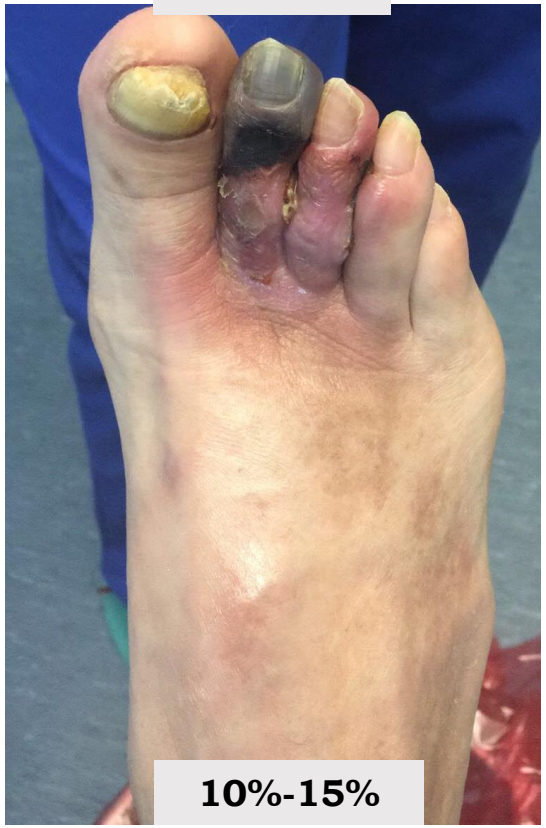
30%

Neuroischemic



50%-60%

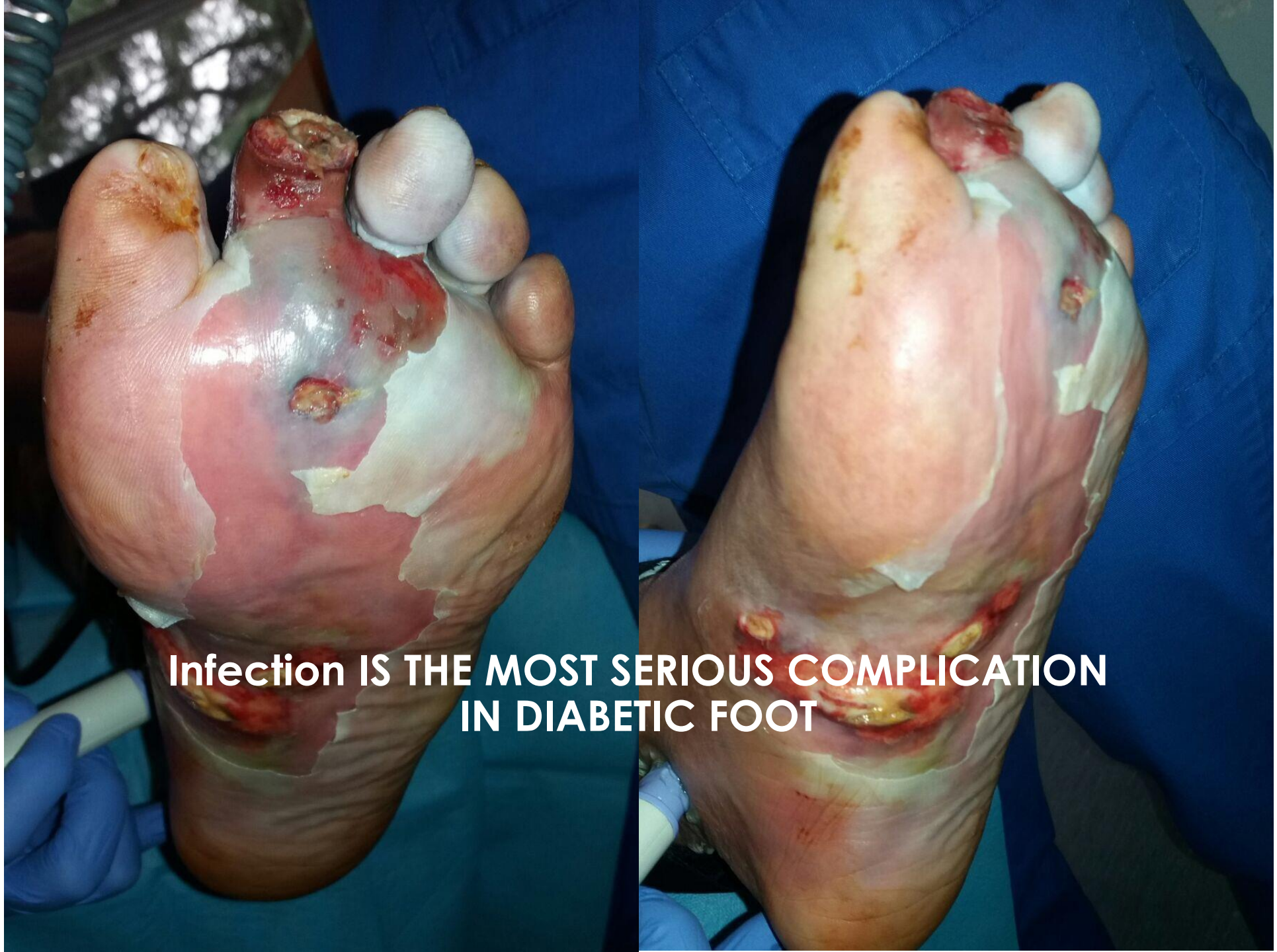
Ischemic



10%-15%

Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K. Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015 based on the IWGDF Guidance Documents. *Diabetes Metab Res Rev* 2016; **32** (suppl 1)**:** 7–15.

Armstrong DG, Cohen K, Courric S , Bharara M, Marston W. Diabetic Foot Ulcers and Vascular Insufficiency: Our Population Has Changed, but Our Methods Have Not. J Diabetes Sci Technol. 2011 Nov; 5(6): 1591–1595.

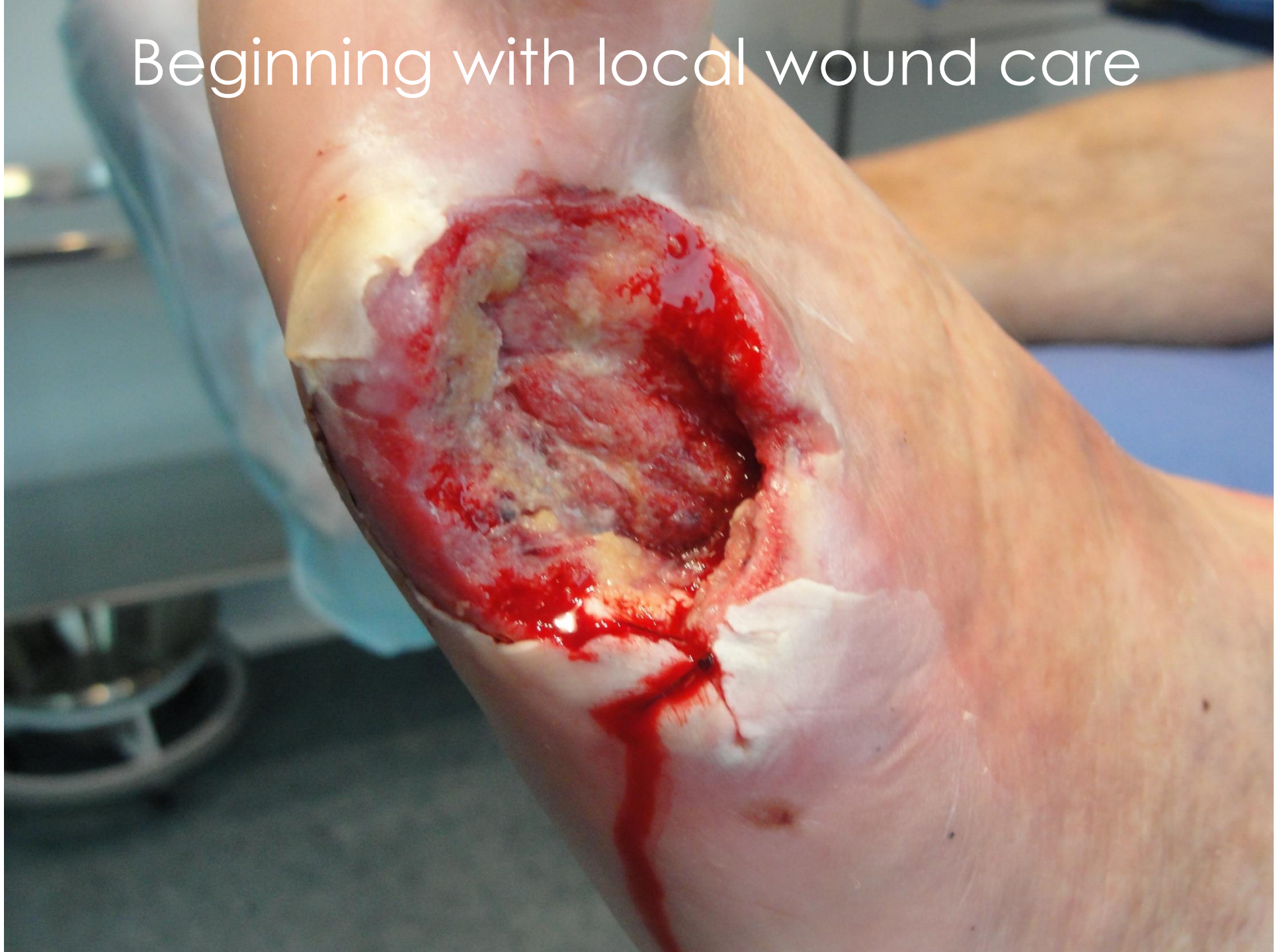


Infection IS THE MOST SERIOUS COMPLICATION IN DIABETIC FOOT

Misdiagnosis Osteomyelitis IS VERY FREQUENT

Underestimate of the process by some DFO clinical presentation

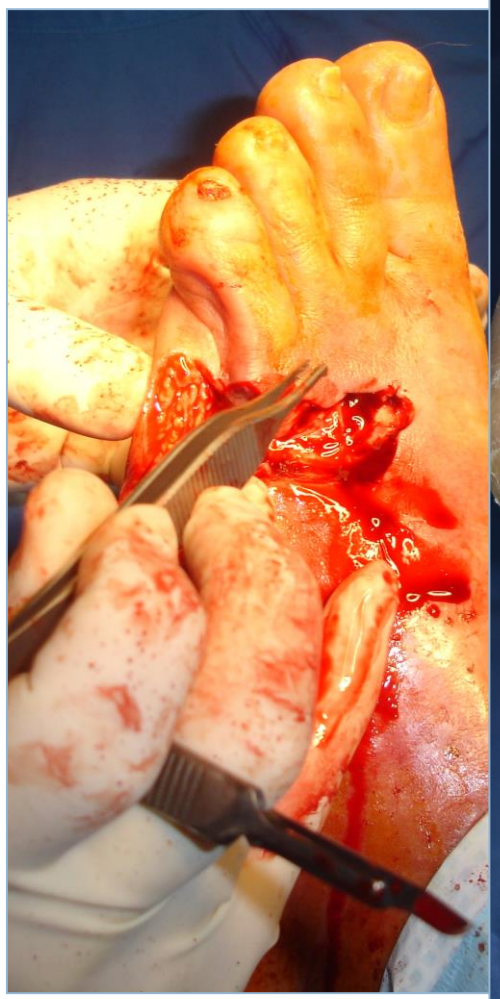
Beginning with local wound care

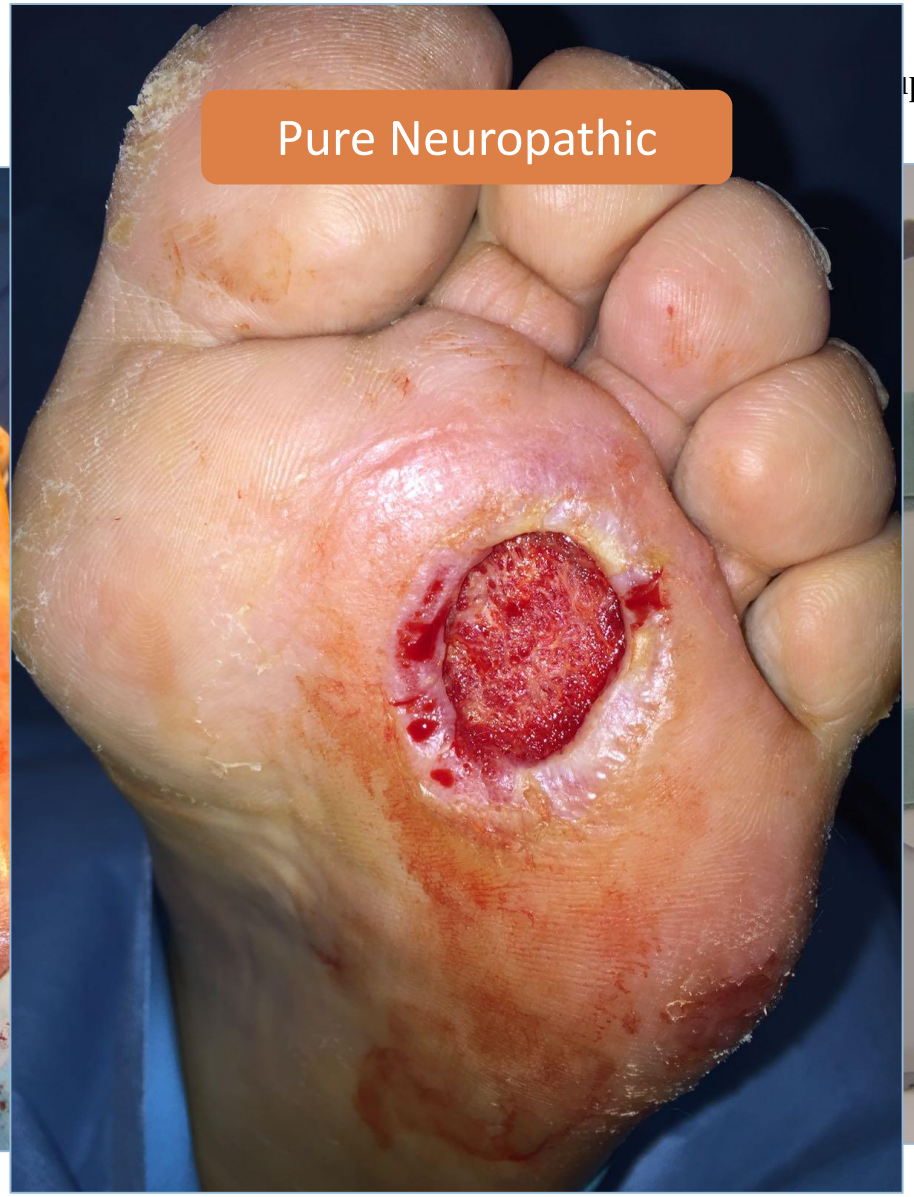


It's not what you put on, but what you take off: techniques for debriding and off-loading the diabetic foot wound.

Armstrong DG, Lavery

ppl 2:S92-9.

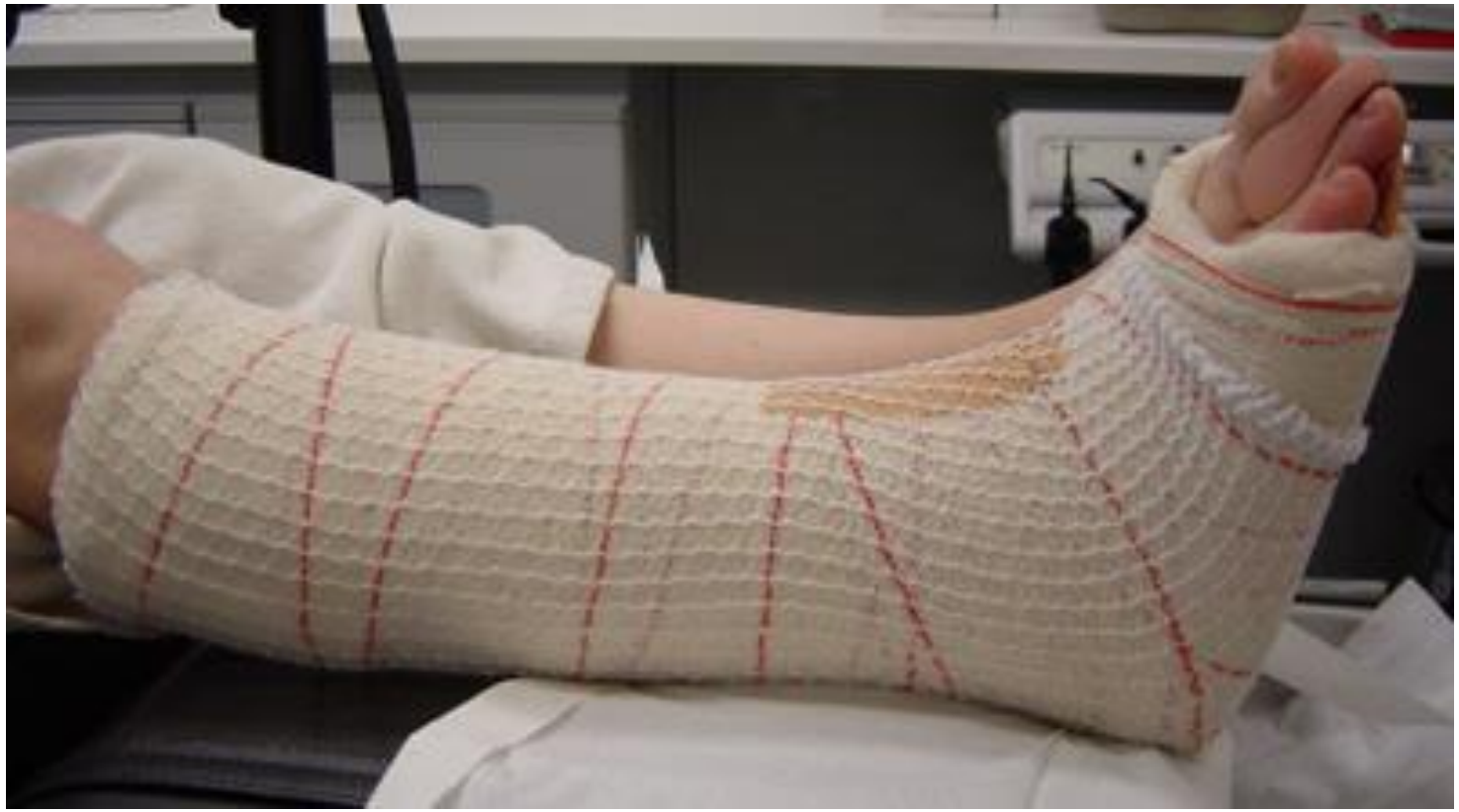




Pure Neuropathic

Choosing Off-loading for Diabetic Foot Ulcers

Total Contact Cast is the "Gold Standard" on DFUs Off-Loading



-Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, Mizel MS, Boulton AJ: A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* 28:555-559, 2005

-Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB: Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 24:1019-1022, 2001

-Saltzman CL, Zimmerman MB, Holdsworth RL, Beck S, Hartsell HD, Frantz RA: Effect of initial weight-bearing in a total contact cast on healing of diabetic foot ulcers. *J Bone Joint Surg Am* 86-A:2714-2719, 2004

-Ha VG, Siney H, Hartmann-Heurtier A, Jacqueminet S, Greau F, Grimaldi A: Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance. *Diabetes Care* 26:2848-2852, 2003

-Caravaggi C, Faglia E, De GR, Mantero M, Quarantiello A, Sommariva E, Gino M, Pritelli C, Morabito A: Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. *Diabetes Care* 23:1746-1751, 2000

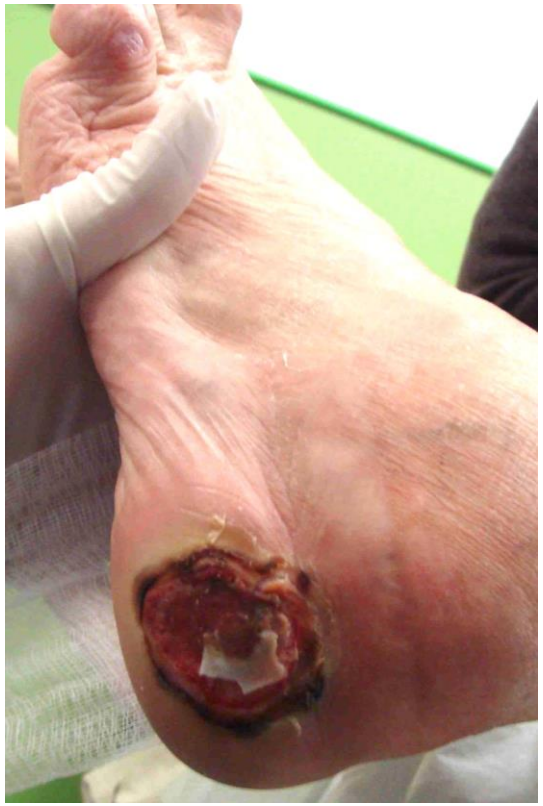
What is the Reality???

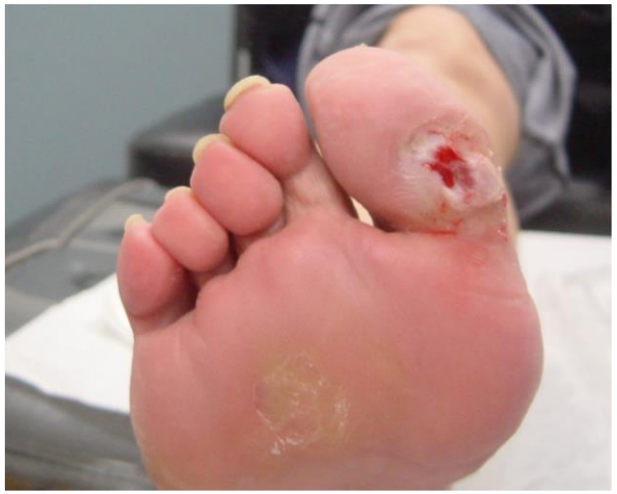
- Just 2%(of 901 centres) used Total Contact Cast (TCC) as a primary method of offloading
- 46% of centres never had used TCC and 58% didn't consider as Gold Standard
- More used offloading were modified shoes
- Only 6% of patients were treated with total contact cast

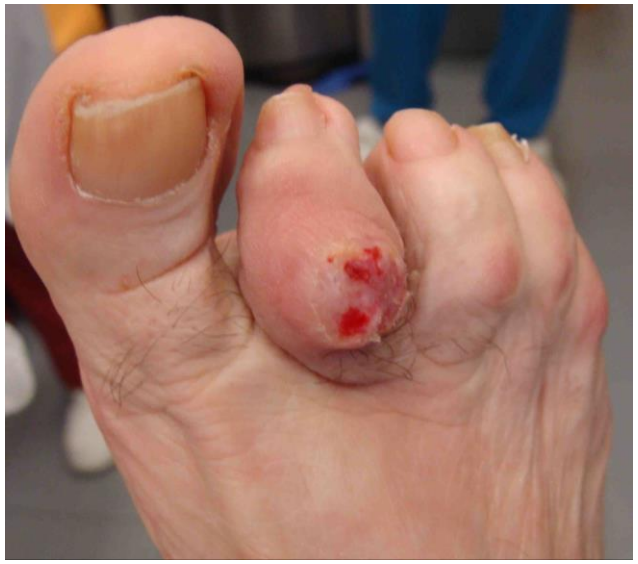
Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care 2008; 31: 2118–2119
Fife CE, Carter MJ, Walker D. Why is it so hard to do the right thing in wound care? Wound Repair Regen 2010; 18: 154–158.

