





## AGENDA

Basic pathway of wound healing

Biochemistry of non-healing ulcers

Medihoney MOA

Dynamics of Dehydrated Amniotic Membrane Allograft  
(DAMA)

RCT of DAMA

Case presentations

Question and Answer



# Wound healing phases

Coordinated sequence of events

Hemostasis

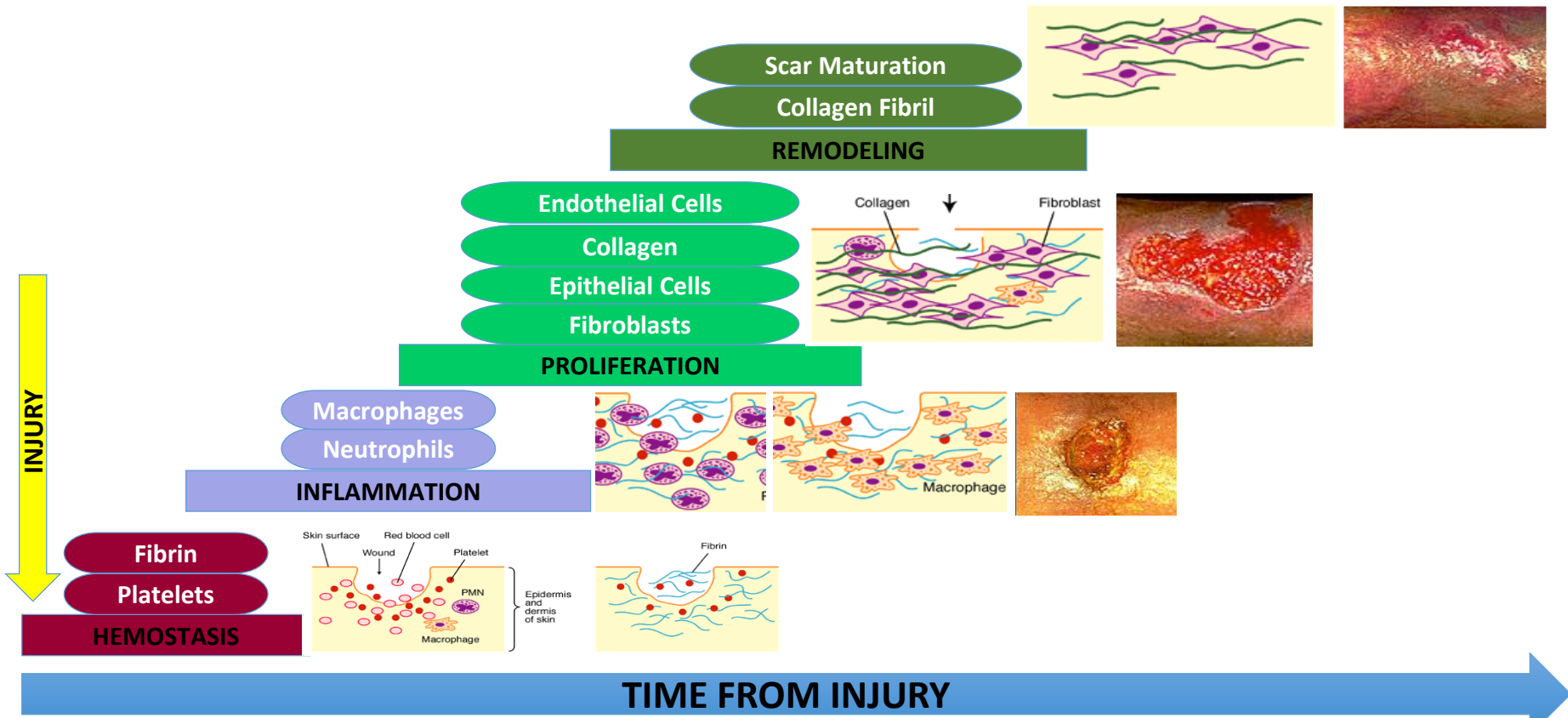
Inflammation

Proliferation

Maturation

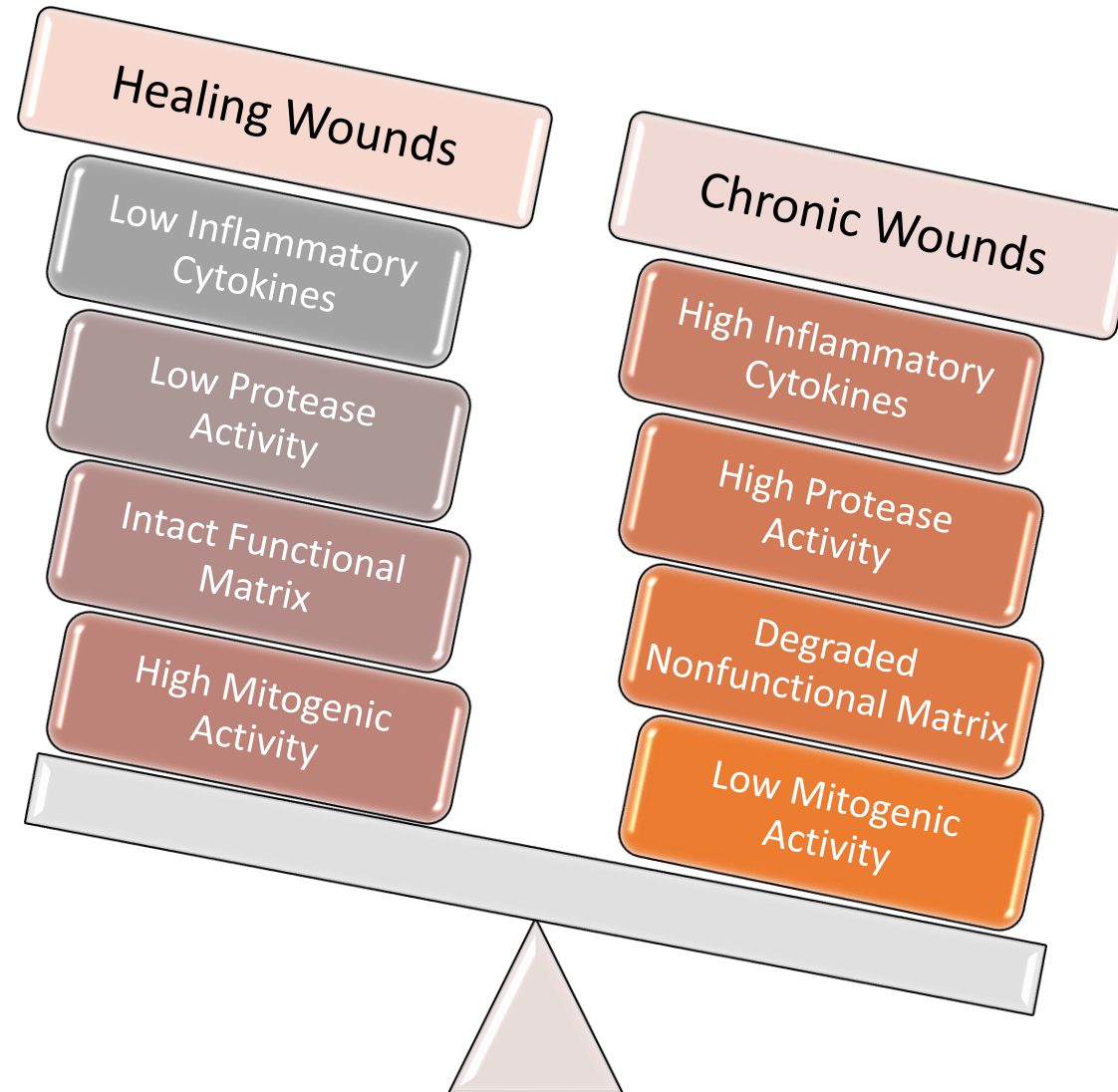


# BACKGROUND: WOUND HEALING



Beanes, SR, et al. Skin repair and scar formation: the central role of TGF- $\beta$ . *Expt Rev Molec Med*, 2003. 5: 1-22  
 Cohen IK, et al. Wound Healing: Biochemical and Clinical Aspects. WB Saunders, 1992. Ch. 22.

# Chronic Wound vs. Healing Wound



Falanga V. The Chronic Wound: Impaired Healing and Solutions in the Context of Wound Bed Preparation. *Blood Cells and Diseases*, 2004;32:88-94



# MEDIHONEY®

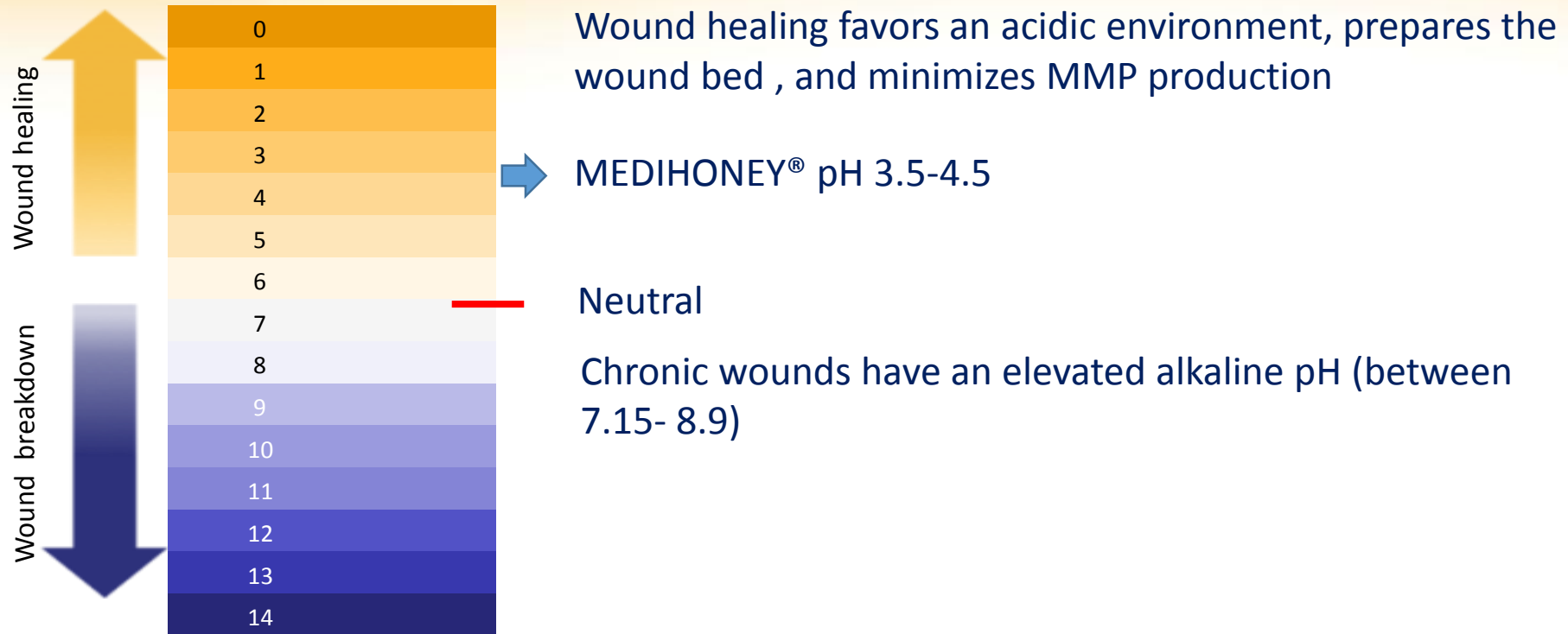
## What is it? What can it do?

- Derived from the pollen and nectar of a specific *Leptospermum Scoparium* species of plant in New Zealand
- Unique among honey – maintains its effectiveness even in the presence of wound fluid
- In an RCT, the mean healing time was faster for wounds treated with MEDIHONEY® impregnated dressings when compared to conventional dressings<sup>1</sup>
- Two key mechanisms of action create an optimal environment to promote the removal of necrotic tissue and healing – High Osmolarity and Low pH



1. Kamaratos AV, Tzirogiannis KN, Iraklianiou SA, Panoutsopoulos GI, Kanellos IE, Melidonis AI. Manuka honey-impregnated dressings in the treatment of neuropathic diabetic foot ulcers. *Int Wound J.* 2012 ; 9: 1-7.

# Medihoney has Low pH



The low pH of MEDIHONEY® (3.5-4.5) helps to lower the pH within the wound environment<sup>5-6</sup>, which has been shown to have wound healing benefits.<sup>7</sup>

5. Gethin G. Influence of Manuka honey on surface pH, MMP-2, MMP-9 and wound size of chronic wounds. European Wound Management Association Conference, Lisbon, Portugal, May 2008.

6 Milne SD, Connolly P. The influence of different dressings on the pH of the wound environment. J Wound Care. 2014 Feb;23(2):53-4, 56-7.

7. Leveen H, Falk G, Borek B, Diaz C, Lynfield Y, Wynkoop B, Mabunda GA et al. Chemical acidification of wounds. An adjuvant to healing and the unfavourable action of alkalinity and ammonia. *Annals of Surgery*. 1973. 178(6): 745-50.



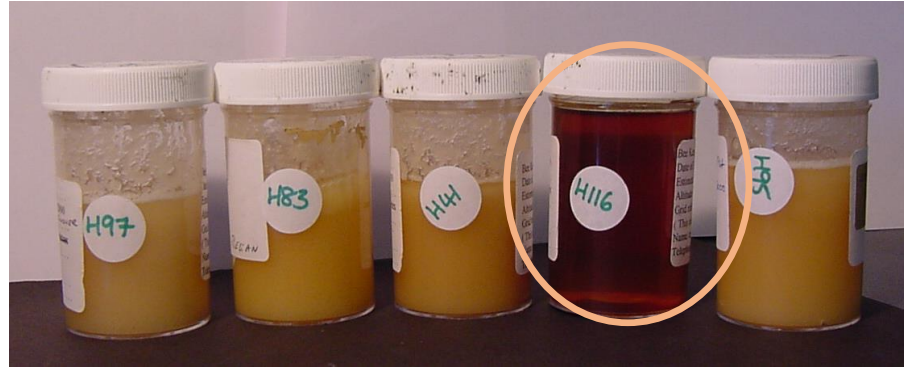
# Not all Honey is the same....