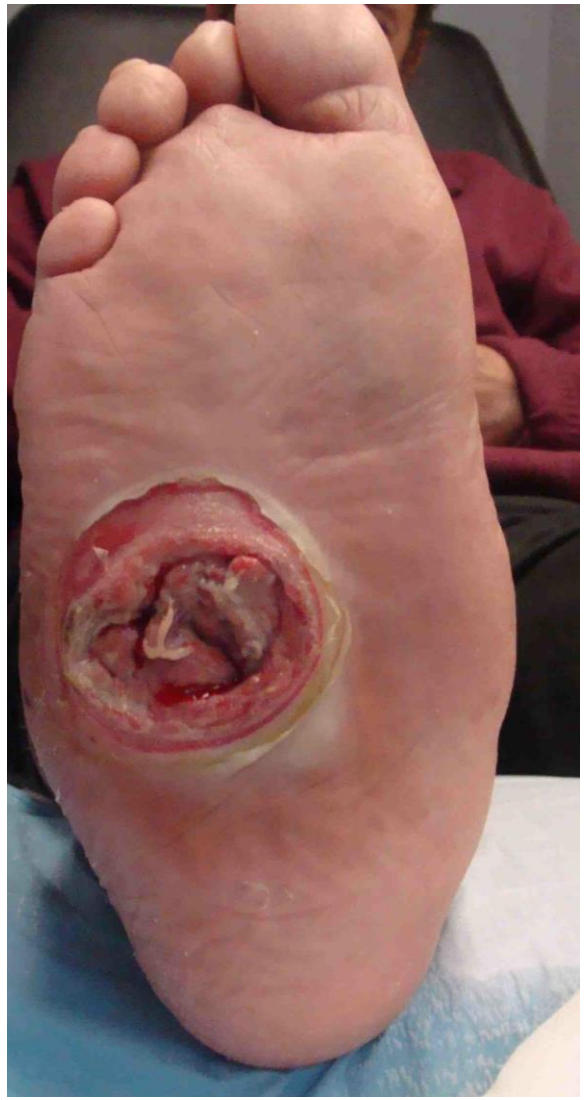
A big gap
implementing Off-loading in Diabetic Foot

Location and Joint Mobility









Hardest to off-load

- Heel: (+ +)
- Midfoot: (+)
- Metartarsal: (-)
- Toes: (- -)

Difficulty level

Influence of the Location of Nonischemic Diabetic Forefoot Osteomyelitis on Time to Healing After Undergoing Surgery

The International Journal of Lower Extremity Wounds
XX(X) 1–5

DOI: 10.1177/1534734613502033
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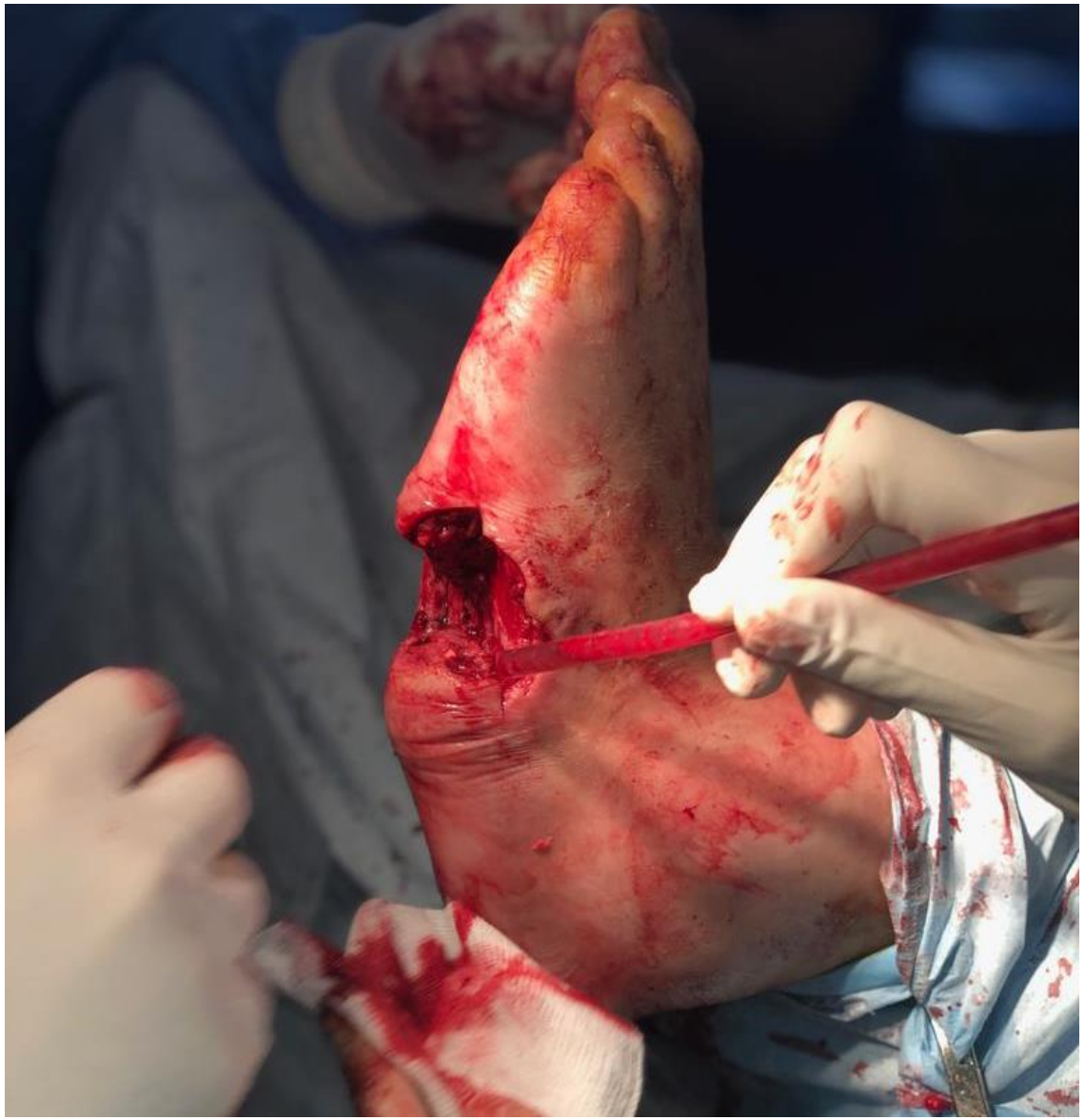
Almudena Cecilia-Matilla, PhD[1], José Luis Lázaro-Martínez, PhD[1], Javier Aragón-Sánchez, MD, PhD[2], Yolanda García-Álvarez, PhD[1], Pedro Chana-Valero, PhD[1], and Juan Vicente Beneit-Montesinos, MD, PhD[1] [AQ: 1]

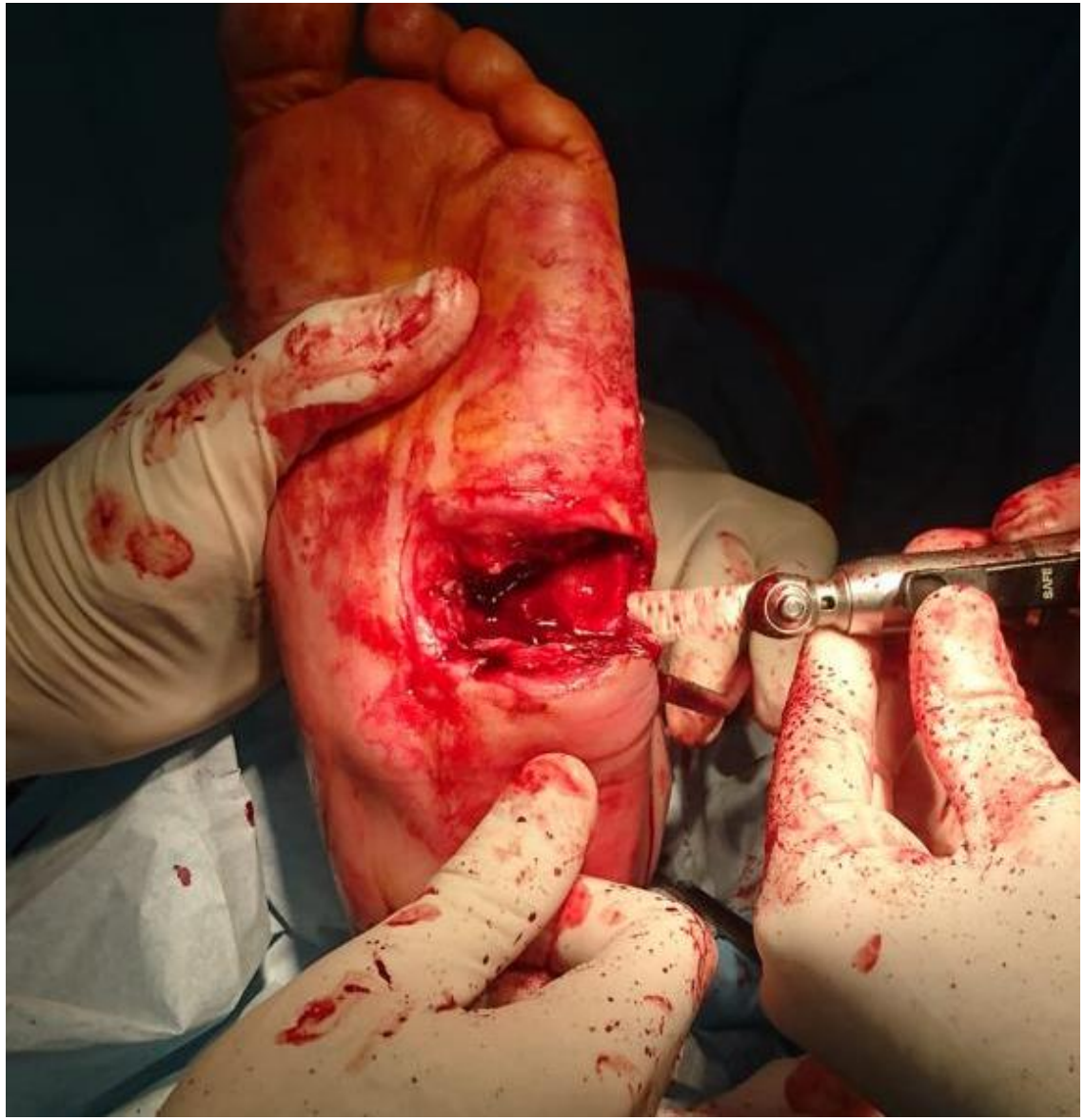
Abstract

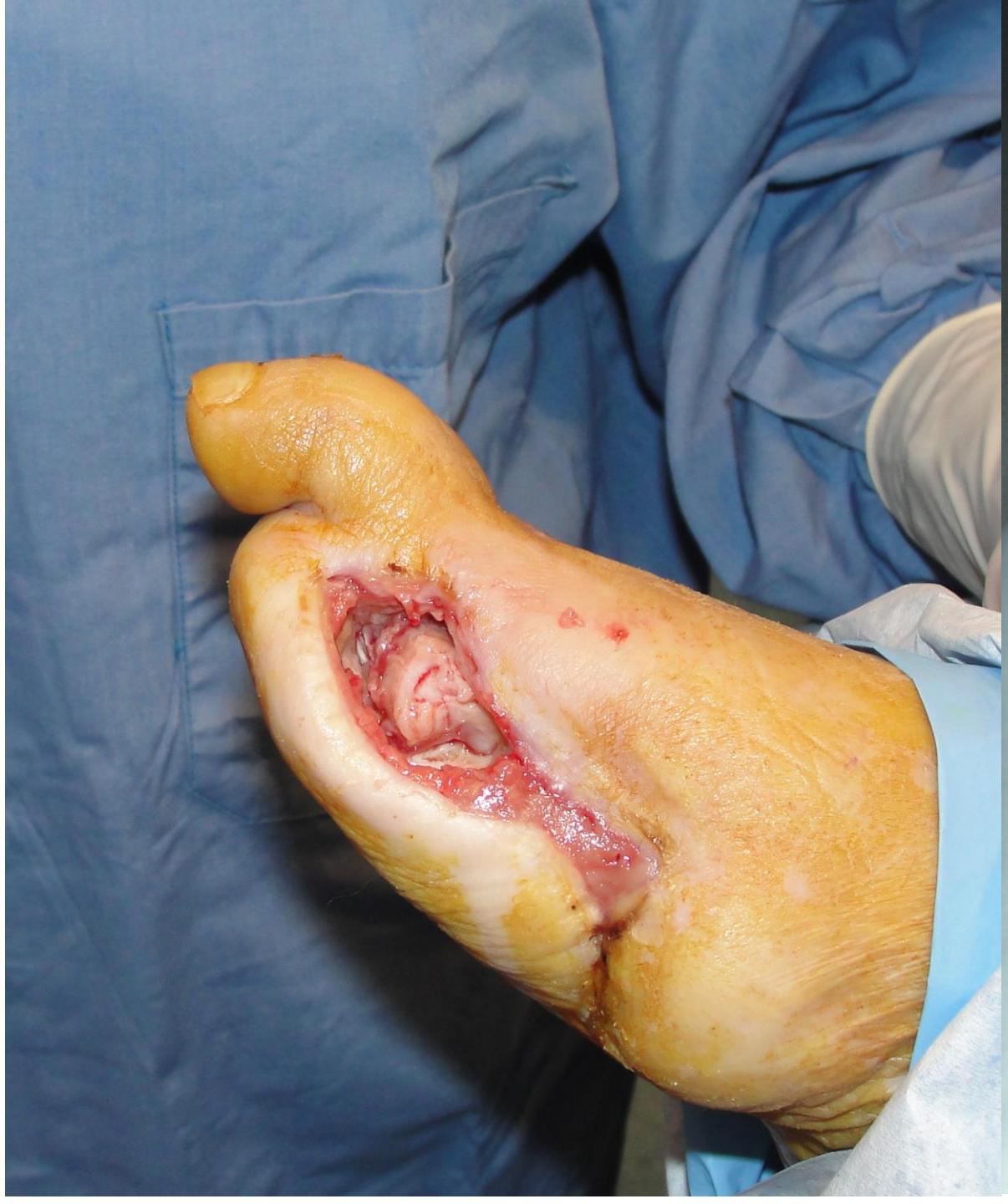
The forefoot has been reported as the most frequent location of osteomyelitis in the feet of patients with diabetes. The forefoot includes toes and metatarsal heads as common locations of bone infections, but the anatomy of these bones is quite different. As a result, such differences in anatomy may have an impact on the outcomes. The aim of the present study was to determine whether different locations of osteomyelitis in the forefoot have any influence on time to healing after undergoing surgery in a prospective series including 195 patients without peripheral arterial disease and osteomyelitis confirmed by histopathology. Location of the lesion was classified into 4 groups: hallux, first metatarsal head, lesser metatarsal heads, and lesser toes. The time required to achieve healing and the cumulative rate of wounds healed and likelihood of healing were analyzed at 4, 8, and 12 weeks after surgery. Time of healing (mean ± SD) in the whole series was 10.7 ± 8.4 weeks. Osteomyelitis located in the lesser toes has a higher probability of healing by the fourth week (odds ratio [OR] = 5.7, 95% confidence interval [CI] = 2.8-11.6, $P < .001$), eighth week (OR = 3.2, 95% CI = 1.6-6.4, $P < .001$), or twelfth week (OR = 3.1, 95% CI = 1.3-7.0, $P = .008$) than other osteomyelitis locations. Osteomyelitis located in the first metatarsal joint was less likely to heal by the eighth week (OR = 0.4, 95% CI = 0.2-0.9, $P = .037$) and 12th week (OR = 0.4, 95% CI = 0.2-1.0, $P = .040$). In conclusion, time to healing is significantly different according to the location of the bone infection in the forefoot.

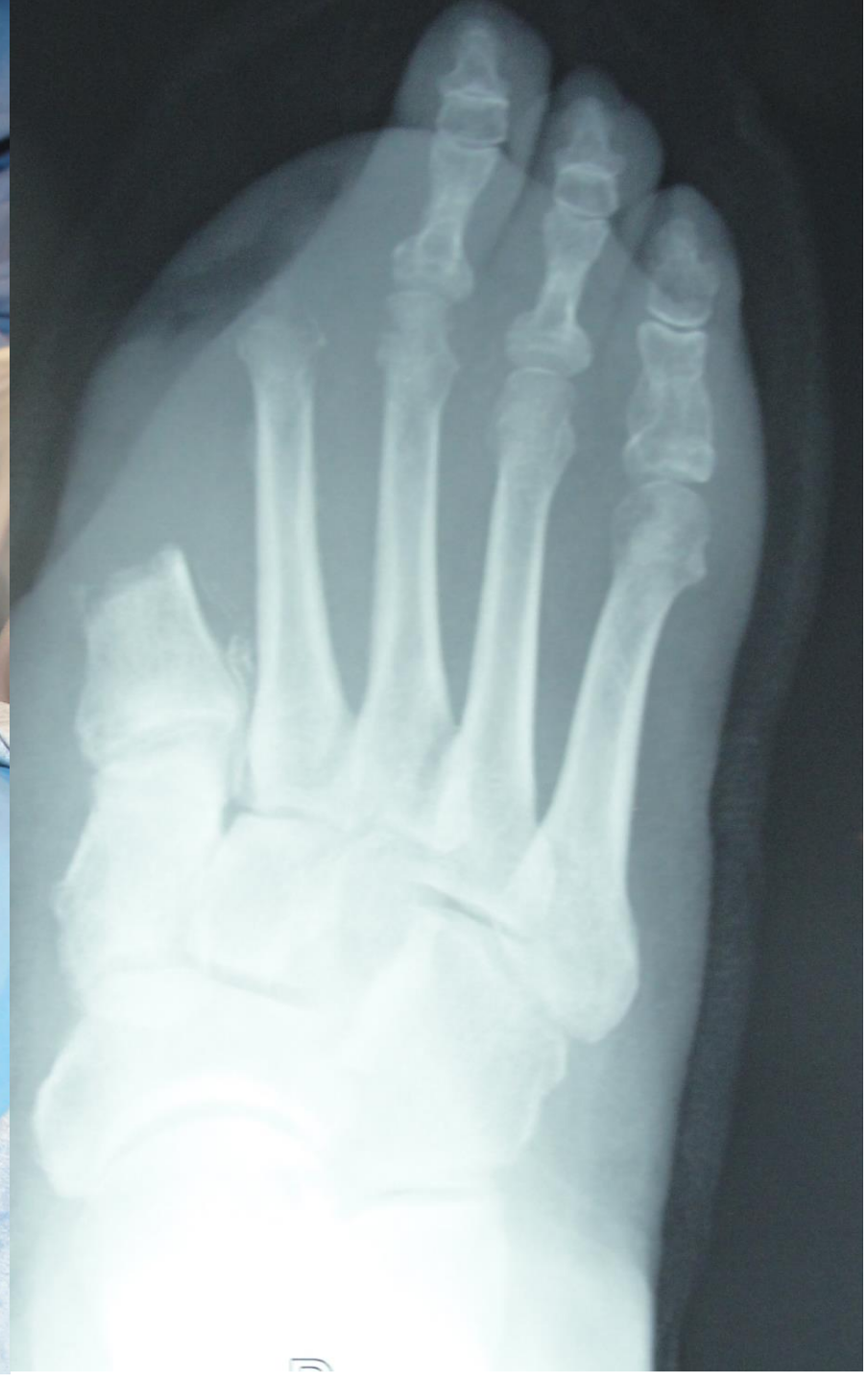
Stepping for a Local Care in DFU

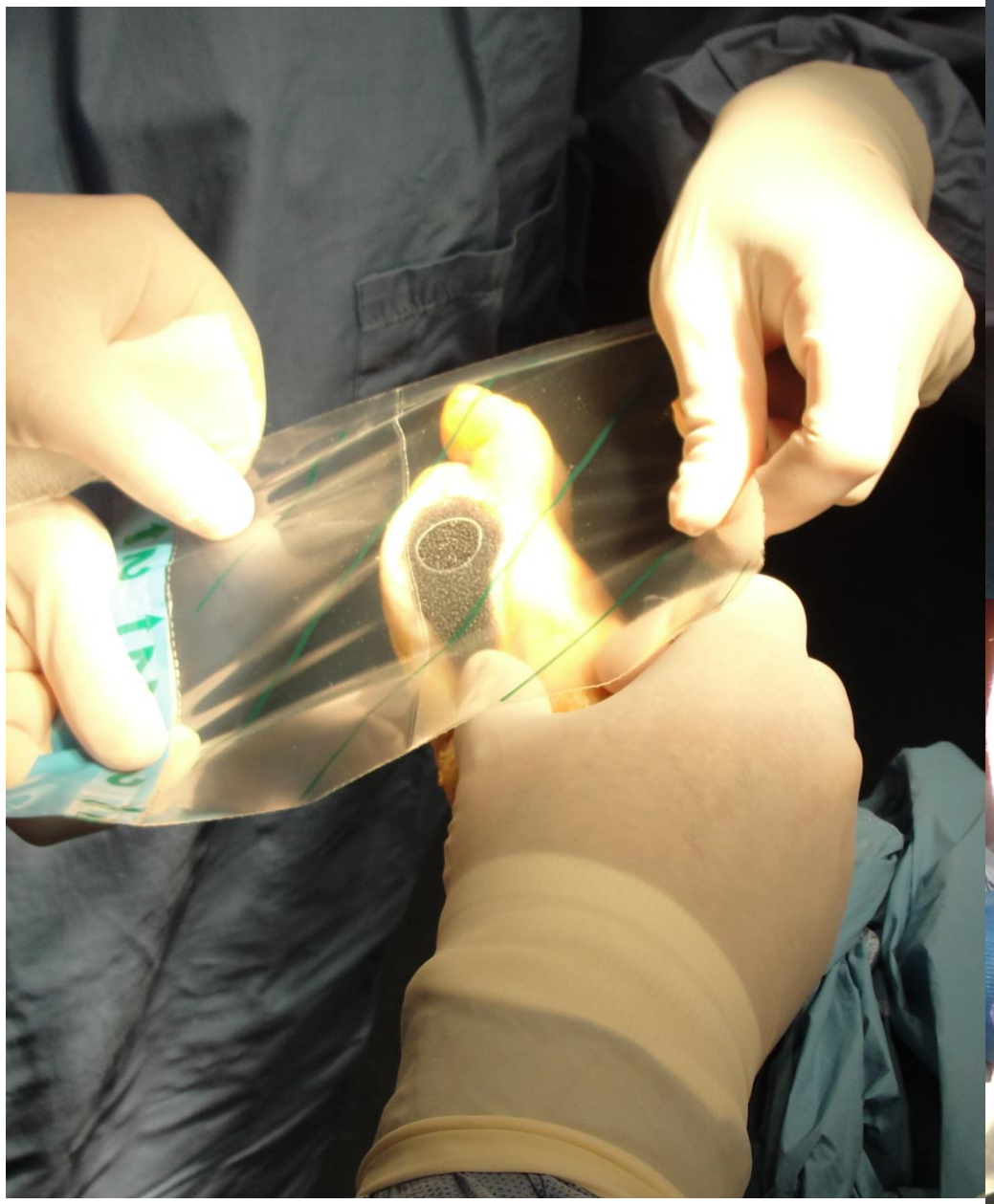
- **Define main objective of the local care therapy:**
  - Promotion/Covering
  - Control/Prevention Infection
  - Biochemical balance/Promotion (faster healing)
  - Protection
- **To schedule revision**
- **Training patients in detection of complications and what he has to do**