## ALL Honey

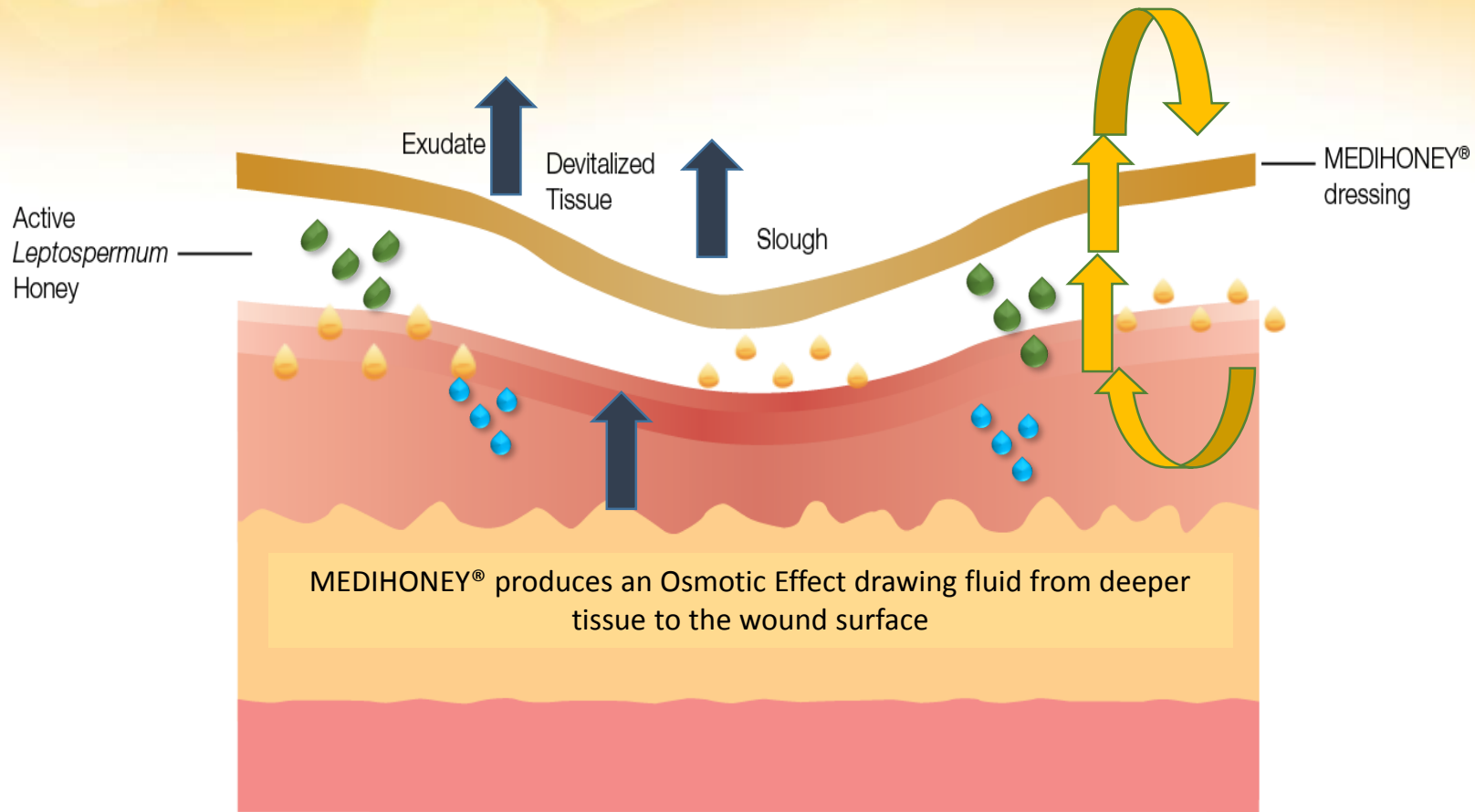
- Low pH
- High Osmolarity

## Active *Leptospermum* Honey

- Low pH
- High Osmolarity
- Standardized level of activity (+15)
- Works in the presence of catalase
- Heat and irradiation resistant
- Sterilized and produced under hygienic conditions
  - No bee venom, No bacterial spores, No pesticides



# High Osmolarity



Works with the body's natural processes to bathe the wound and promote the removal of necrotic tissue<sup>2,3</sup>

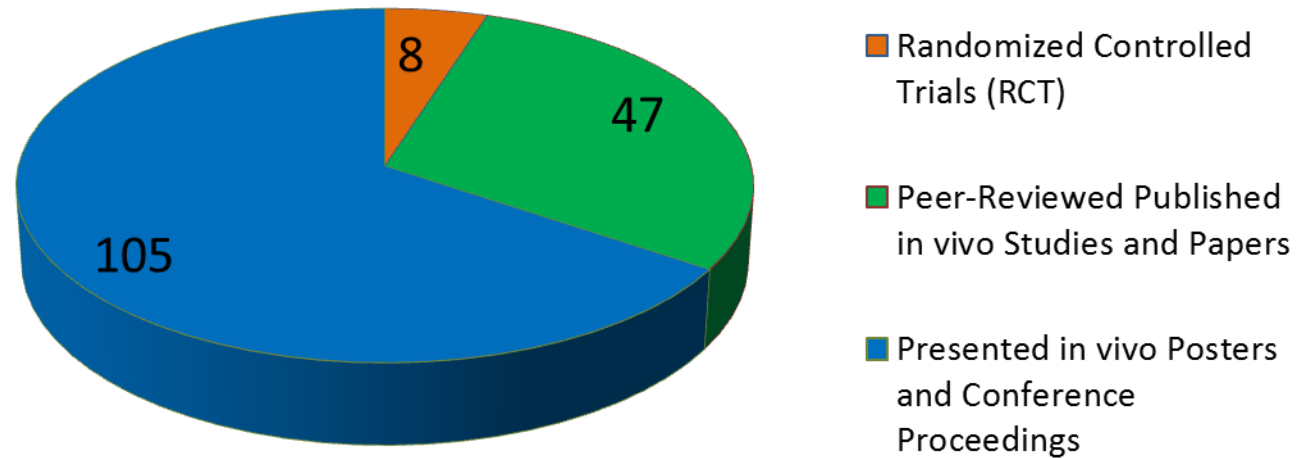
# Differences in pH by depth

- pH changes by wound depth, which is significant as deeper wounds are less acidic and more alkaline
- Stage I- pH 5.7 (+/- 0.5)
- Stage II- pH 6.9 (+/- 1.0)
- Stage III- pH 7.6 (+/- 0.2)



# The Body of Evidence Supporting the Clinical Efficacy of MEDIHONEY® Dressings

There are over 160 pieces of evidence including 8 RCTs, 47 peer-reviewed published studies and papers and 105 posters and conference proceedings showing MEDIHONEY® is an effective product for promoting the removal of necrotic tissue and healing.