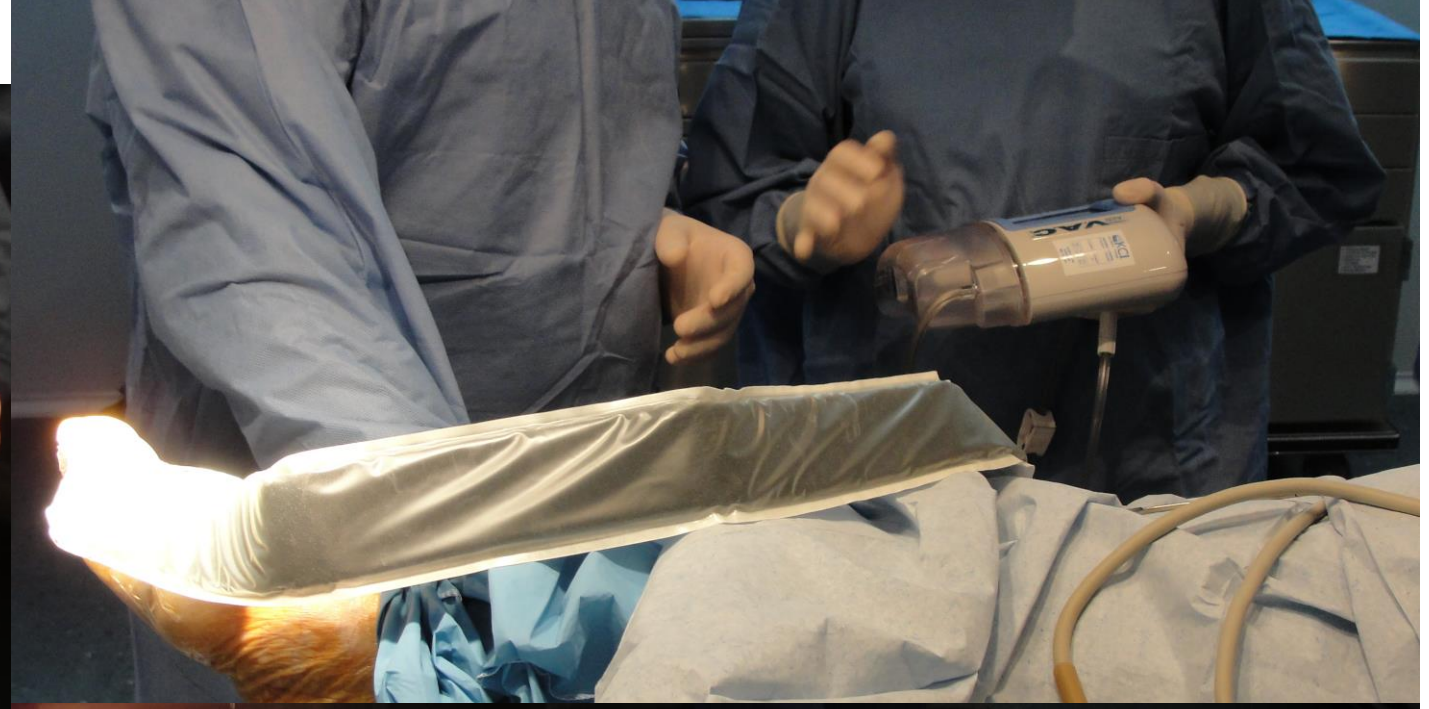


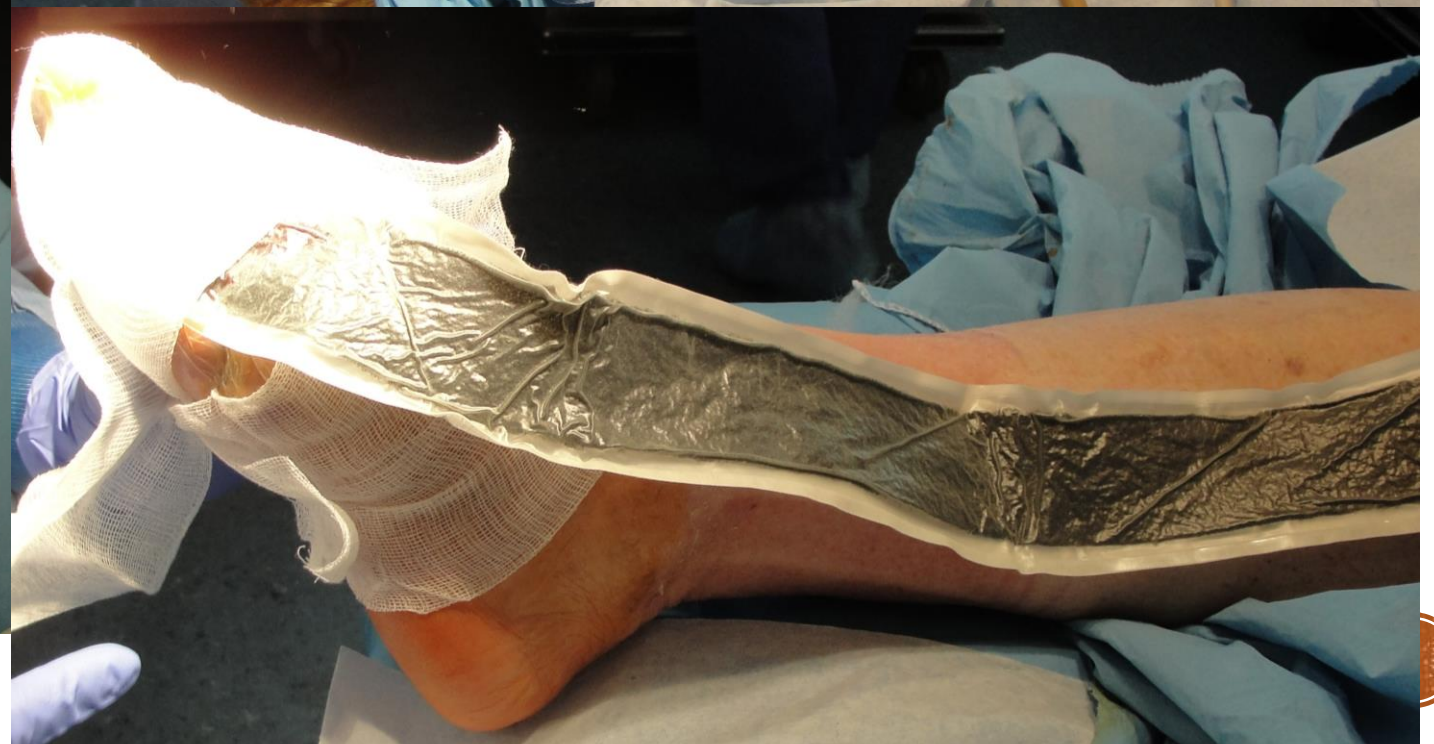




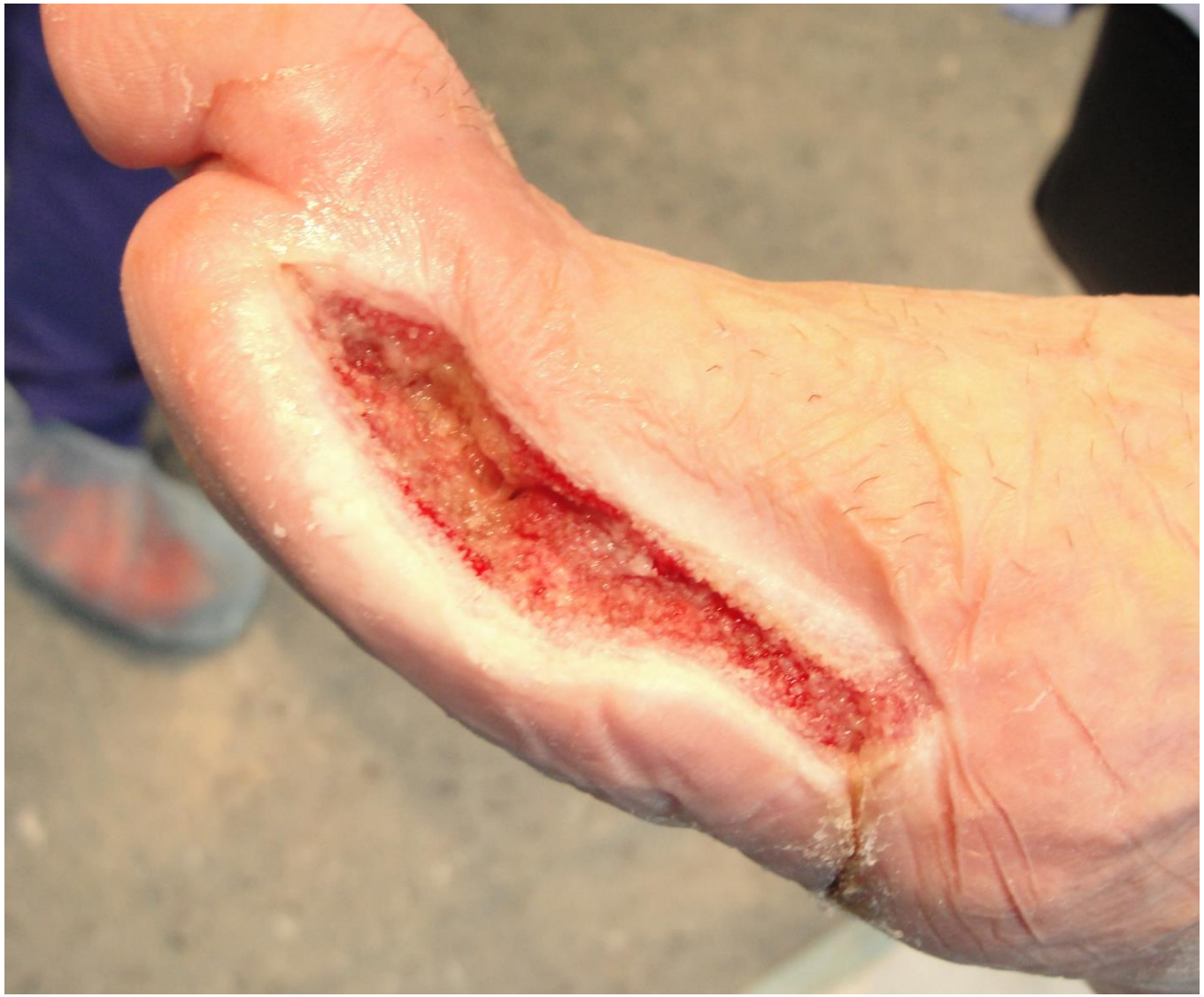






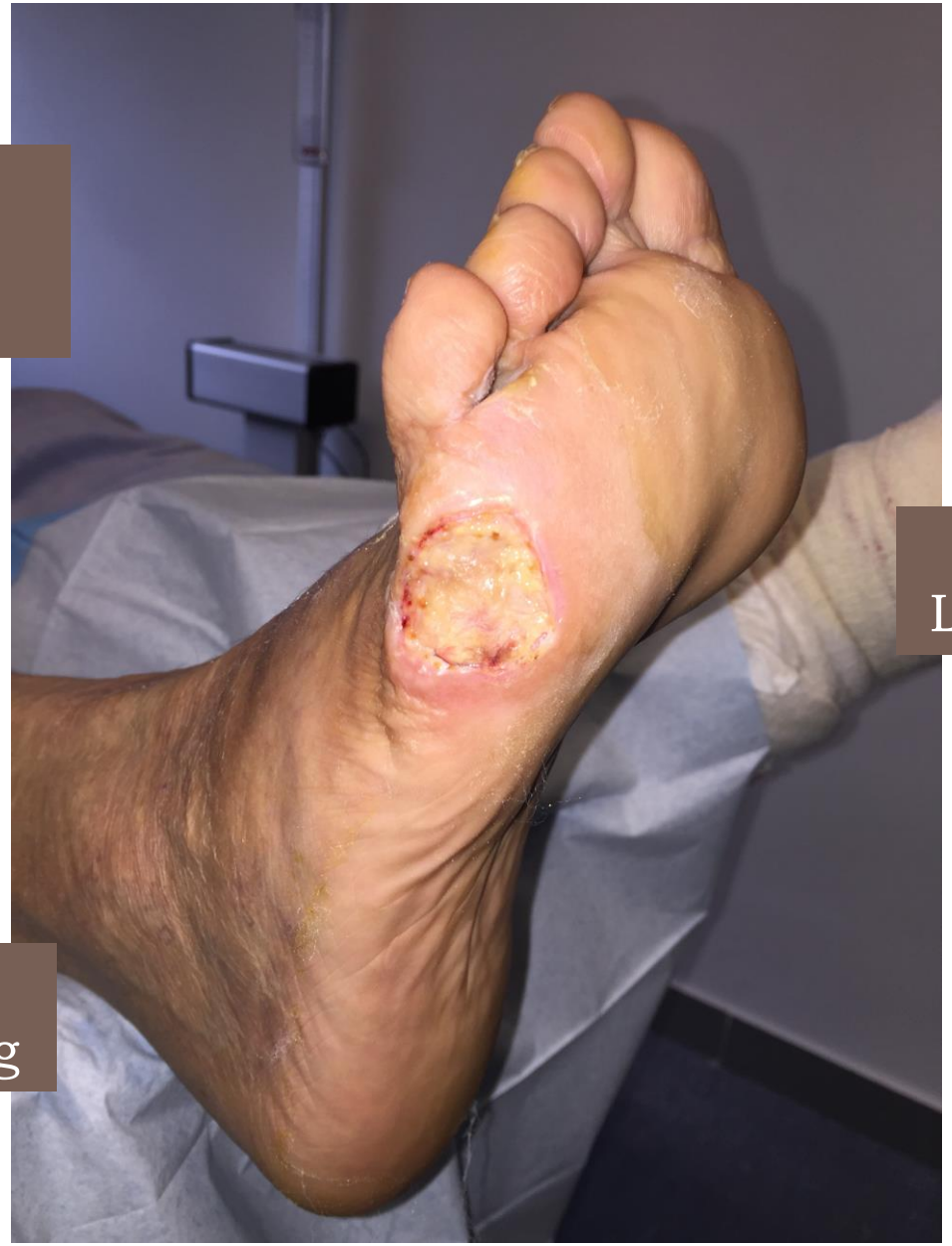


First Objective: Promotion Granulation Tissue



Neuroischemic diabetic foot ulcer

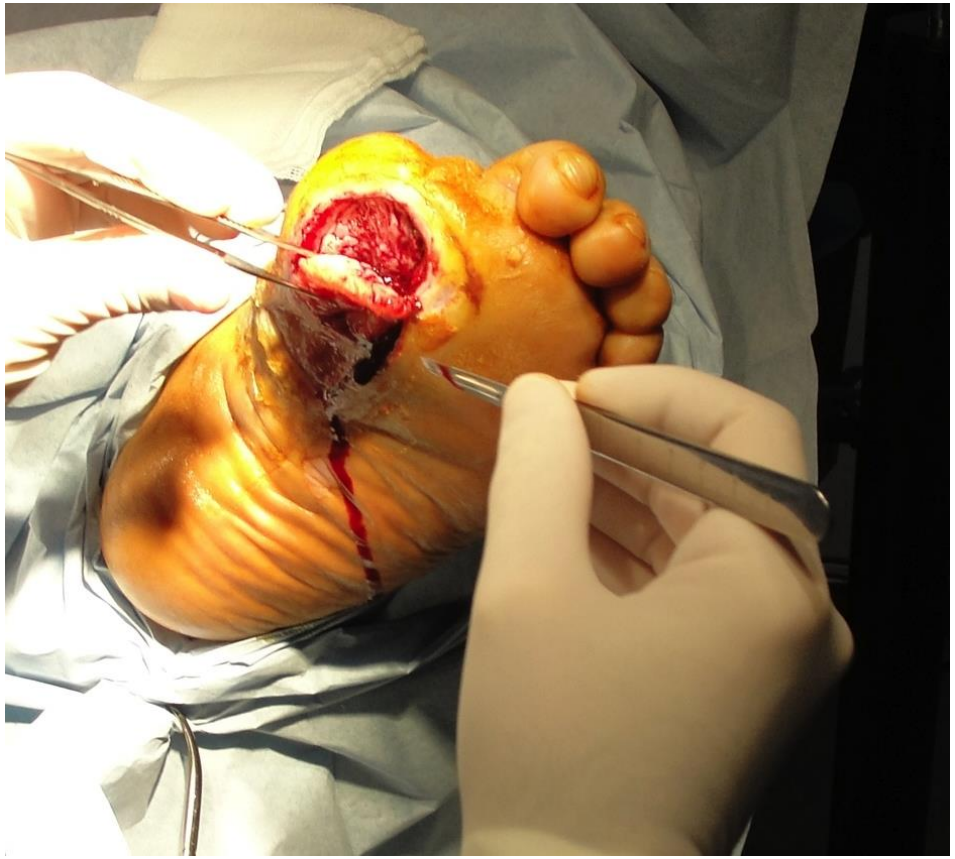
Limitation with Surgical Debridement

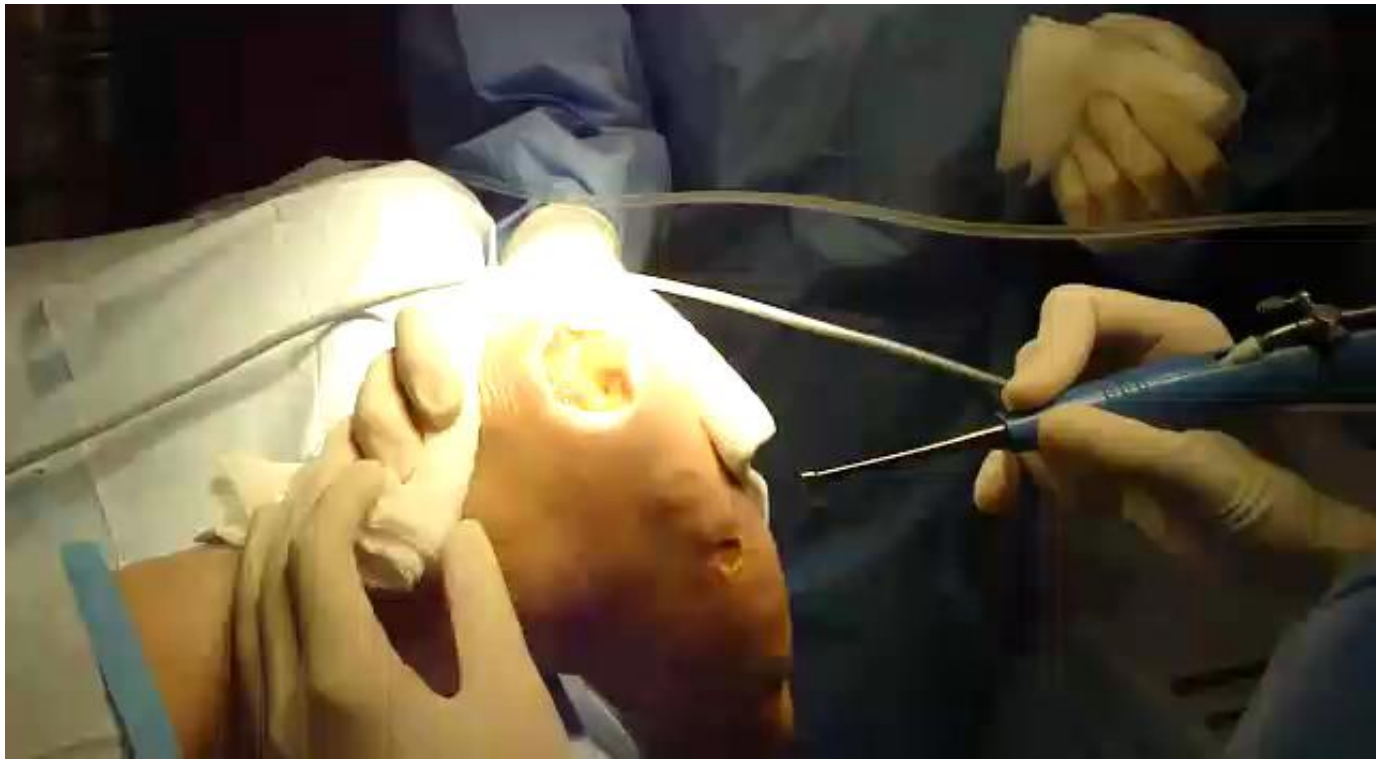


No evidences in Local Wound Care

Limitation with Type of Offloading

Alternatives to Surgical debridement





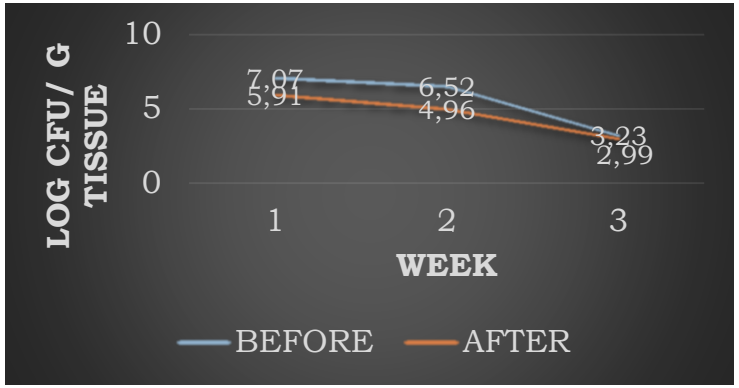
Gibbons GW, Orgill DP, Serena TE, Novoung A, O'Connell JB, Li WW, Driver VR.A prospective, randomized, controlled trial comparing the effects of noncontact, low-frequency ultrasound to standard care in healing venous leg ulcers. Ostomy Wound Manage. 2015 Jan;61(1):16-29

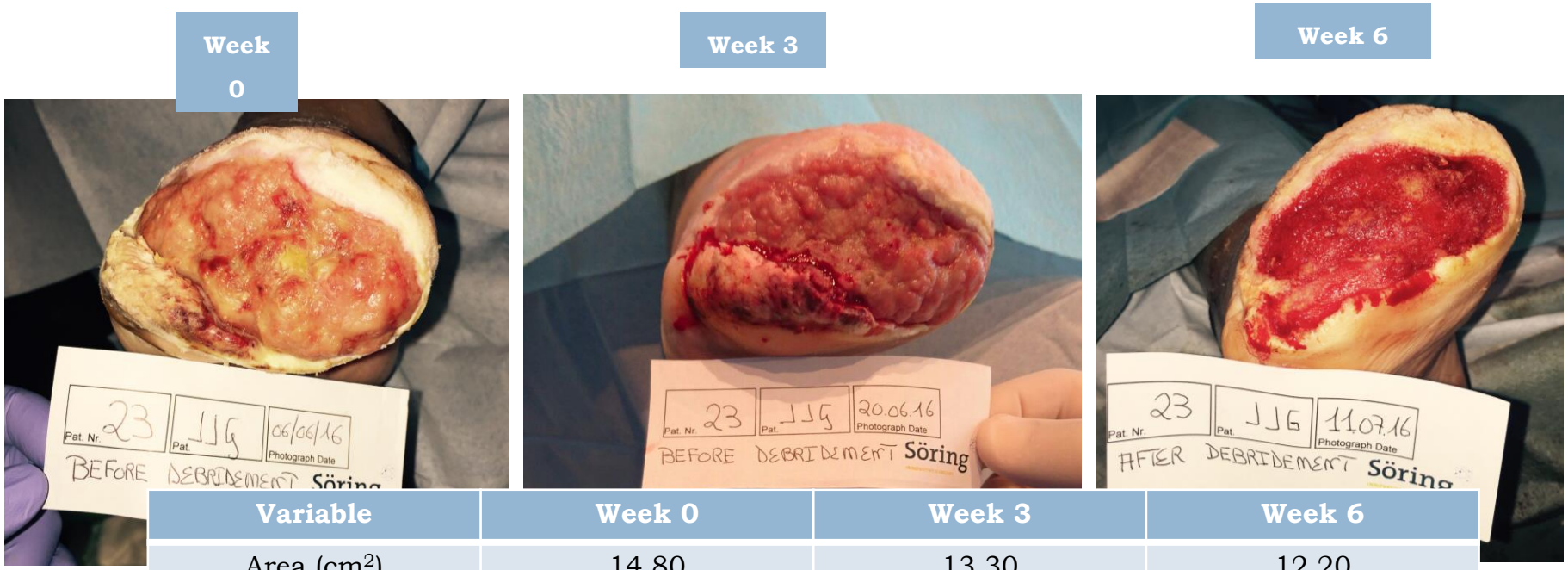
Ultrasound-assisted debridement of neuroischaemic diabetic foot ulcers, clinical and microbiological effects: a case series

Objective: To evaluate the clinical and microbiological effects of sequential wound debridement in a case series of neuroischaemic diabetic foot ulcers (DFUs) using an ultrasound-assisted wound debridement (UAW) device.
Method: A prospective, single-centre study, involving a case series of 24 neuroischaemic DFUs, was conducted to evaluate sequential wound debridement with UAW during a six-week treatment period. Soft tissue punch biopsies were taken every second week of treatment, both before and after wound debridement sessions. Qualitative and quantitative microbiological analysis was performed and wounds were assessed at patient admission, and before and after each debridement procedure.
Results: Wound tissue quality scores improved significantly from a mean score of 2.1±1.3 points at patient inclusion, to 5.3±1.7 points (p=0.001). Mean wound sizes were 4.45cm^2 (range: 2–12.25cm^2) at week zero, and 2.75cm^2 (range: 1.67–10.70cm^2) at week six (p=0.04). The mean number of bacterial species per culture determined at week zero and at week six was 2.53±1.55 and 1.90±1.16, respectively (p=0.023). Wound debridement resulted in significant decreases in bacterial counts (1.17, 1.31 and 0.77 log units in colony forming units (CFU) for week zero, three and six, respectively). The average bacterial load in tissue samples before and after wound debridement after the six-week treatment was Log 5.55±0.91CFU/g and Log 4.59±0.89CFU/g, respectively (p<0.001).
Conclusions: The study results showed a significant bacterial load reduction in DFU tissue samples as a result of UAW debridement, independent of bacterial species, some of which exhibited antibiotic-resistance. Significant bacterial load reduction was correlated with improved wound conditions and significant reductions of wound size.
Declaration of interest: The UAW device was provided by the manufacturer, Söring GmbH, Germany. The company had no role in the design, data collection, analysis, review, or approval of the manuscript.