*No other honey brand has this many pieces of evidence*

# Different Configurations to assist Wound Bed Preparation



MEDIHONEY® Paste



MEDIHONEY® Gel



MEDIHONEY®  
HCS

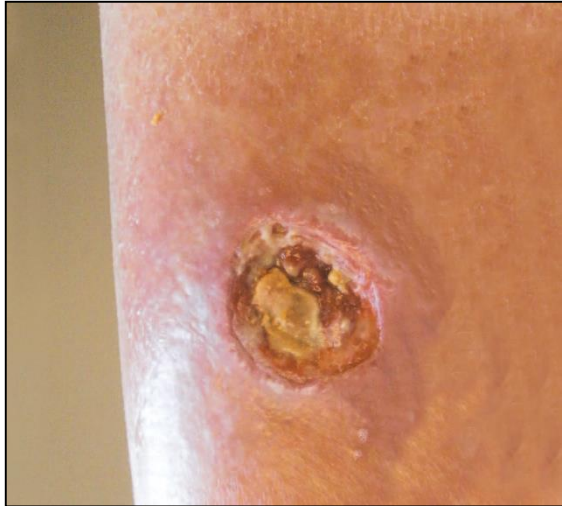


MEDIHONEY®  
Calcium Alginate



MEDIHONEY®  
Honeycolloid

# Venous Leg Ulcer



2-10-11



2-23-11

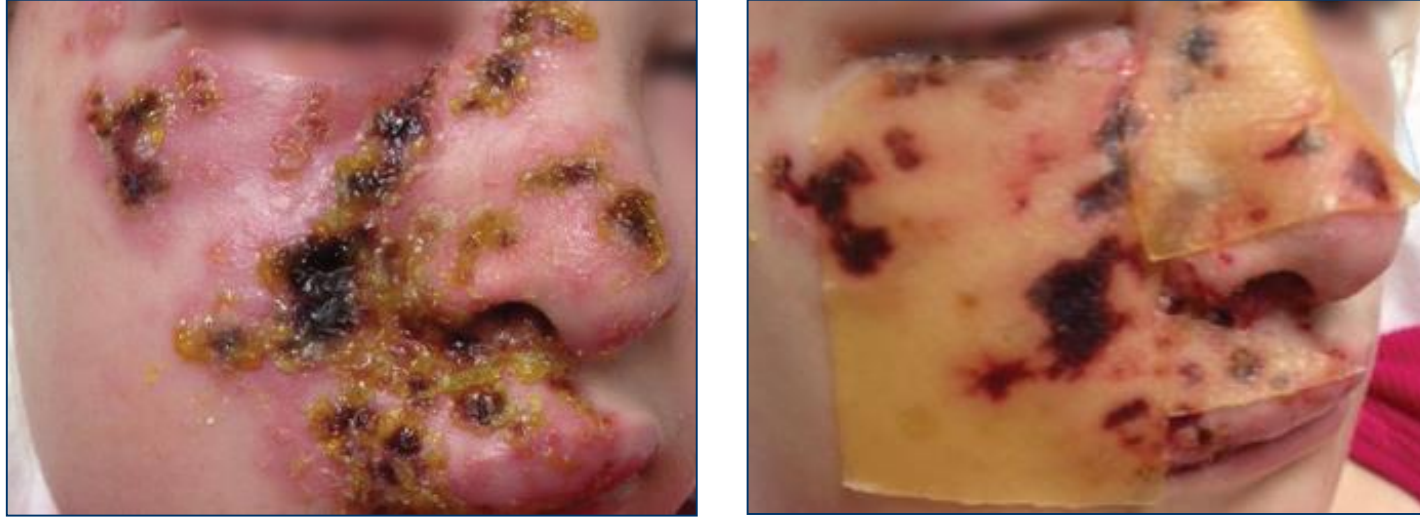


3-17-11

- 72 year old male with several year history of multiple VLUs
- Previous treatments included compression and moist wound healing prior to initiation of MEDIHONEY® gel on 2-10



# Vesicular and Ulcerative Lesions



11-8-12

- 15 yo female, severe right-sided facial with vesicular and ulcerative lesions
- 8 cm x 8 cm with depth ranging from 0.1 cm to 0.3 cm.
- Wound bed was 100% slough or hyperpigmented eschar. Multiple full thickness and partial thickness open wounds scattered over side of face with edema and erythema.

# Vesicular and Ulcerative Lesions



11-12-12



12-4-12

# Diabetic Foot Ulcer



6/22/11: 3.0 cm x 3.0 cm  
with 100% necrotic tissue.



7/01/11: 3.0 cm x 3.0 cm

- Silver sulfadiazine cream was applied as the first topical treatment on admission 6/22/11 with little improvement
- MEDIHONEY<sup>®</sup> initiated 6/29/11
  - 2 days after MEDIHONEY<sup>®</sup> initiated, wound now has yellow stringy slough and granulation tissue

# Diabetic Foot Ulcer



**7/8/11: 3.0 cm x 3.0 cm**

- After 4 applications of MEDIHONEY<sup>®</sup> the wound has 30% yellow stringy slough and granulation tissue



7/15/11: 2.5 cm x 2.0 cm

7/18/11: Patient was discharged

- After 2 more applications of MEDIHONEY<sup>®</sup>, the wound has 20% yellow stringy slough with 80% granulation tissue

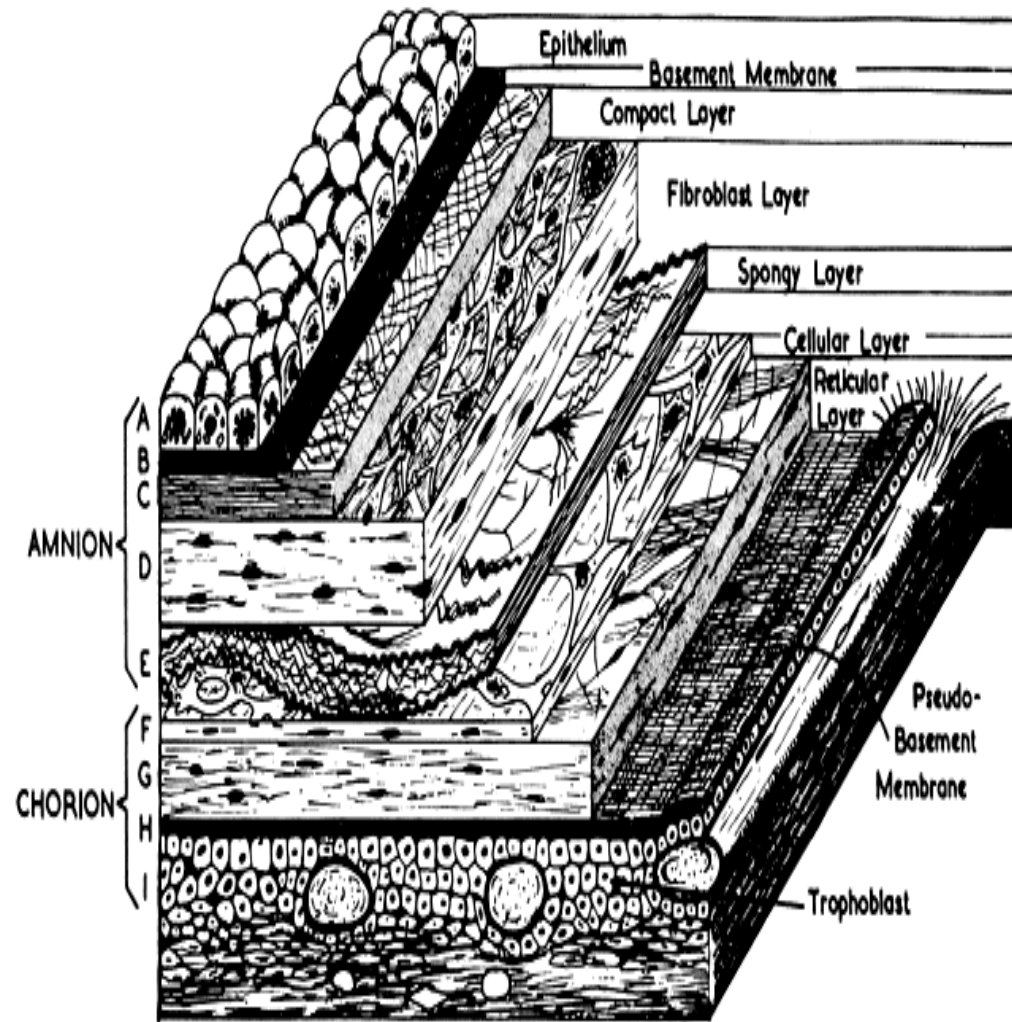
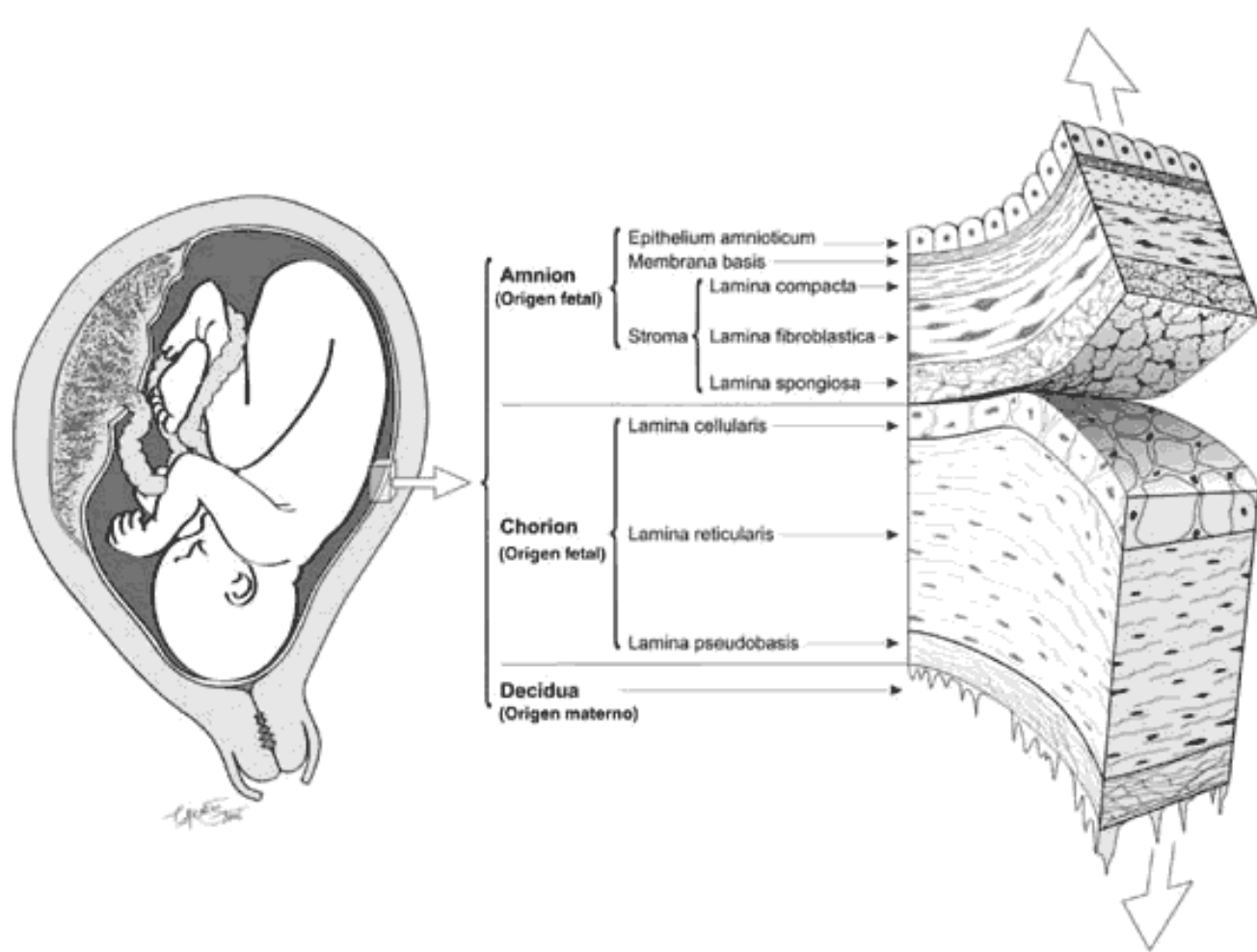