José Luis Lázaro-Martínez,[1] PhD; **Francisco Javier Álvaro-Afonso,**[1] PhD; **Yolanda García-Álvarez,**[1] PhD; **Raúl Juan Molines-Barroso,**[1] PhD; **Esther García-Morales,**[1] PhD; **David Sevillano-Fernández,**[1] PhD
***Corresponding author email:** diabetes@ucm.es
1 Diabetic Foot Unit, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain. **2** Section of Microbiology, Department of Medicine, School of Medicine. Universidad Complutense de Madrid.

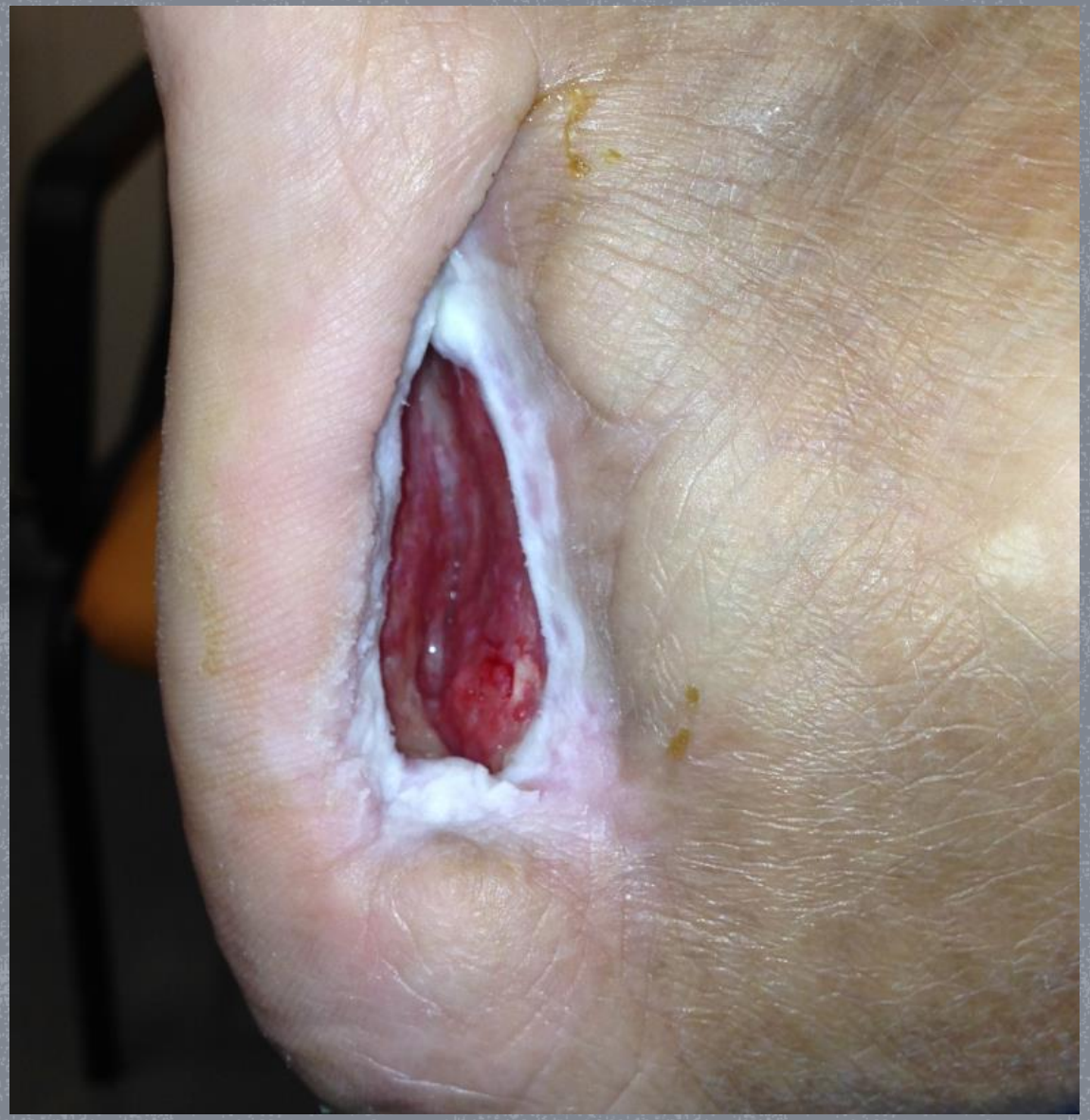
Association between bacteria load reduction and clinical improving

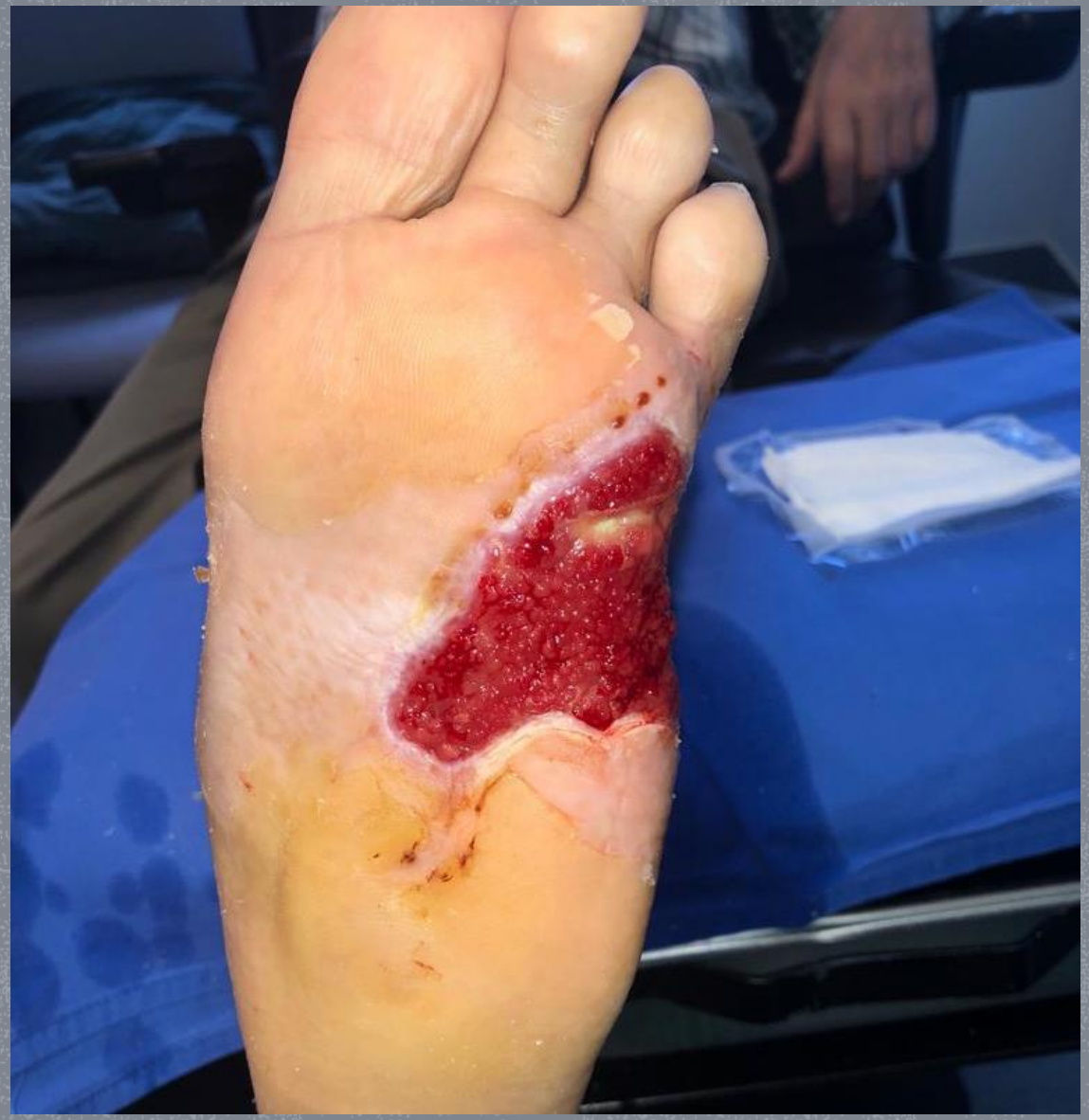


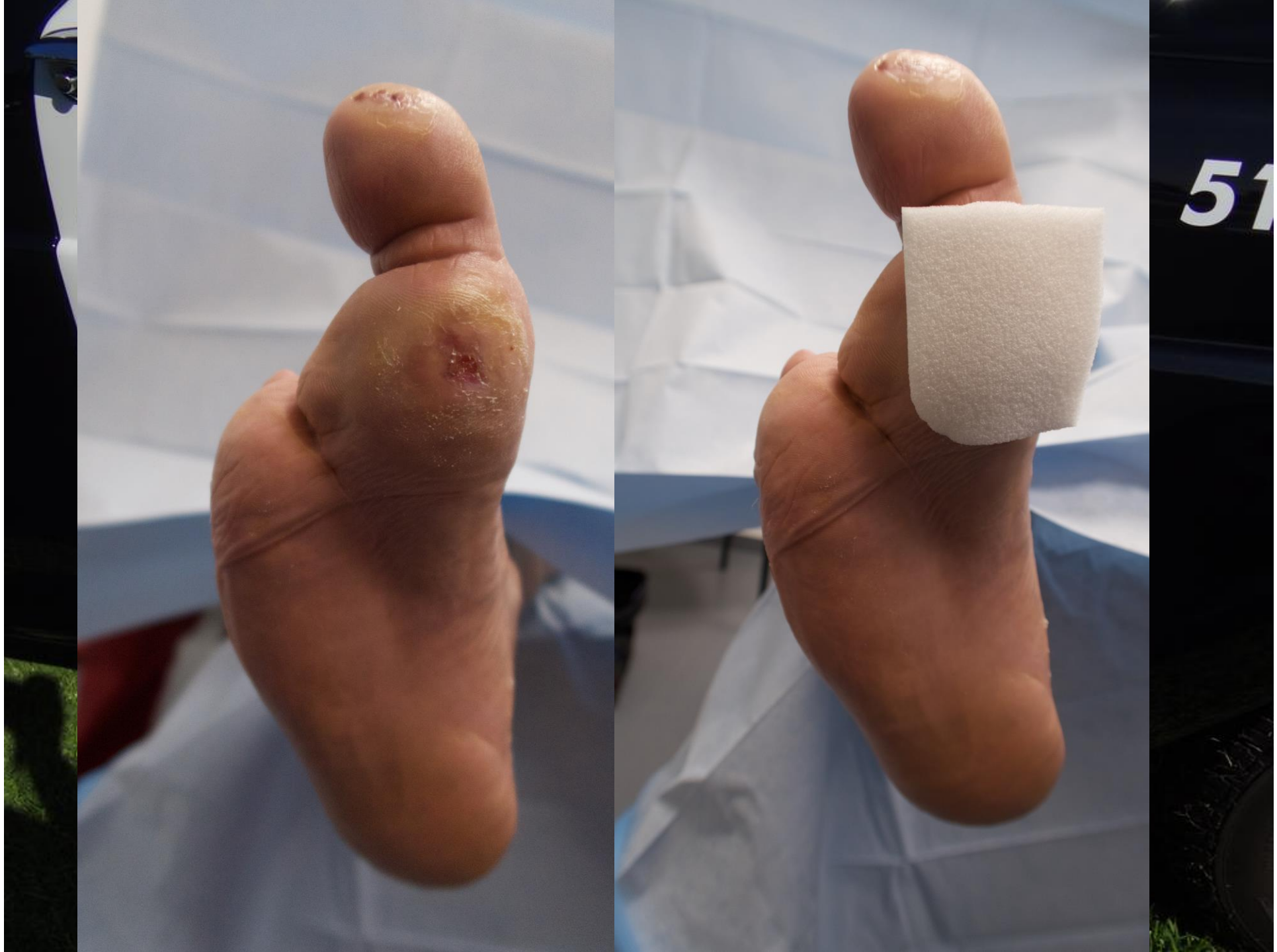


Variable	Week 0	Week 3	Week 6
Area (cm^2)	14.80	13.30	12.20
Wollina Score	2	3	5

Lazaro-Martínez JL, Alvaro-Afonso FJ, Garcia-Morales E, Garcia-Alvarez Y, Molines-Barroso R, Sanz-Corbalan I. Clinical and microbiological outcomes after sequential low-frequency ultrasound wound debridement of neuroischemic diabetic foot ulcers. Oral Presentation. 13th annual meeting of the DFSG 9-11 September 2016. Stuttgart. Germany

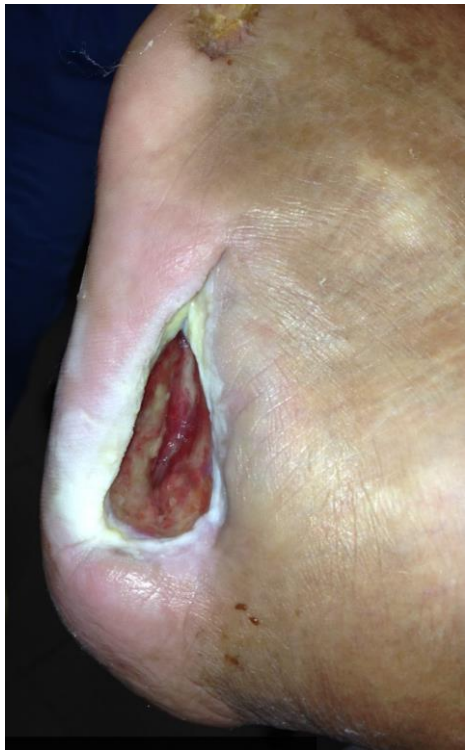


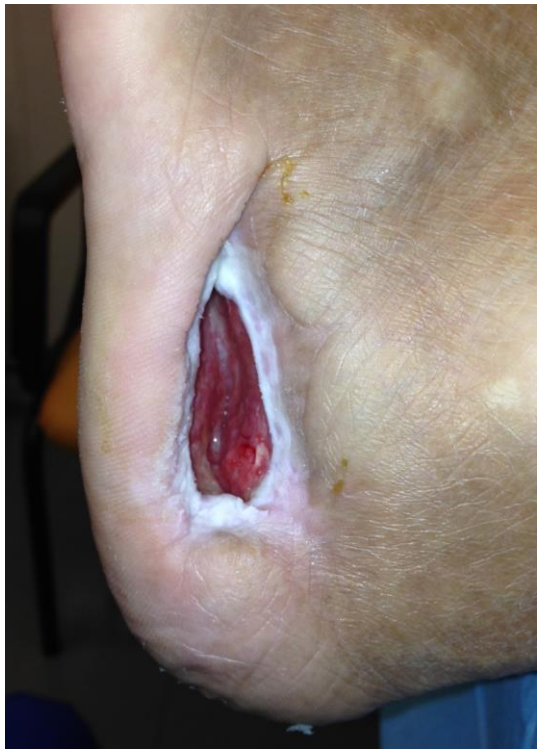




Re-assess DFU every 2/4 weeks

- Wound Area Reduction less tan 30% or 50% after 2 or 4 weeks, respectively

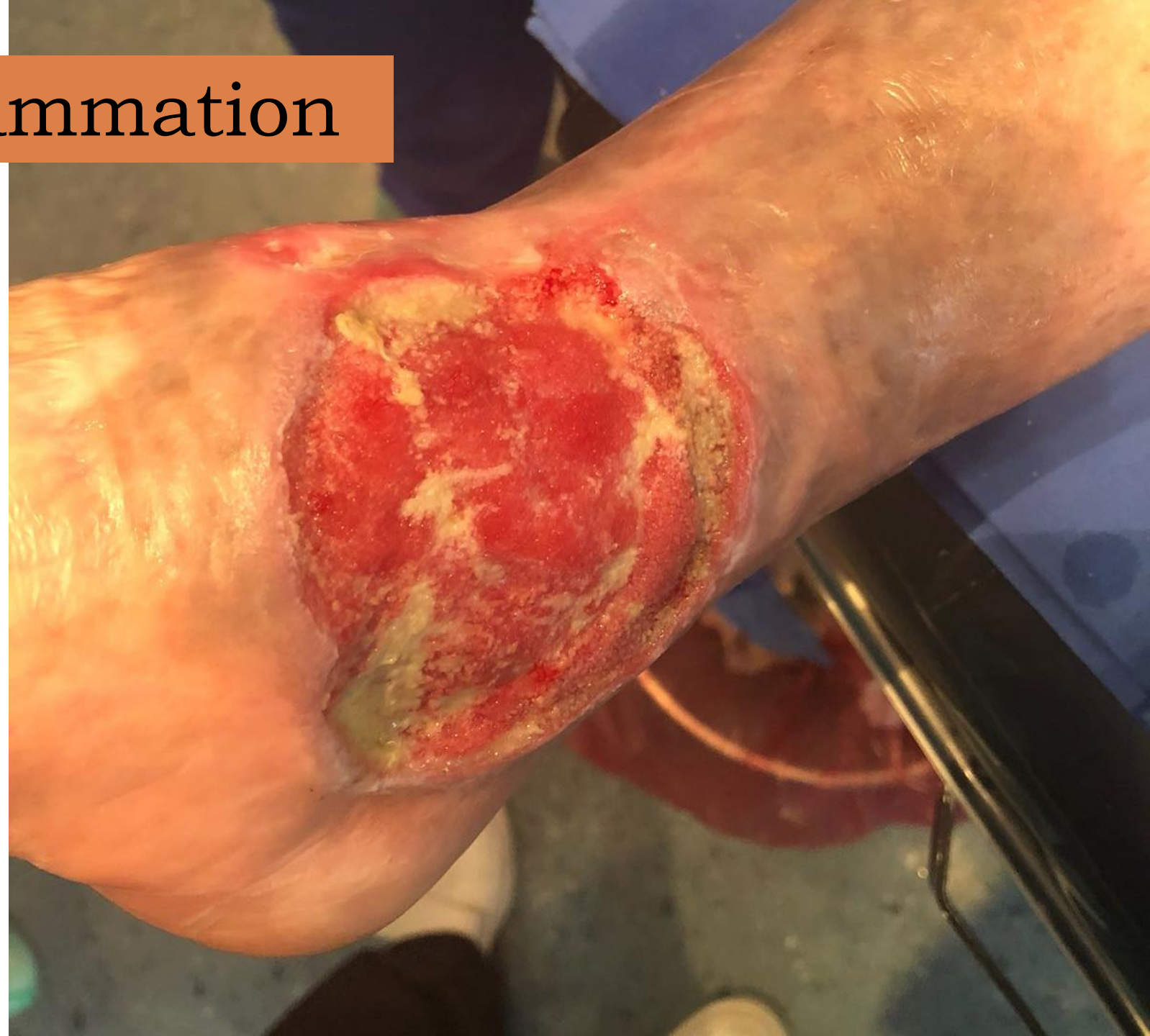




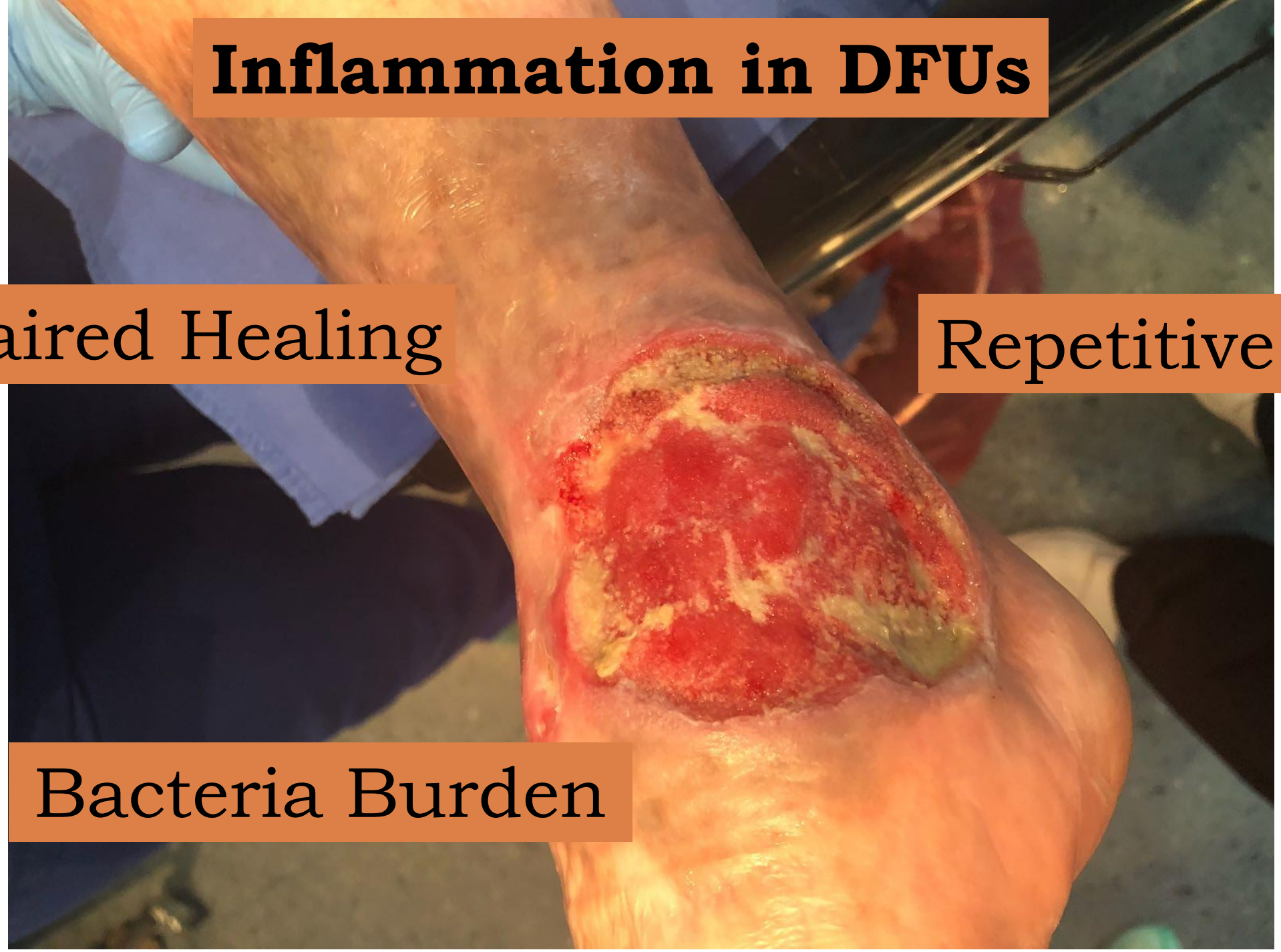
Game FL, Attinger C, Hartemann A, et al. IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes/metabolism research and reviews 2016; 32 Suppl 1: 75-83.

Inflammation

The Main Enemy in Healing Process



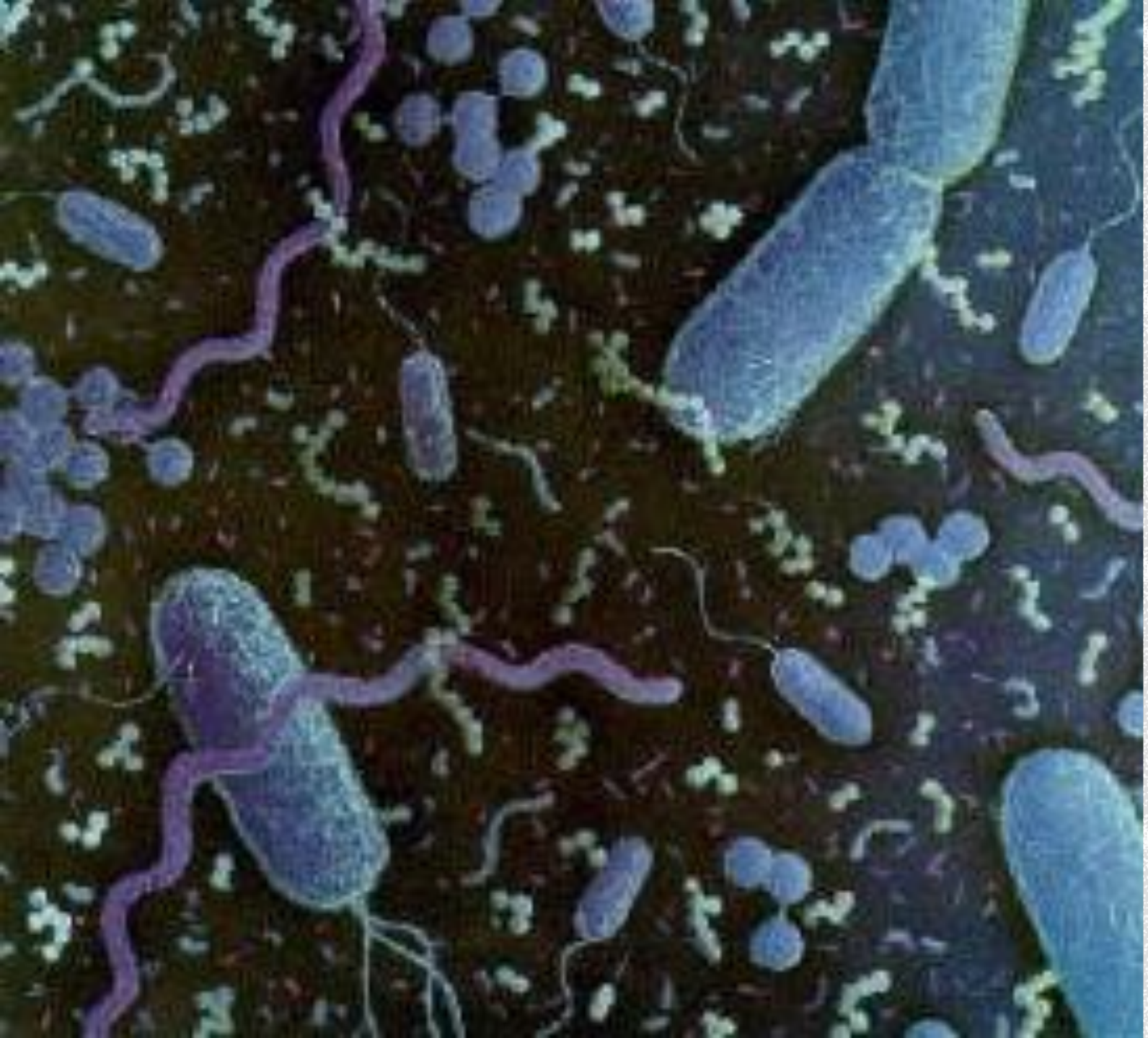
Inflammation in DFUs



Impaired Healing

Repetitive stress

Bacteria Burden



Bacteria Load (bioburden)

Bacterial Load Predicts Healing Rate in Neuropathic Diabetic Foot Ulcers Ling Xu, Susan V. McLennan, Lisa Lo, Anas Natfaji, Thyra Bolton, Yu Liu, Stephen M. Twigg, and Dennis K. Yue Diabetes Care 2007 30: 378-380

Elevated levels of MMPs in DFUs is very Likely

JWC
journal of wound care

education

Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence

• **Objective:** In the past 20 years, research and clinical trials on the healing process of chronic wounds have highlighted the key role of the family of enzymes called matrix metalloproteinases (MMPs). If a strong correlation between the course of healing of chronic wounds and the levels of a biological marker can be demonstrated, then it may be possible to: i) identify the best marker threshold to predict the clinical evolution of the pathology; and ii) if causality has been found between the marker and pathology, to improve the healing outcome, to change the marker level.
• **Method:** The databases Medline and Embase were searched to identify clinical trials pertaining to the assessment of MMPs in chronic wounds with the following keywords 'metalloproteinase' or 'metalloprotease' and 'wound healing'. Clinical trials were considered for inclusion if they enrolled patients with cutaneous chronic wounds and were published in English. More than 50 clinical trials, consensus documents and guidelines were assessed for this review.
• **Results:** MMPs play key roles in the wound healing process, and excessive expression and activation of some of these enzymes is seen in chronic cutaneous wounds where healing is delayed. Levels of MMPs are affected by a number of factors, including patient and wound characteristics.
• **Conclusion:** Levels of MMPs can be used to indicate the prognosis of chronic wounds and protease modulating treatments used to improve healing rates.
• **Declaration of interest:** The authors report no conflicts of interest in this work.

Internal Factors

Specially associated with bacteria burden and an poor vascular status

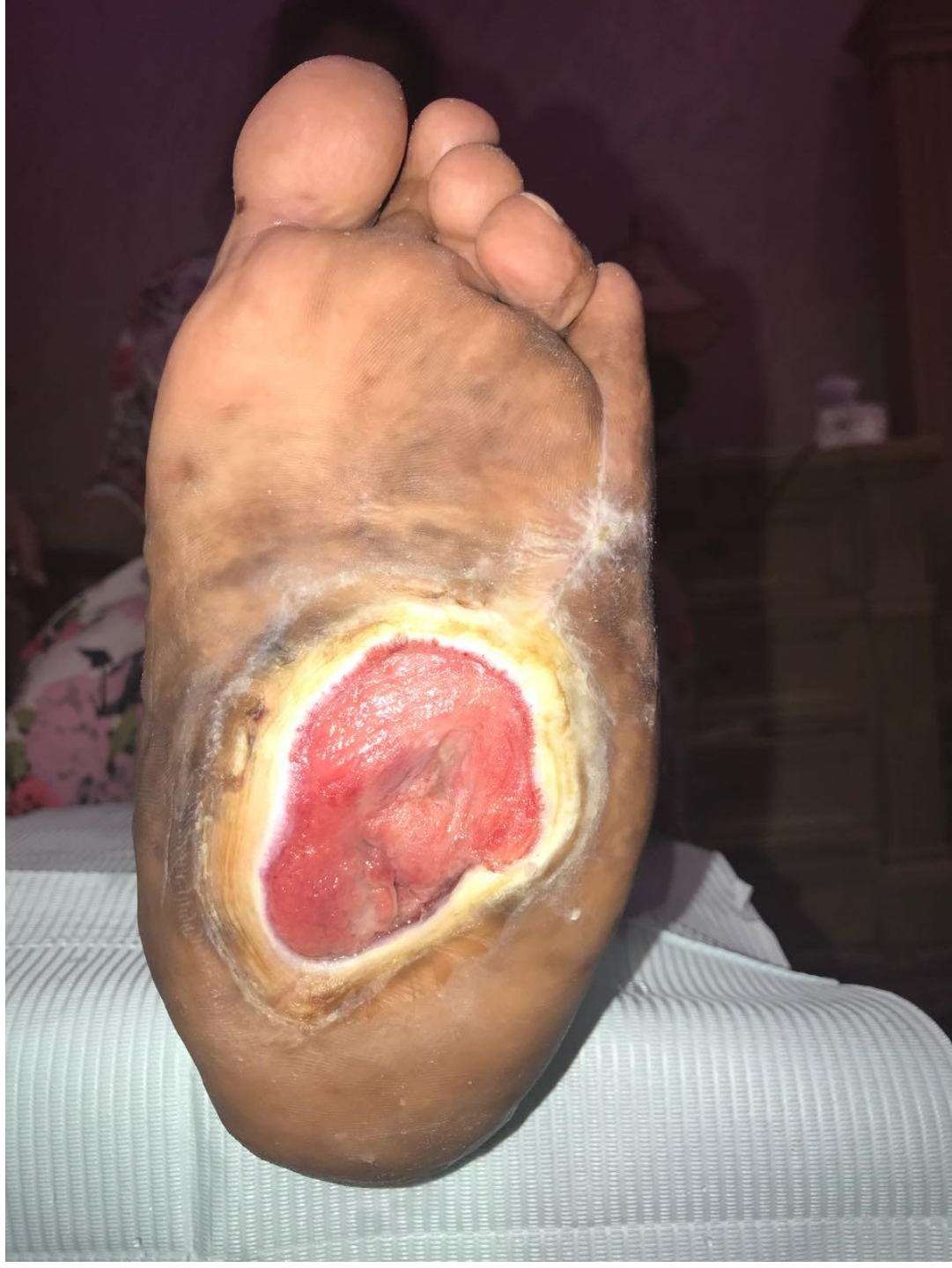
External Factors

Repetitive stress (Mainly DFUs are located in foot pressures' areas)

65-70% DFUs have elevated levels of MMPs

MMP9, **MMP2** and **MMP-1/TIMP-1** ratio

¿Cause or consequence?



Lobmann R, et al. (2002) Expression of matrix-metalloproteinases and their inhibitors in the wound of diabetic and nondiabetic patients. Diabetologia 45:1011-1016.

Liu Y, et al. (2009) Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers. Diabetes Care 32:117–119.

Muller M, et al. (2008) Matrix metalloproteinases and diabetic foot ulcers: the ratio of MMP-1 to TIMP-1 is a predictor of Wound healing. DiabetMed 25:419–426

THE LANCET
Diabetes & Endocrinology

Volume 6 · Issue 1 · January 2018 www.thelancet.com/diabetes-endocrinology

Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial

Michael Edmonds, José Luis Lázaro-Martínez, Jesus Manuel Alfayate-García, Jacques Martini, Jean-Michel Petit, Gerry Rayman, Ralf Lobmann, Luigi Uccioli, Anne Sauvadet, Serge Bohbot, Jean-Charles Kerihuel, Alberto Piaggesi

Summary

Background Diabetic foot ulcers are serious and challenging wounds associated with high risk of infection and lower-limb amputation. Ulcers are deemed neuroischaemic if peripheral neuropathy and peripheral artery disease are both present. No satisfactory treatment for neuroischaemic ulcers currently exists, and no evidence supports one particular dressing. We aimed to assess the effect of a sucrose octasulfate dressing versus a control dressing on wound closure in patients with neuroischaemic diabetic foot ulcers.

Methods We did a randomised, double-blind clinical trial (Explorer) in 43 hospitals with specialised diabetic foot clinics in France, Spain, Italy, Germany, and the UK. Eligible participants were inpatients or outpatients aged 18 years or older with diabetes and a non-infected neuroischaemic diabetic foot ulcer greater than 1 cm² and of grade IC or IIC (as defined by the University of Texas Diabetic Wound Classification system). We excluded patients with a severe illness that might lead to them discontinuing the trial and those who had surgical revascularisation in the month before study entry. We randomly assigned participants (1:1) via a computer-generated randomisation procedure (concealed block size two); stratified by study centre and wound area (1–5 cm² and 5–30 cm²), to treatment with either a sucrose octasulfate wound dressing or a control dressing (the same dressing without sucrose octasulfate) for 20 weeks. Both groups otherwise received the same standard of care for a 2-week screening period before randomisation and throughout the 20-week trial. Dressings were applied by nursing staff (or by instructed relatives for some outpatients). Frequencies of dressing changes were decided by the investigator on the basis of the clinical condition of the wound. Patients were assessed 2 weeks after randomisation, then monthly until week 20 or occurrence of wound closure. The primary outcome, assessed by intention-to-treat, was proportion of patients with wound closure at week 20. This trial is registered with ClinicalTrials.gov, number NCT01717183.

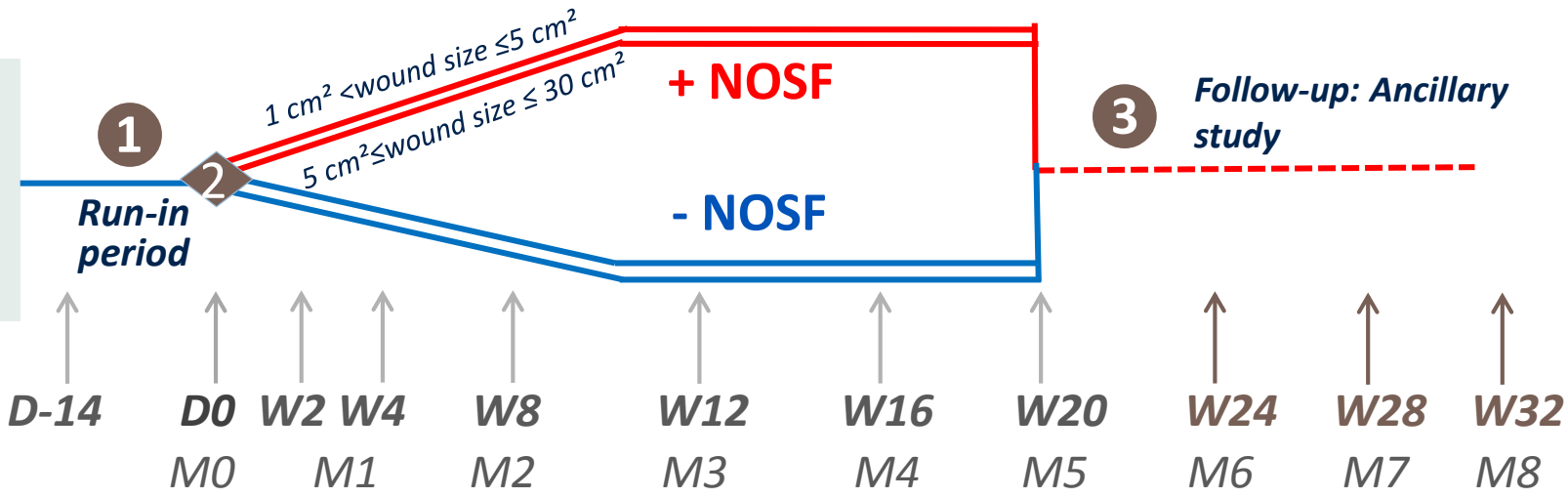
Findings Between March 21, 2013, and March 31, 2016, we randomly assigned 240 individuals to treatment: 126 to the sucrose octasulfate dressing and 114 to the control dressing. After 20 weeks, wound closure occurred in 60 patients (48%) in the sucrose octasulfate dressing group and 34 patients (30%) in the control dressing group (18 percentage points difference, 95% CI 5–30; adjusted odds ratio 2·60, 95% CI 1·43–4·73; p=0·002). In both groups, the most frequent adverse events were infections of the target wound: 33 wound infections in 25 (20%) patients of 126 in the sucrose octasulfate dressing group and 36 in 32 (28%) patients of 114 in the control dressing group. Minor amputations not affecting the wound site were also reported in one (1%) patient in the sucrose octasulfate dressing group and two (2%) patients in the control dressing group. Three (2%) patients assigned to the sucrose octasulfate dressing and four (4%) assigned to the control dressing died, but none of the deaths were related to treatment, procedure, wound progression, or subsequent to amputation.

The EXPLORER RCT - Design

- Randomised, double blind, controlled and stratified trial, conducted in two parallel groups

1 *Run-in period*

- Patient consent
- Validation of inclusion and exclusion criteria
- Prescription of an off- loading system



2 *Randomisation (D0) + Treatment period (D0 – W20)*

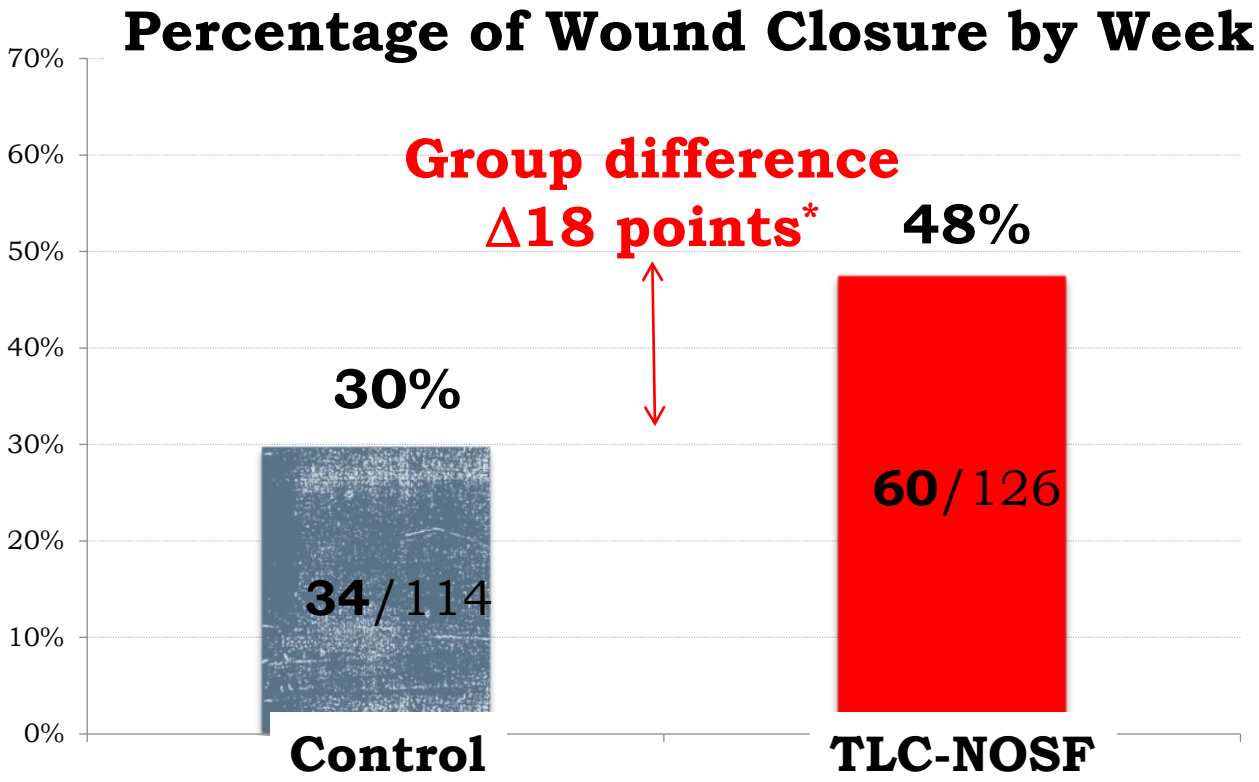
- Δ Wound surface area D_{-14} vs W_0 ≤ 30%
- No infection (whatever wound, whatever limb)
- Off- loading compliance confirmed
- HbA1c ≤10% (if not available at D-14)

3 *Follow-up: Ancillary study*

All the patients will participate to the follow-up study.
In case of wound closure, at any time of the follow-up, the epithelialisation will be confirmed two weeks after.

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:186-96.

RESULTS - Primary Endpoint
Wound Closure by Week 20. Main efficacy analysis, ITT population



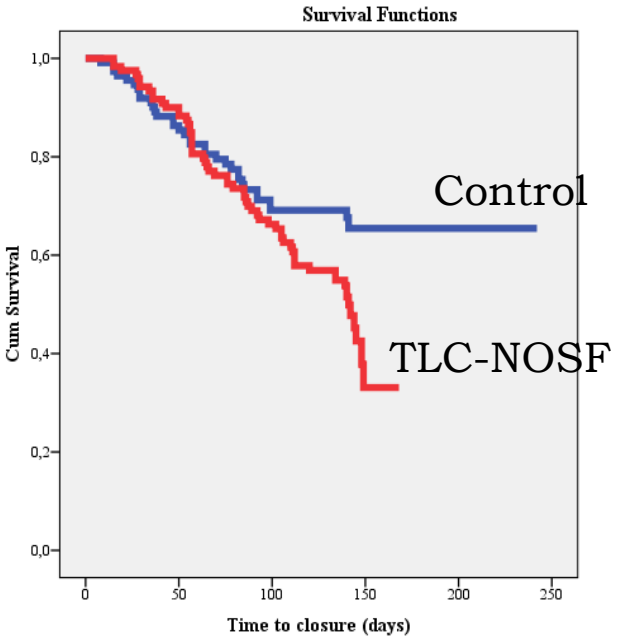
95% CI of the difference: 5% to 30%

Significantly more wound closure were observed in the TLC-NOSF group.

Wound closure: Defined as 100% epithelialization with no drainage and confirmed two weeks later by the investigators.
Chi-square test, 2-sided: ***p=0.005***

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:186-96.

RESULTS - Secondary Endpoints
Time to closure (in days) by week 20 – Kaplan Meier analysis



	Control group (n=114)	TLC-NOSF group (n=126)	Time to Closure Difference (Control-Treatment)	Log rank (Mantel-Cox)
ITT analysis	**180 ± 9** (163-198)	**120 ± 5** (110-129)	**60 days**	***p*=0.029**

Data are given as mean ± SE (95% CI). Median value are not given as the control group did not reach 50% of wound closure.
Estimation is limited to the largest survival time if it is censored. Confirmed closure population.

- **TLC-NOSF shortened the mean time to closure by 60 days compared to an advanced neutral dressing.**

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:186-96.

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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REVIEW

Collagen-based wound dressings for the treatment of diabetes-related foot ulcers: a systematic review

Crystal Holmes[1]
James S Wrobel[1]
Mark P MacEachern[2]
Blaise R Boles[3]

[1]Department of Internal Medicine, University of Michigan Medical School, [2]A Alfred Taubman Health Sciences Library, University of Michigan, [3]Department of Molecular, Cellular, and Developmental Biology, University of Michigan, Ann Arbor, MI, USA

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
18 January 2013
Number of times this article has been viewed

Background: Diabetic foot ulcers are a major source of morbidity, limb loss, and mortality. A prolonged inflammatory response, extracellular matrix degradation irregularities, and increased bacteria presence have all been hypothesized as major contributing factors in the delayed healing of diabetic wounds. Collagen components such as fibroblast and keratinocytes are fundamental to the process of wound healing and skin formation. Wound dressings that contain collagen products create a biological scaffold matrix that supports the regulation of extracellular components and promotes wound healing.

Methods: A systematic review of studies reporting collagen wound dressings used in the treatment of Diabetic foot ulcers was conducted. Comprehensive searches were run in Ovid MEDLINE, PubMed, EMBASE, and ISI Web of Science to capture citations pertaining to the use of collagen wound dressings in the treatment of diabetic foot ulcers. The searches were limited to human studies reported in English.

Results: Using our search strategy, 26 papers were discussed, and included 13 randomized designs, twelve prospective cohorts, and one retrospective cohort, representing 2386 patients with diabetic foot ulcers. Our design was not a formal meta-analysis. In those studies where complete epithelialization, 58% of collagen-treated wounds completely healed (weighted mean 67%). Only 23% of studies reported control group healing with 29% healing (weighted mean 11%) described for controls.

Conclusion: Collagen- based wound dressings can be an effective tool in the healing of diabetic foot wounds. The current studies show an overall increase in healing rates despite limitations in study designs. This study suggests that future works focus on biofilms and extracellular regulation, and include high risk patients.

Keywords: bio films, matrix, wound healing, scaffold, dressings

- **ORC/Collagen** dressing decreases in collagenase-like activity; gelatinase, matrix metalloproteinase (MMP)-2, and MMP-9 levels; and increased scavenged free radicals and binding of growth factors
- **Conclusion:** Collagen- based wound dressings **can be an effective tool in the healing of diabetic foot wounds**. The current studies show an overall increase in healing rates despite limitations in study designs. This study suggests that future works focus on biofilms and extracellular regulation, and include high risk patients.

Our personal published experience

Originales

Localizador web
Artículo 198.352

Estudio aleatorizado y comparativo de un apósito de colágeno y celulosa oxidada regenerada en el tratamiento de úlceras neuropáticas de pie diabético

José Luis Lázaro-Martínez[a], Esther García-Morales[a], Juan V. Beneit-Montesinos[a], Fermín R. Martínez-de-Jesús[b] y Francisco Javier Aragón-Sánchez[c]

[a]Unidad de Pie Diabético. Clínica Universitaria de Podología. Universidad Complutense de Madrid. Madrid. España.
México.
. Las Palmas. España.

RANDOMIZED COMPARATIVE TRIAL OF A COLLAGEN/OXIDIZED REGENERATED CELLULOSE DRESSING IN THE TREATMENT OF NEUROPATHIC DIABETIC FOOT ULCER

Introduction. Diabetic foot is a complication of diabetes mellitus that manifests with the development of ulcers that frequently precede amputation. Several studies have verified that the environment of the diabetic neuropathic foot ulcer contains a high concentration of metalloproteinases. The aim of the present study was to evaluate the efficacy of a protease-modulating dressing in the treatment of neuropathic diabetic foot ulcers.

Material and method. A randomized controlled trial was conducted in 40 patients with a 6-week or longer history of neuropathic diabetic foot ulcer. The patients were randomized to two groups: group 1 (n = 20) received treatment with the protease-modulating dressing while the control group (group 2; n = 20) received the treatment specified in the standardized protocol for good wound care. The patients were then followed-up for 6 weeks.

Results. After 6 weeks, healing was achieved in 12 patients (63% of n = 19) in group 1 under treatment with the protease-modulating dressing versus three patients (15% of n = 19) in the control group ($p < 0.03$).

The mean time to healing was 23.3 ± 9.9 days in group 1 and 40.6 ± 1.15 days in group 2 ($p < 0.01$).

Conclusions. The results confirm the hypothesis that the use of protease-modulating dressings in patients with neuropathic diabetic foot ulcers leads to better tissue regeneration than good wound care.

HEALTH ECONOMICS

A Retrospective Analysis of the Cost-effectiveness of a Collagen/Oxidized Regenerated Cellulose Dressing in the Treatment of Neuropathic Diabetic Foot Ulcers

José Luis Lázaro-Martínez; Francisco Javier Aragón-Sánchez; Esther García-Morales; Juan Vicente Beneit-Montesinos; and Máximo González-Jurado **[AU: Please provide credentials — eg, MD, PhD — for each author.]**

Abstract

Oxidized regenerated cellulose and collagen matrix dressings (ORC+C) have shown evidence of clinical effectiveness in the treatment of neuropathic diabetic foot ulcers (DFUs). A retrospective study to analyze cost-effectiveness was performed using results from an earlier, 6-week randomized clinical trial carried out on patients (n = 40) with neuropathic DFU treated with an ORC+C dressing. The patients were randomized to two groups: group 1 (n = 20) was treated with an ORC+C dressing and group 2 (n = 20), the control group, received wound care in accordance with the standard protocol in use at the authors' healthcare center. Effectiveness was defined as the percentage of patients whose wounds had healed at the end of the study. Total cost of care (including staff, ancillary supplies, dressings, and patient transport costs), the number of patients needing to treat (NNT), the mean cost, the incremental cost, and the average cost effectiveness were analyzed. NNT was 2.11 (95% CI: 1.34-4.96. $P = 0.03$). Treatment effectiveness was 63% in group 1 and 16% in group 2. Incremental cost-effectiveness was $683.18, the amount needed to avoid nonhealing in the control group. Average cost effectiveness was $561.48 in group 1 versus $2,577.65 in group 2 (total cost/effectiveness in each group). Treating neuropathic ulcers with an ORC+C dressing provides an excellent cost-benefit ratio that saves an average of $2,280.13 per patient over 6 weeks of treatment. This saving may be even greater in longer-term treatment programs and among patients with ulcers that show little tendency to heal.

Key Words: diabetic foot, cost-effectiveness analysis, metalloproteinase, wound healing

Index: *Ostomy Wound Management* 2010;56(11A):4–8

Main Conclusion of these studies

- Patients with DFUs treated with ORC/Collagen healed in half time that control group (23.3 ± 9.9 days in group ORC/Collagen vs 40.6 ± 1.15 days in control g
- More proportion
  ORC/Collagen g
  weeks of treatment (63% vs 15%; p < 0.03)
- Treating neuropathic ulcers with an ORC/Collagen dressing provides an excellent cost-benefit ratio that saves an average of $2,280.13 per patient over 6 weeks of treatment.

Where is the trick?

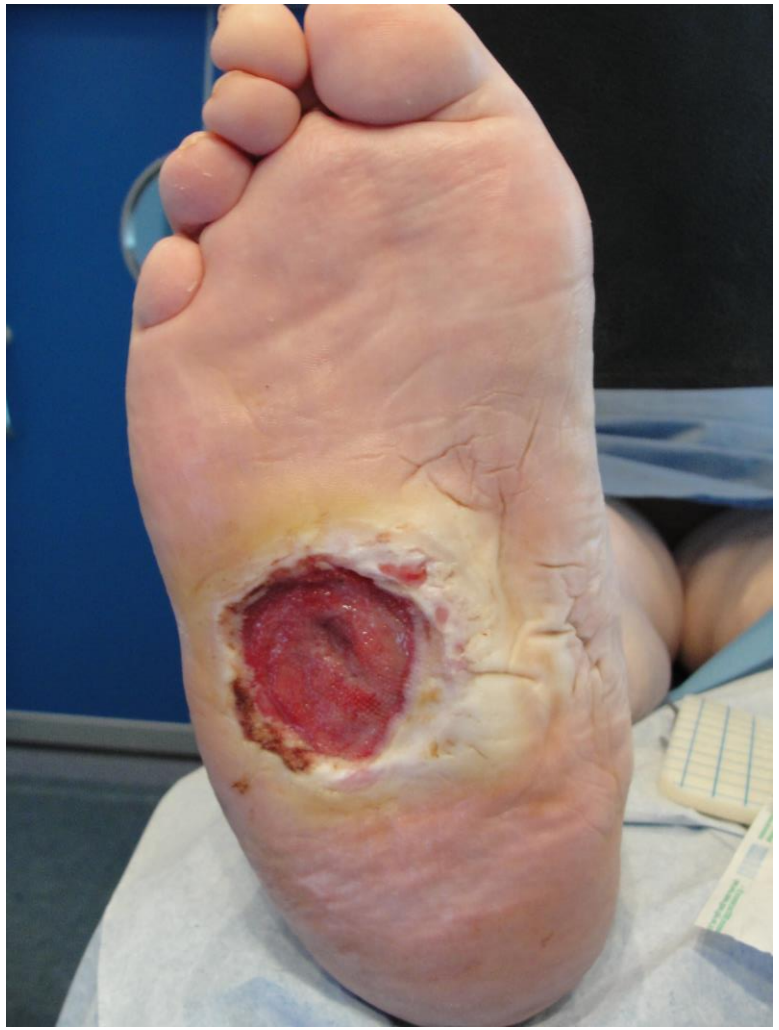
More patients
n less time
and saving money

Personal Tricks and Tips

- Applying always after a good standard of care (There are no miracles in dressing)
- Assuring that the ulcer is clean and well debrided (but remember debridement is not always a single step……Frequent debridement helps healing and dressing action: i.e. UAWD)
- The sooner you apply the dressing the faster ulcer heals (Why wait 4 weeks if the indication is clear????)
- Giving time for an ulcer's response (a dressing is not a gun shooting……) at least 4-6 weeks in neuropathic or 10-12 weeks in neuroischemic
- Checking if the dressing is working (stay on, dressing dissolved or digested….)
- If something is getting wrong sometimes the fault is ours (bad indication, wrong indication, misdiagnosis)

All this Wound Bed are welcoming MMPs control dressings

When and how to act .....



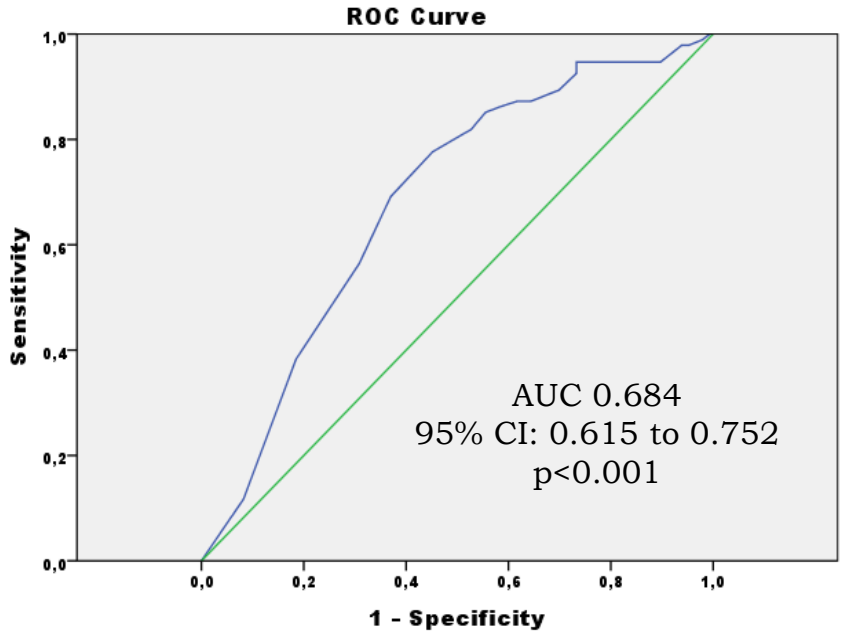
Wound Area Reduction **up to 50%** by **4 weeks** is a good predictor of complete healing

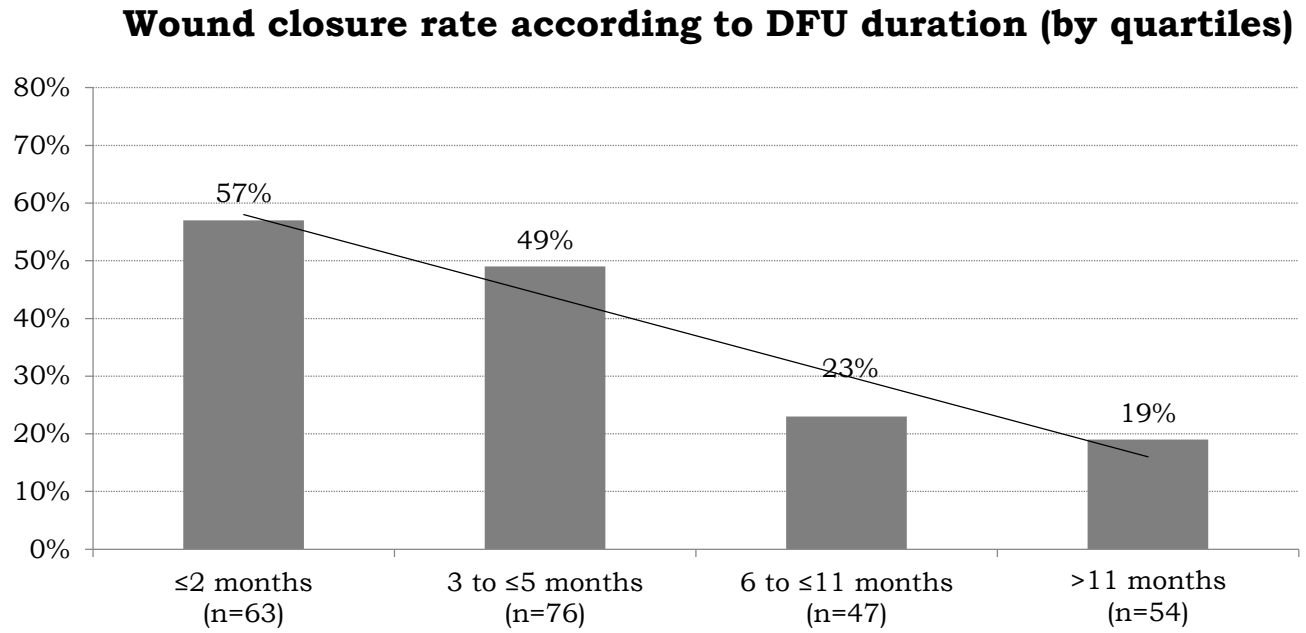
•Sheehan P, Jones P, Caselli D, et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healling in a 12-week prospective trial. Diabetes Care 2003; 26: 1879-82.

•Snyder RJ, Cardinal M, Dauphinée DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010; 56(3): 44-50.

•Lavery L, Seaman JW, Barnes SA, Armstrong DG, Keith MS. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. Diabetes Care 2008; 31(1): 26-29.

RESULTS –
DFU Duration and Wound Closure Rate (The global cohort)

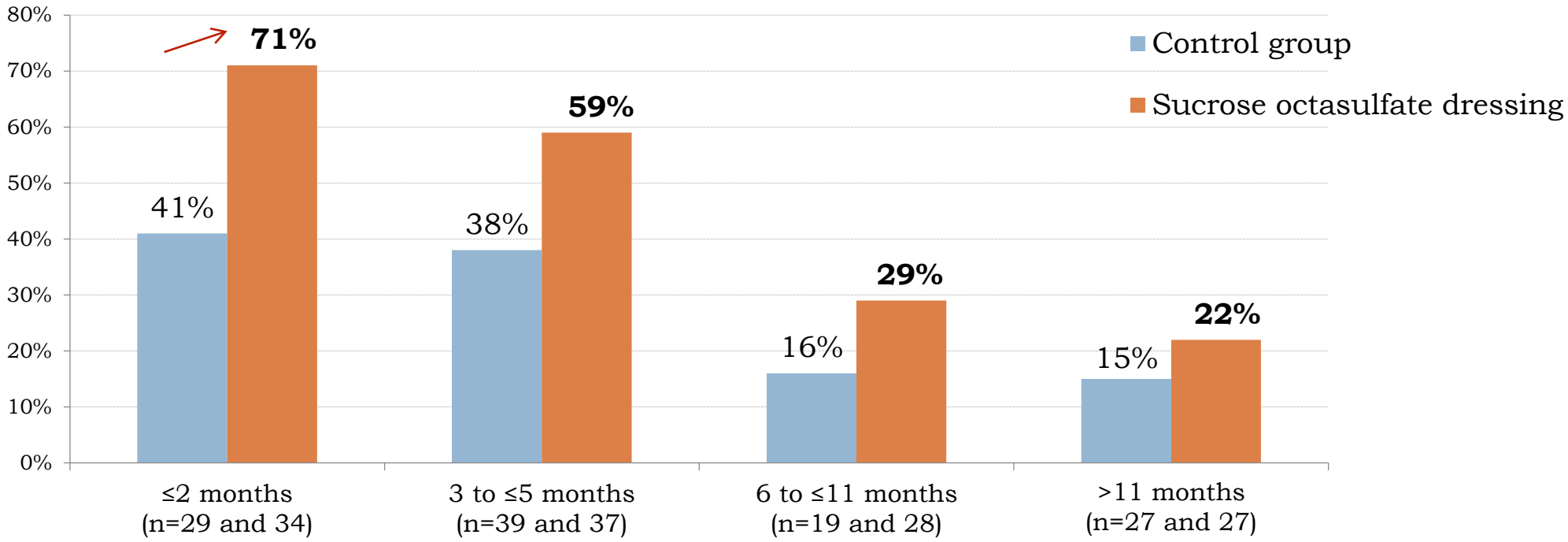




- **The duration of neuro-ischaemic DFU significantly impacts wound closure.**
- **Without regard to the treatment received, the shorter the DFU duration, the higher the wound closure rate.**

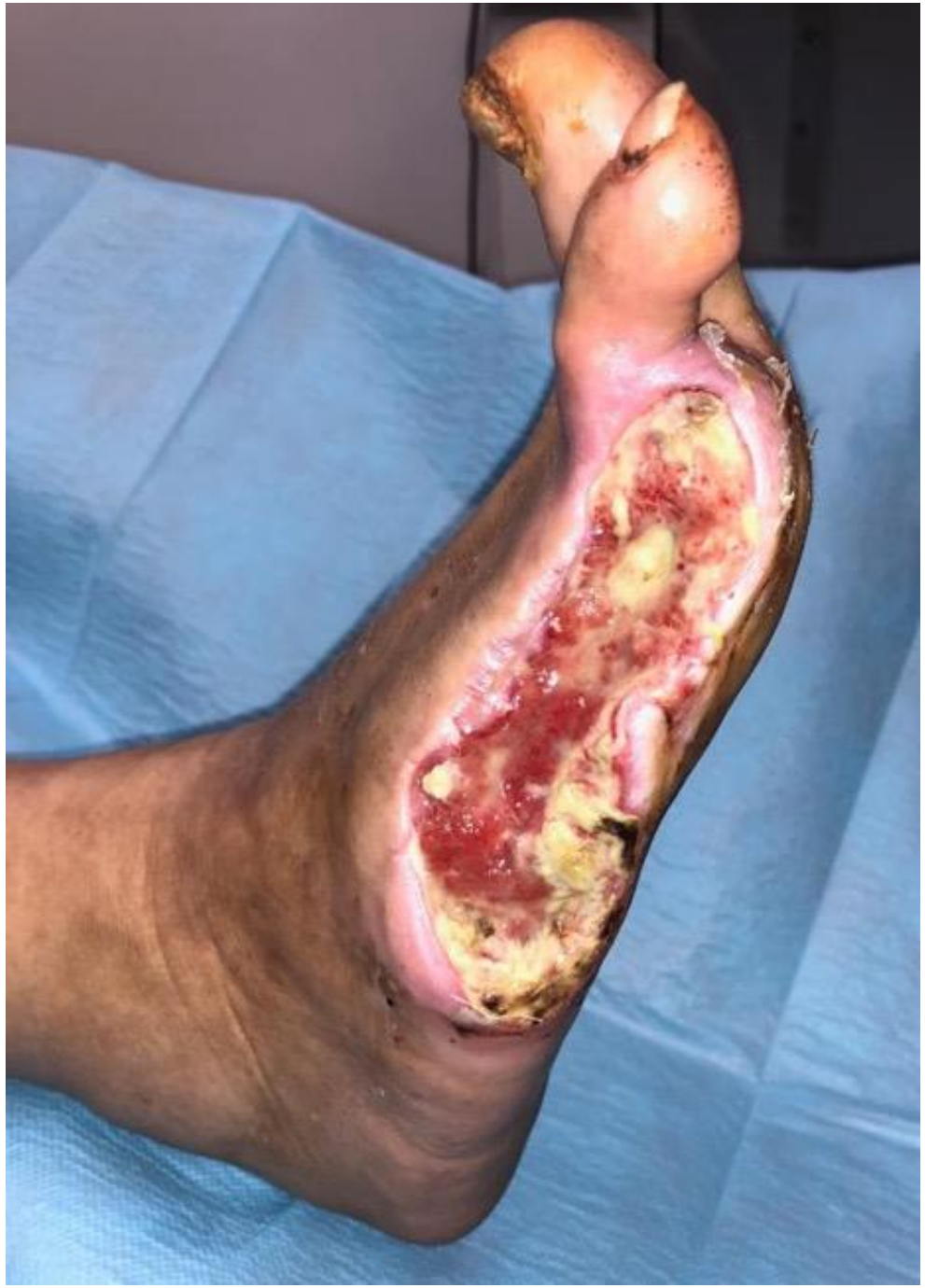
Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:186-96.

RESULTS –
DFU Duration and Wound Closure Rate (TLC-NOSF *vs* Control)



- **In each DFU duration quartile, more wound closure occurred in the sucrose octasulfate group.**
- **The highest wound closure rate was reached in patients with the most recent wounds.**

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:186-96.



❑ Neurological Assessment

- 5,07 10g. Monofilament: Affected
- Vibration: Affected

❑ Vascular Assessment

- Pulses: No palpable
- ABI: 110/130 = 0,84
- TBI: 55/130= 0,42
- TcPO2: 44 mmHg

❑ DFU diagnosis

Neuroischemic Ulcer 12 weeks duration

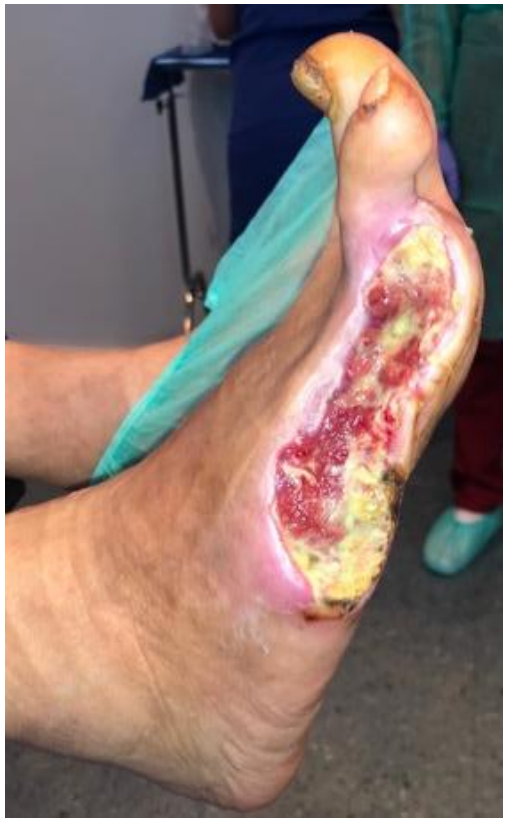
- Wagner 3
- Texas IIIC
- Pedis 3

❑ Therapeutic approach

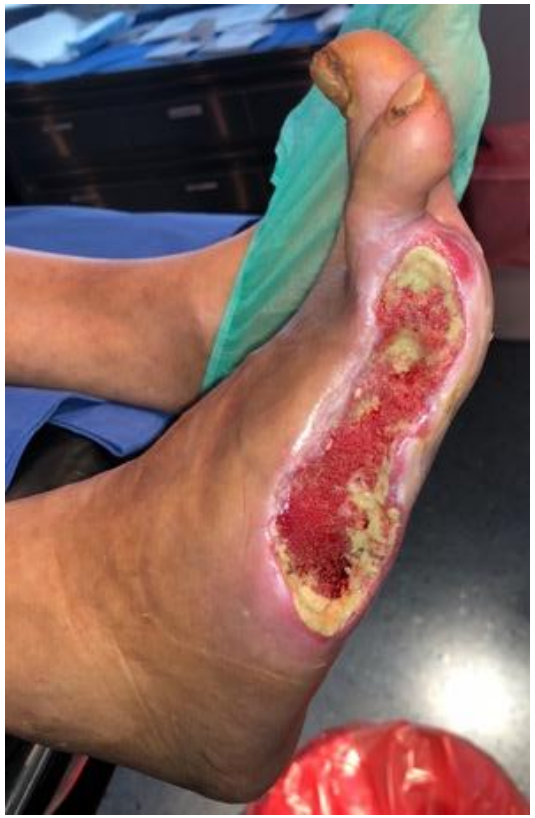
15.10.18

Fifth ray removal+ NPWT

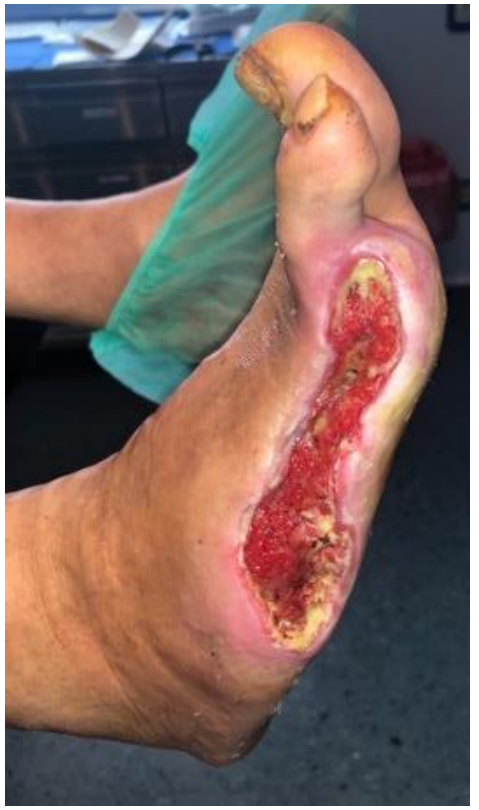
SURGERY + NPWT



MPWT REMOVAL / Antimicrobial dressing



MMPs modulator dressing

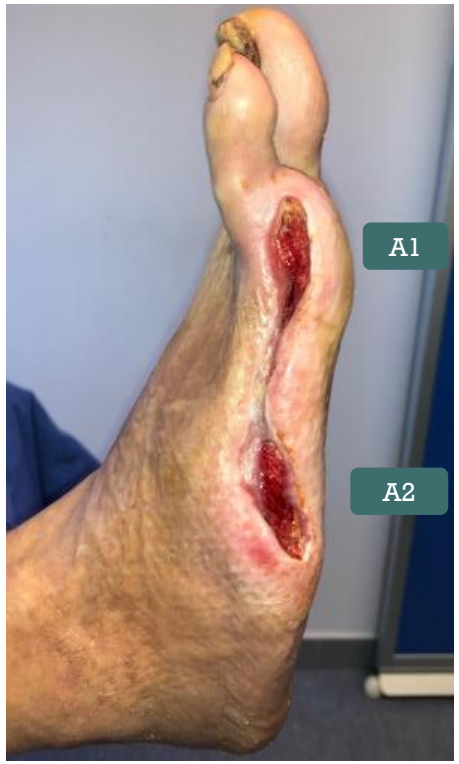


1st WEEK

2nd WEEK

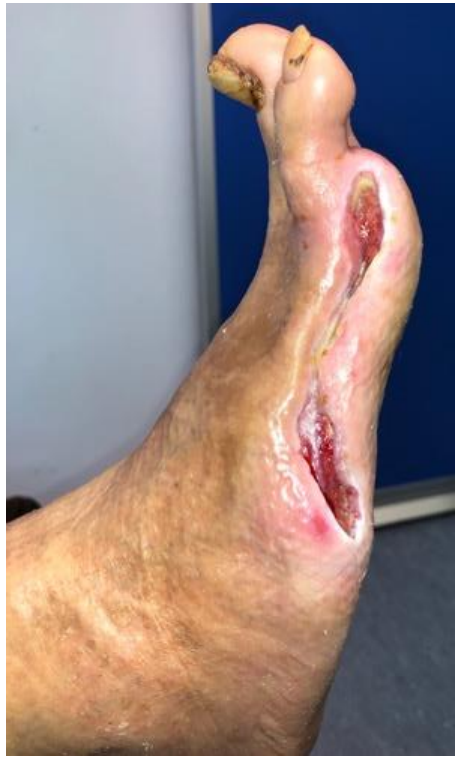
10 WEEKS

WEEK 10



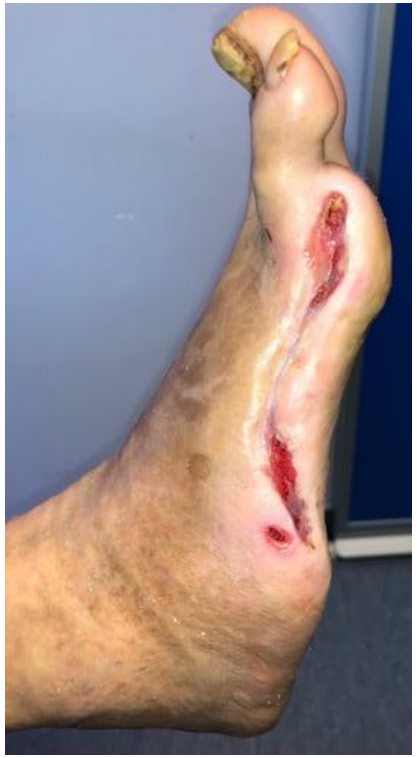
SURFACE: A1: 4,7cm^2 (3,1x1,8)
A2: 4,9cm^2 (4,3x1,6)

WEEK 12



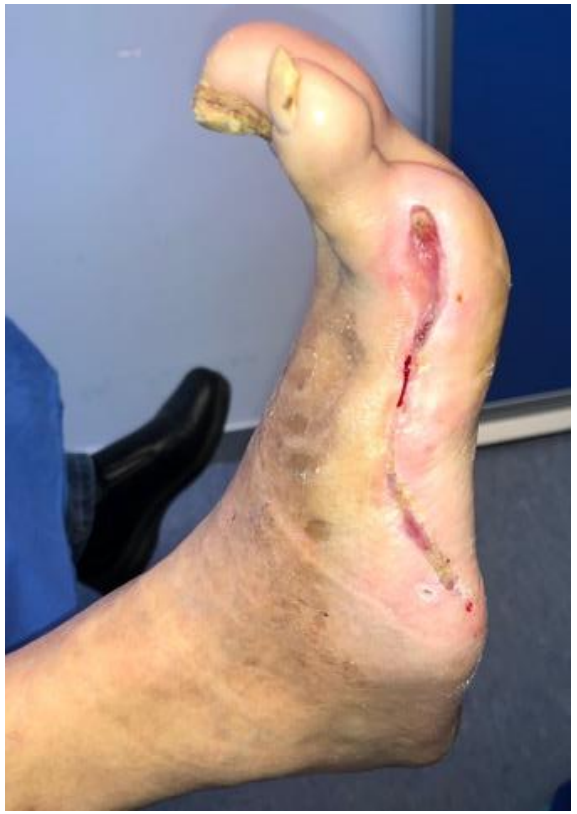
SURFACE: A1: 3,9cm^2 (3,5 x1,2)
A2: 4,3cm^2 (4,0 x1,6)

WEEK 14



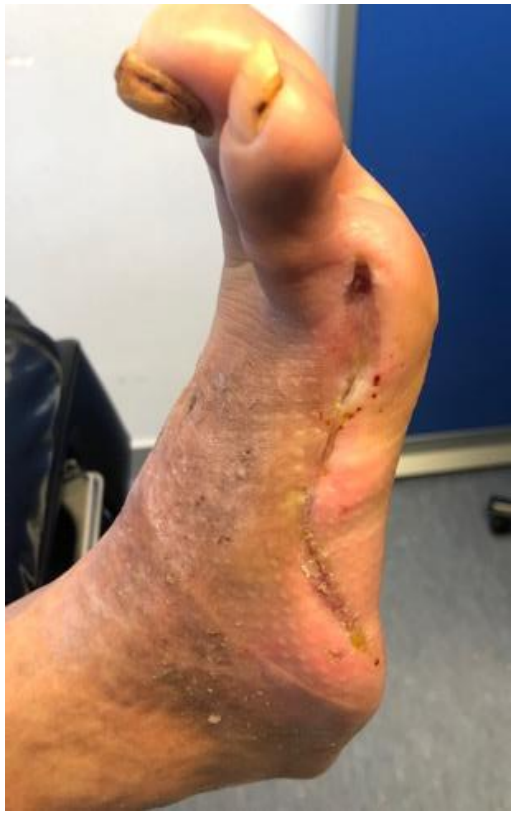
SURFACE; A1: 3,2cm^2 (2,6x1,0)
A2: 2,5cm^2 (3,5x1,0)

WEEK 16



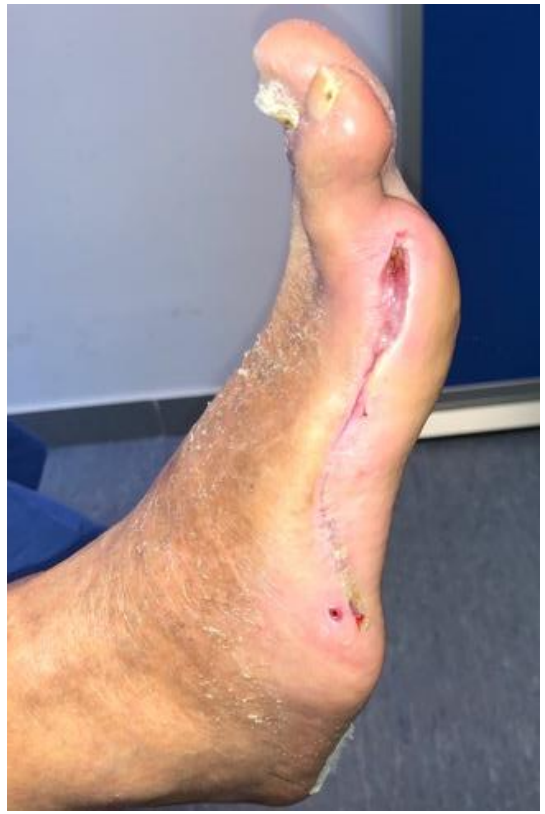
SURFACE: A1 2,3cm^2 (2,5 x 0,5)
A2 : -

WEEK 18



SURFACE: A1: 1,5cm^2 (2,0x 0,5)
A2 : -

WEEK 20



SURFACE:A1: 1,5cm^2 (1,5 x 0,4)
A2 : -

practice

Hard-to-heal diabetic foot ulcers treated using negatively charged polystyrene microspheres: a prospective case series

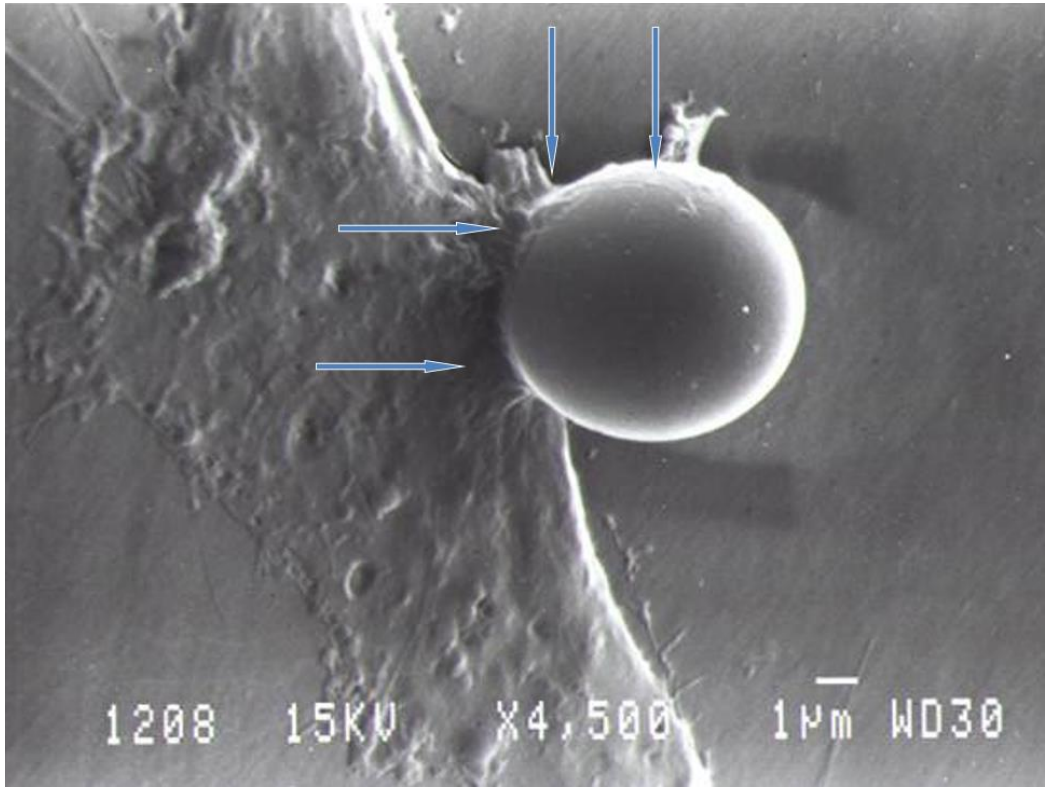
Objective: To describe the outcomes of a new product based on negatively charged polystyrene microspheres (NCM) technology, in non-responding diabetic foot ulcers (DFU).
Methods: A clinical case series of patients with a hard-to-heal DFU treated with NCM were recruited between March and June 2017 in a specialised diabetic foot unit. DFUs were treated daily with NCM over four weeks, although the health professional could decide to continue NCM treatment in some patients. Cases were followed up for 12 weeks. Wollina score (granulation, colour and consistency tissue), wound area (cm^2), percentage reduction and wound closure (%) were measured.
Results: A total of 22 ulcers (19 patients) were included, of which three patients (five ulcers) were withdrawn due to adverse events: four infections and one necrosis. None were associated with the product. NCM treatment was completed in 17 ulcers (16 patients). The mean patient age was 61.53±9.57 years. At baseline, mean duration time of the DFU was 7.88±8.65 weeks, the median area was 5.35cm^2, the interquartile range (IQR) was 1.45 to 4.65cm^2 and positive probe-to-bone test (PTB+) was recorded at 29.4%. After four weeks of treatment, an increase in Wollina score (3.65±2.12 to 5.69±1.18; p=0.000), a 62.2% reduction of the ulcer area (5.35 cm^2; IQR: 1.45 to 4.65cm^2) to 3.33cm^2 (IQR: 0.25 to 1.70cm^2; p<0.001) and complete healing in 17.6% of ulcers was observed. The mean time of NCM treatment was 6.2±1.2 weeks. At 12 weeks, 100% achieved complete healing, including those ulcers with PTB+.
Conclusion: After NCM use, a reactivation of the healing process in non-responding wounds was observed, having a significant improvement in Wollina score as well as reduction of the wounds. Complete healing was achieved in all ulcers at 12 weeks, including PTB+.
Declaration of interest: The authors have no conflict of interest.

diabetic foot ulcers • neuroischaemic • peripheral vascular disease • polystyrene microspheres

Lázaro-Martínez JL, García-Álvarez Y, Álvaro-Afonso FJ, García-Morales E, Sanz-Corbalán I, Molines-Barroso RJ. Hard-to-heal diabetic foot ulcers treated using negatively charged polystyrene microspheres: a prospective case series. J Wound Care. 2019 Feb 2;28(2):104-109.

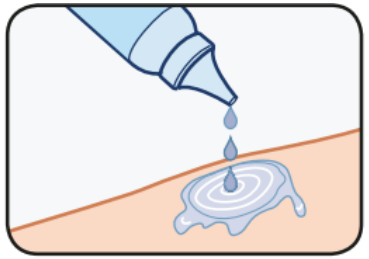
Mechanism of Action

Synthetic 5-micron polystyrene microspheres (NCM) to

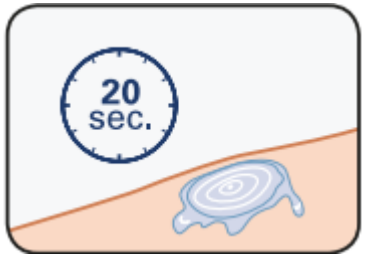


Promote neoangiogenesis, granulation tissue formation and wound healing

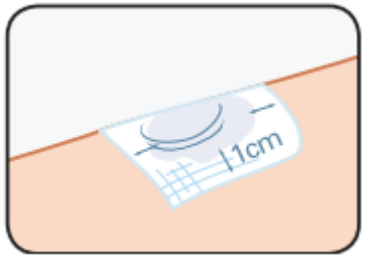
Application



1. After the bottle was shaken, several drops of the solution were applied to the wound's surface in order to moisten and cover the wound bed and edges



2. The wound was left exposed for 20–30 seconds to promote absorption of the suspension



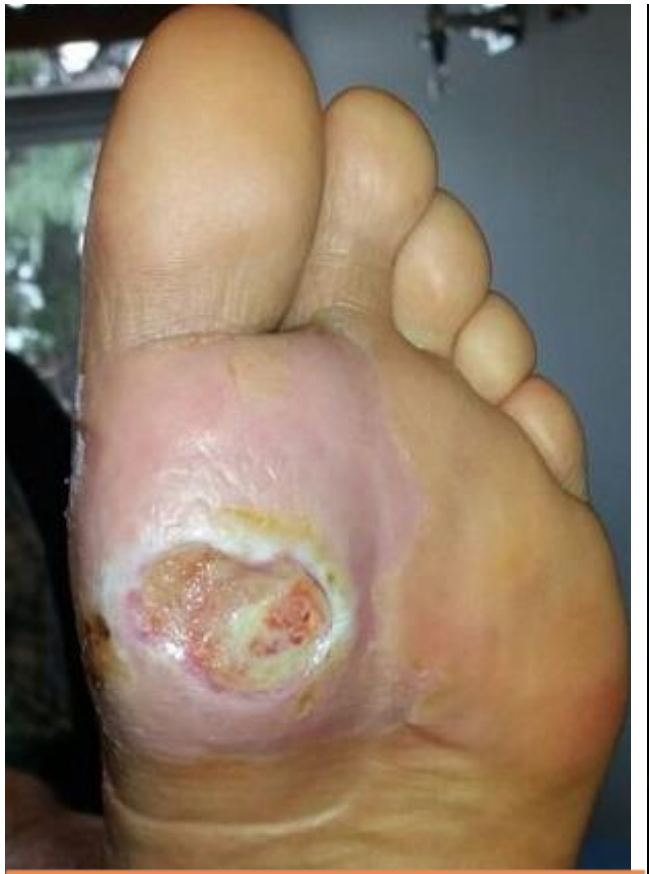
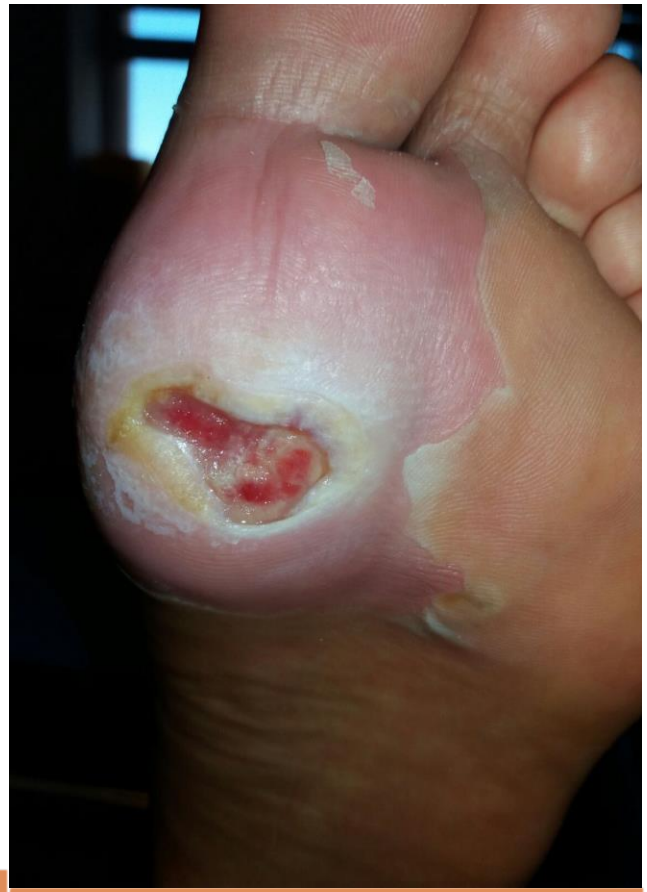
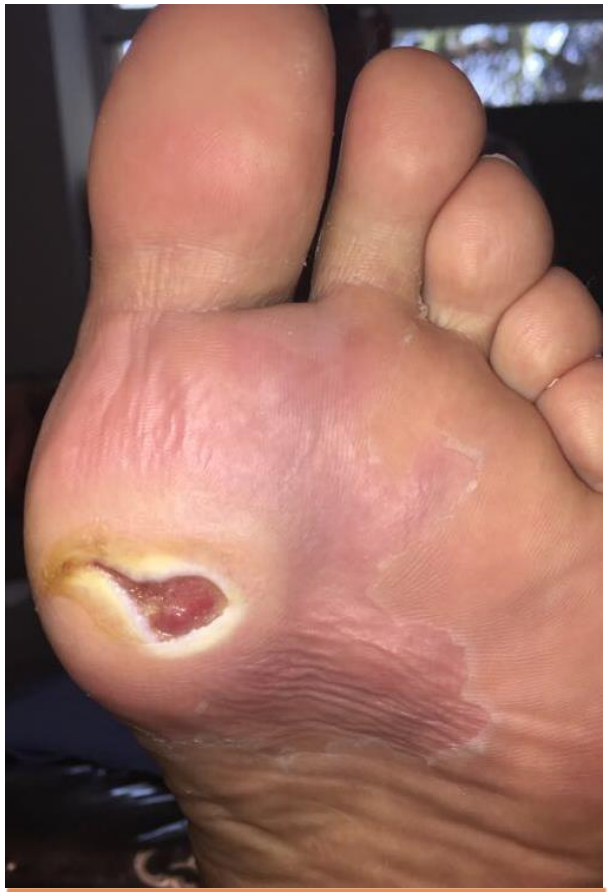
3. sterile dry gauze pad covered the wet gauze pad and the entire wound area was wrapped using a cotton bandage

Table 2. Weekly classification of the Wollina score and wound area surface

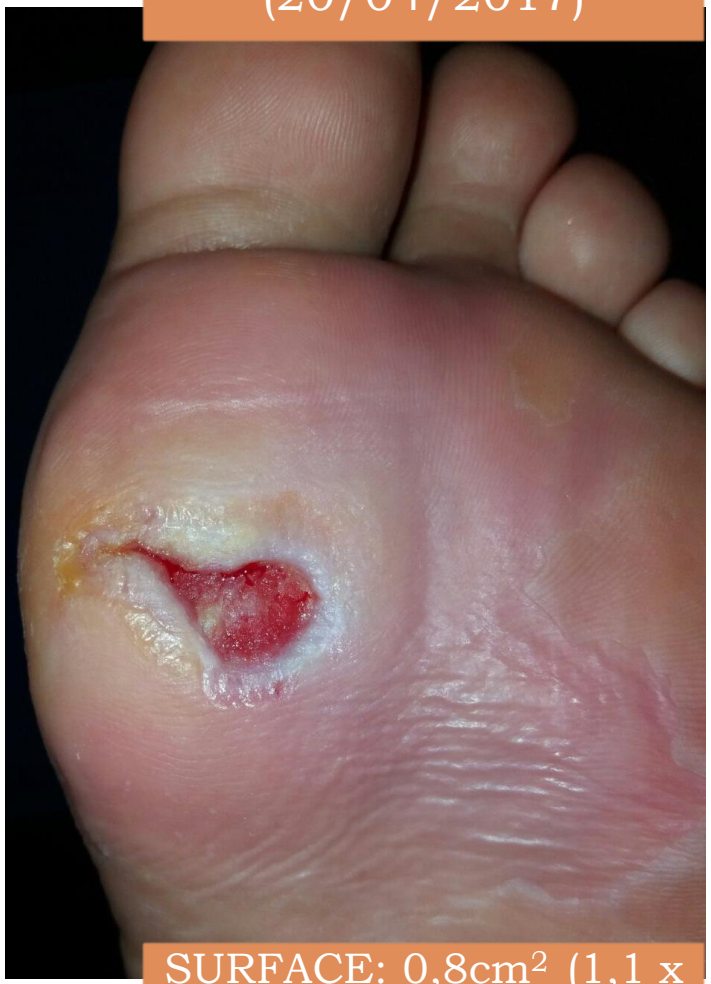
Wollina Score	Day 0	Day 7	Day 14	Day 21	Day 28	p-value
Granulation tissue (maximum 4)	2.18±1.19	2.41±1.18	2.81±0.98	3.06±0.85	3.23±0.73	0.000*
Colour (maximum 2)	1.06±0.75	1.18±0.81	1.25±0.68	1.56±0.63	1.54±0.66	0.009*
Consistence (maximum 1)	0.41±0.51	0.71±0.45	0.88±0.34	0.88±0.34	0.92±0.28	0.000*
Total score (maximum 7)	3.65±2.12	4.18±2.22	4.94±1.69	5.5±1.41	5.69±1.18	0,000*
Wound surface area (cm^2)	5.35±9.21	4.17±8,79	4.52±9.53	3.61±9.05	3.33±9.37	0.000*

* Statistically significant ($p<0.05$)

Lázaro-Martínez JL, García-Álvarez Y, Álvaro-Afonso FJ, García-Morales E, Sanz-Corbalán I, Molines-Barroso RJ. Hard-to-heal diabetic foot ulcers treated using negatively charged polystyrene microspheres: a prospective case series. J Wound Care. 2019 Feb 2;28(2):104-109.

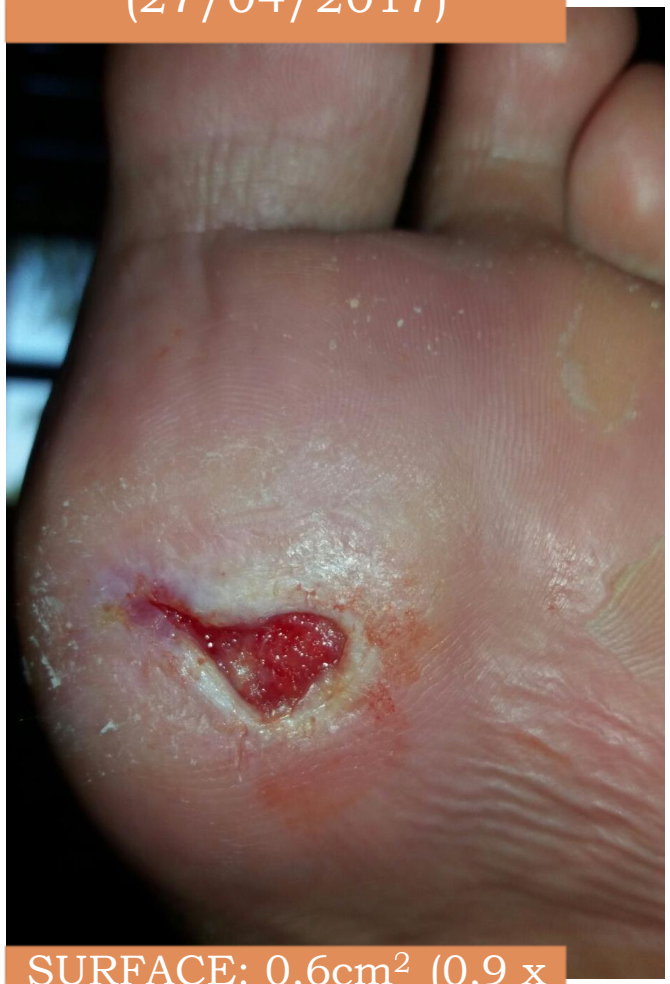
DAY 0 (30/03/2017)	DAY 7 (06/04/2017)	DAY 14 (13/04/2017)
		
SURFACE: 4,9 cm^2 (2,9 x 2,3) Wollina: 1	SURFACE: 1,7 cm^2 (1,6 x 1,9) Wollina: 3	SURFACE: 0,9 cm^2 (0,9 x 1,9) Wollina:5

DAY 21
(20/04/2017)



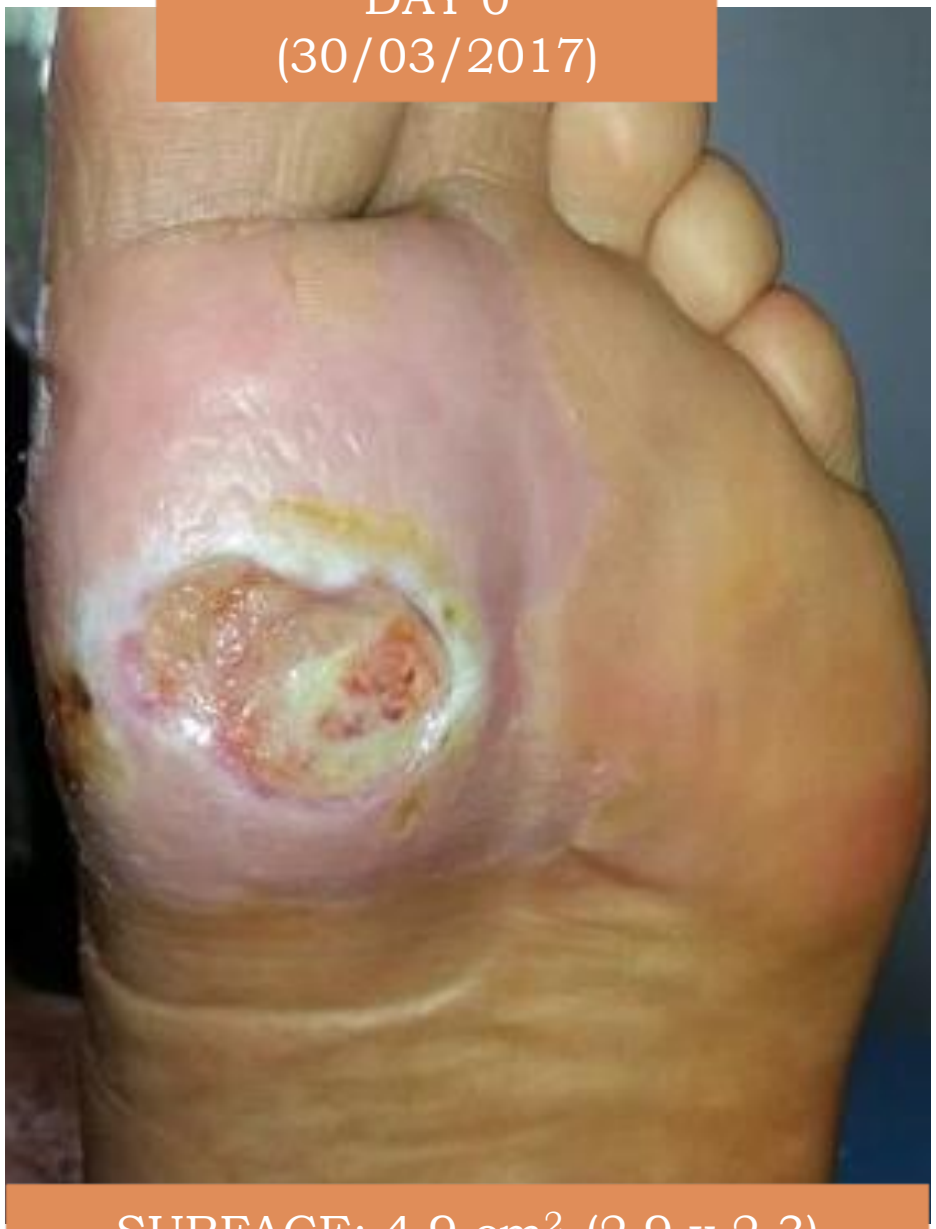
SURFACE: 0,8cm^2 (1,1 x 1,4)
Wollina: 6

DAY 28
(27/04/2017)



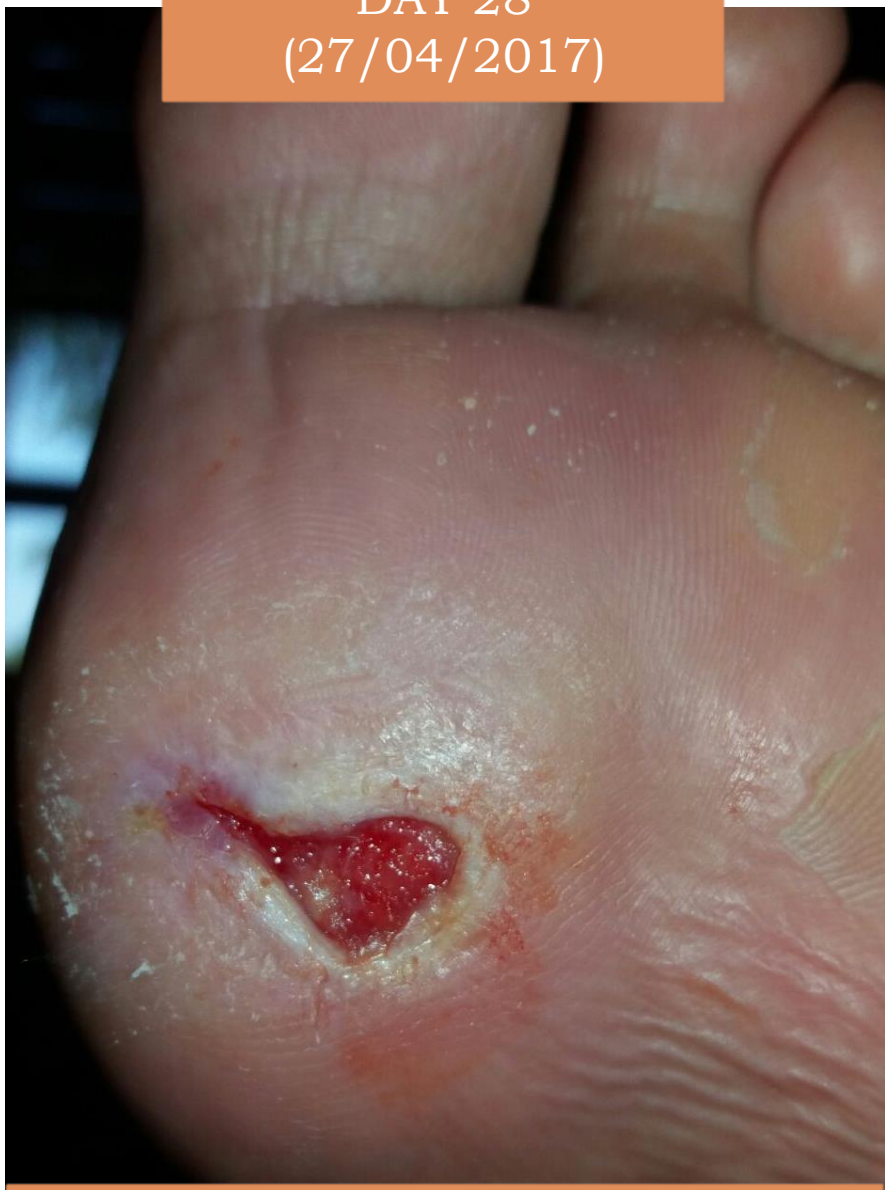
SURFACE: 0,6cm^2 (0,9 x 1,5)
Wollina: 6

DAY 0
(30/03/2017)

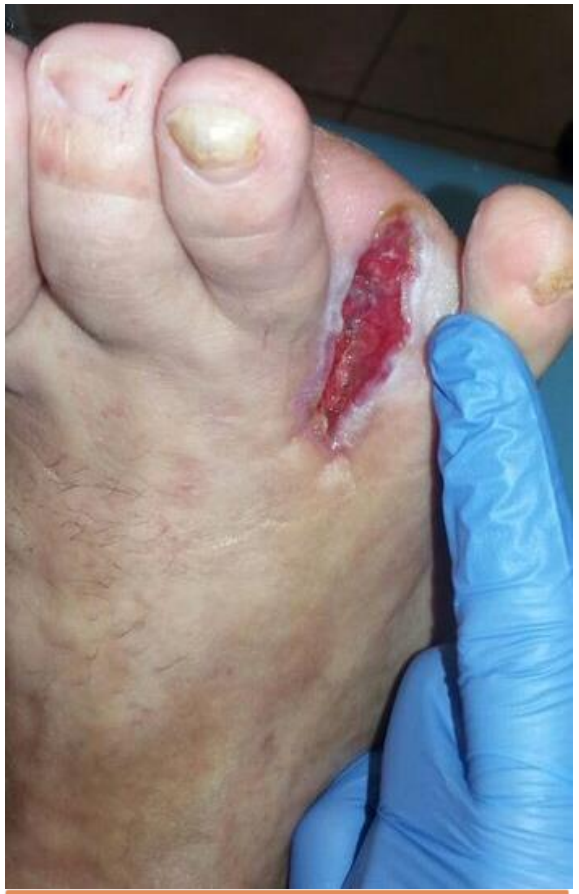
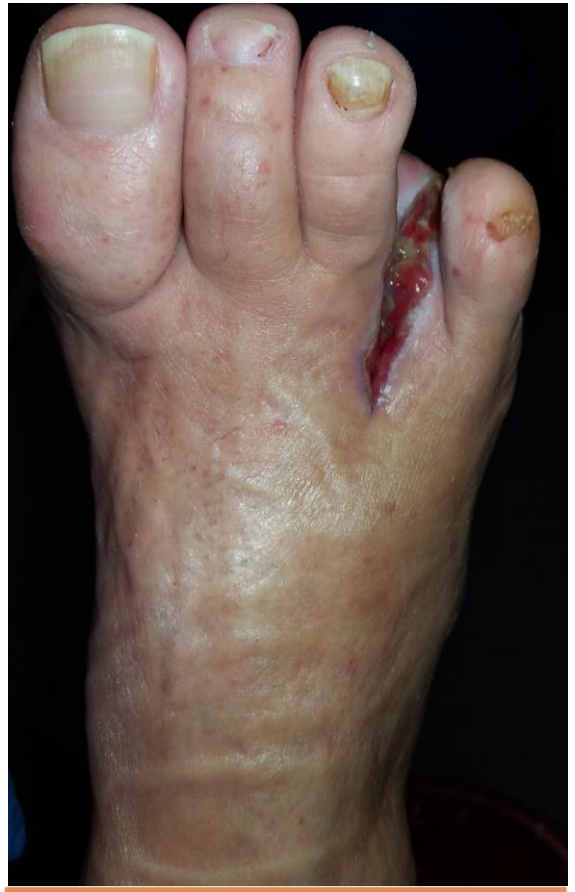
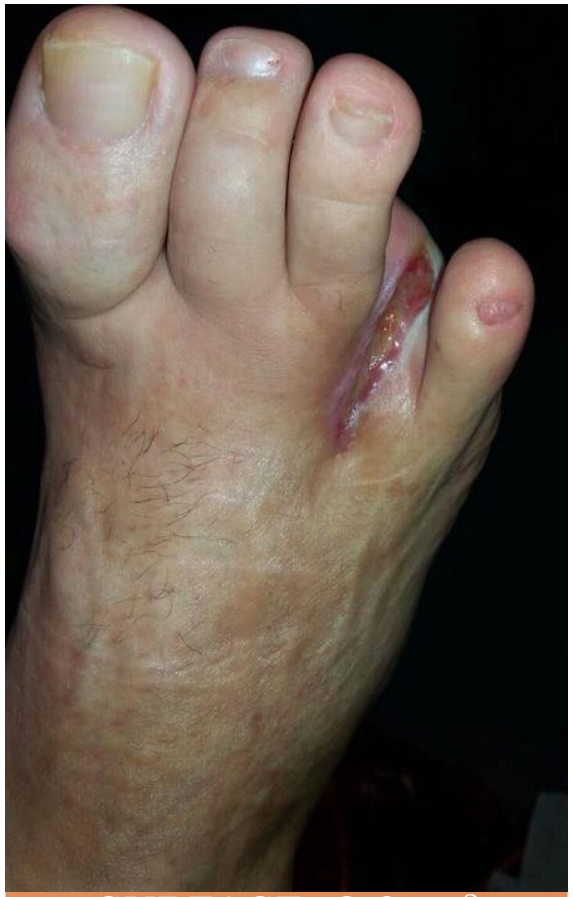


SURFACE: 4,9 cm^2 (2,9 x 2,3)
Wollina: 1

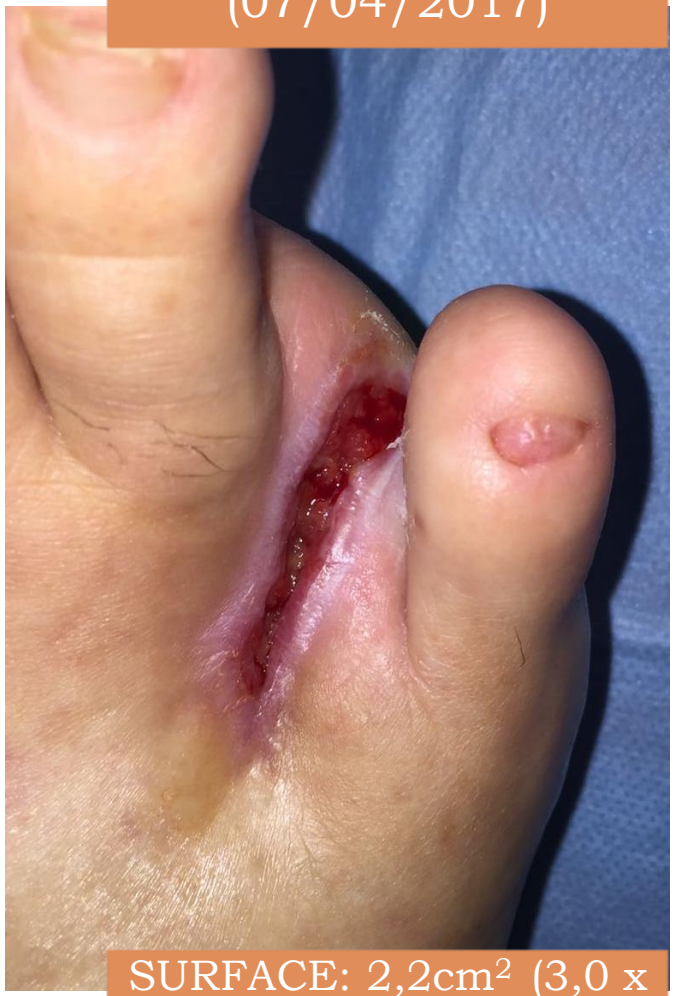
DAY 28
(27/04/2017)



SURFACE: 0,6cm^2 (0,9 x 1,5)
Wollina: 6

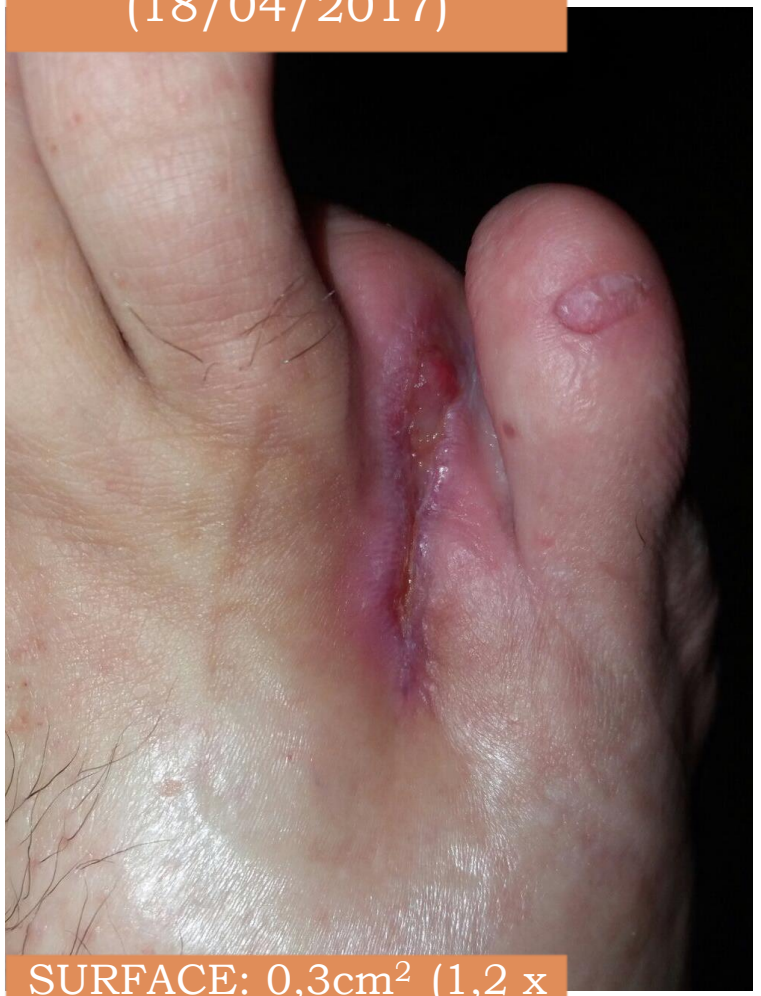
DAY 1 (17/03/2017)	DAY 7 (24/03/2017)	DAY 14 (30/03/2017)
		
SURFACE: 2,8cm^2 (3,5x1,1) Wollina: 6	SURFACE: 2,1cm^2 (3,1x0,9) Wollina: 6	SURFACE: 2,0cm^2 (1,1x3,7) Wollina: 5

DAY 21
(07/04/2017)



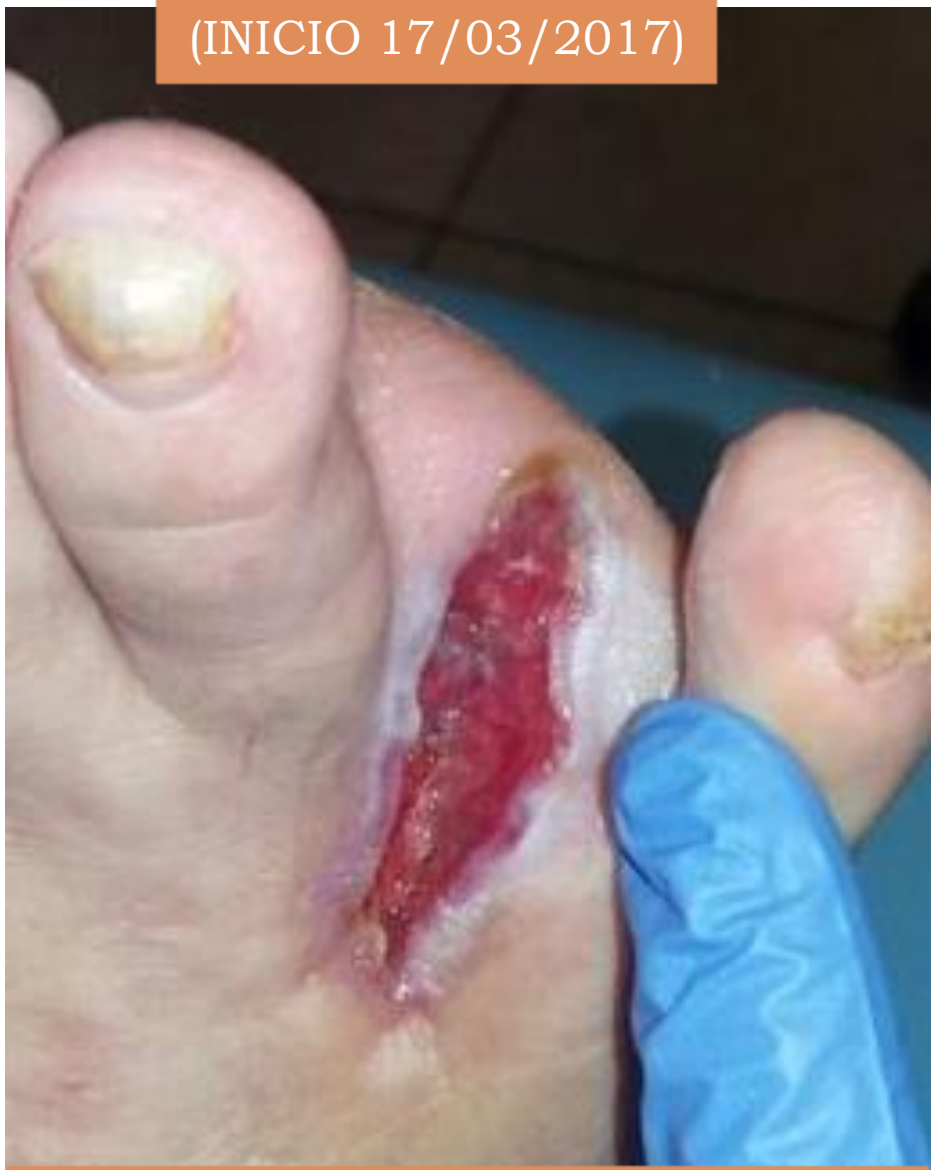
SURFACE: 2,2cm^2 (3,0 x 1,1)
Wollina: 7

DAY 28
(18/04/2017)



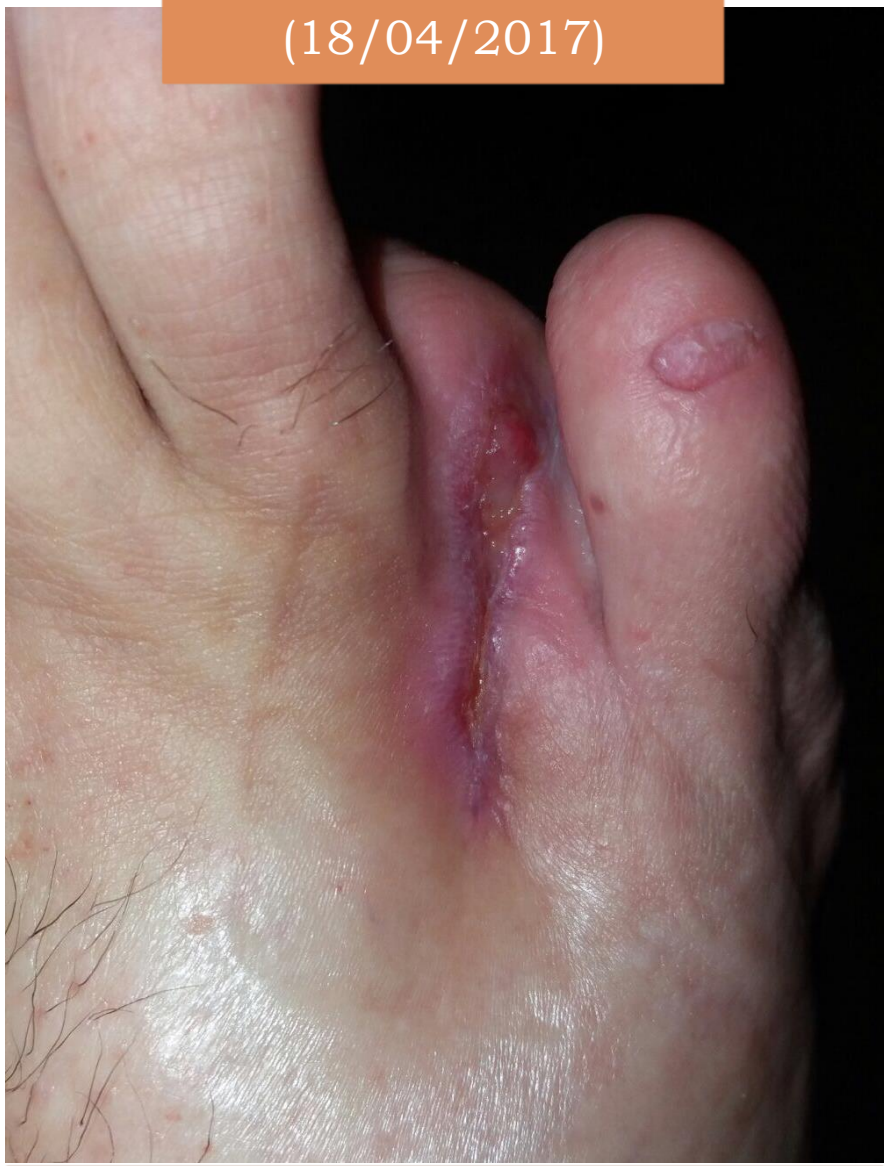
SURFACE: 0,3cm^2 (1,2 x 0,5)
Wollina: 7

DAY 0
(INICIO 17/03/2017)



SURFACE: 2,8cm^2 (3,5x1,1)
Wollina: 6

DAY 28
(18/04/2017)



SURFACE: 0,3cm^2 (1,2 x 0,5)
Wollina: 7

Assure a Good Vascular Supply and planning revascularization if ulcer not improving (neuroischemic ulcer)

Implementing the best and most efficacy offloading that the patient accept to wear

Removing non-viable tissue and control MMPs level (specially neuroischemic ulcers)

Discard Infection and treating aggressive if is present (specially moderate and severe)

Thanks for Your Attention