# *AMNIOTIC TISSUE*



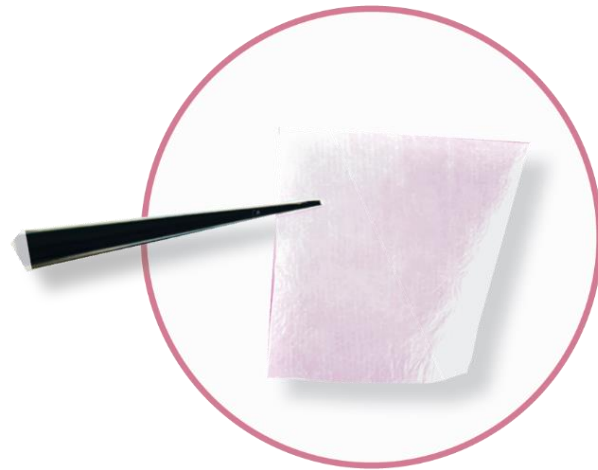


# Amniotic Tissue



(Bourne GL. The microscopic anatomy of the human amnion and chorion. Am J Obstet Gynecol 79:1070, 1960)

AMNIOTIC ALLOGRAFT MEMBRANE  
**AMNIOEXCEL**<sup>®</sup>



## IDENTIFY PROBLEM WOUNDS EARLY & TRANSITION TO ADVANCED THERAPY

### “Good” Wound Care

- History
- Assessment
- Debridement
- Moist Environment
- Off-loading
- Topical Care



### Advanced Wound Care

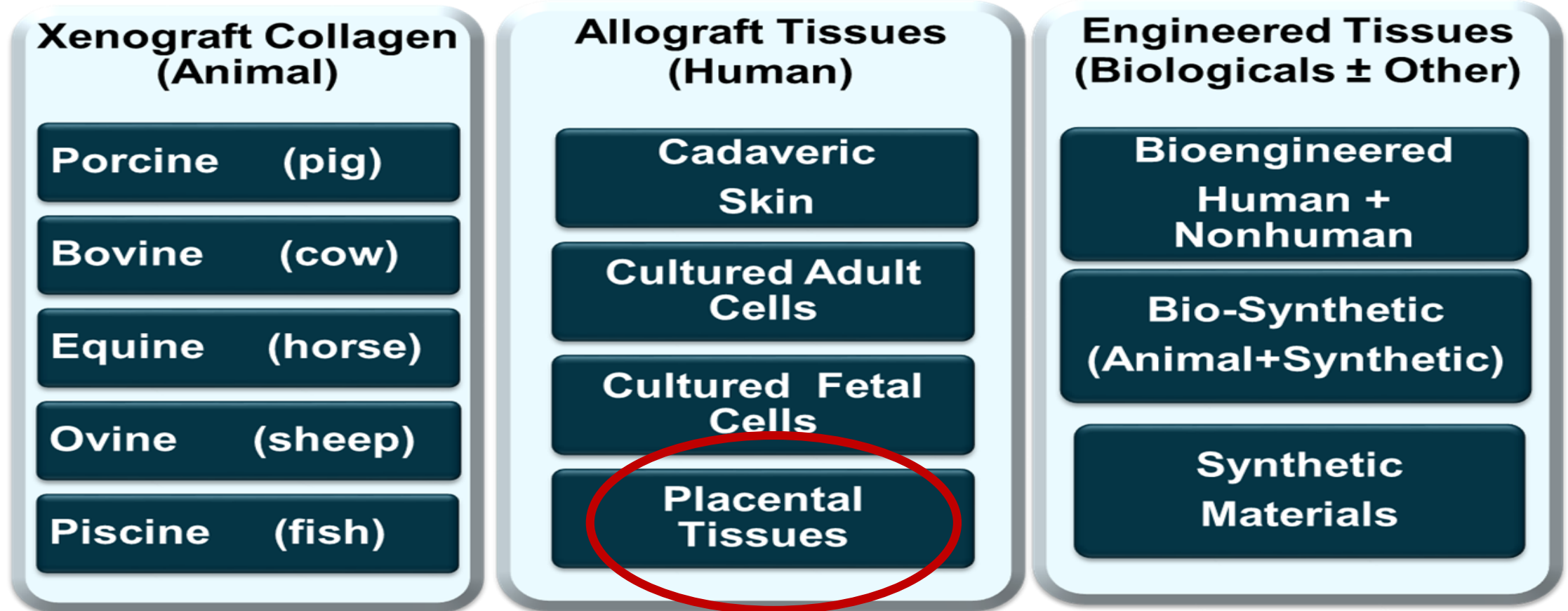
- Hyperbaric Medicine
- Growth Factors
- Amniotic Allografts
- Bioengineered Alternative Tissues
- Negative Pressure Therapy
- Biologic Dressings
- Active Topicals
- Plastic Surgery
- Curative Surgery

## HISTORY OF AMNIOTIC TISSUE THERAPY

- Use goes back to the early 1900s
  - Used on burns and ulcers
  - Decreased pain
  - Increased epithelialization
- First medical use 1914 by Dr. Davis at John's Hopkins for ocular injury and burns in 550 cases
- Used throughout the 1940s, 50s and until 1970s
  - Emergence of HIV/AIDS limited use
- 2007 an aseptic technique to recover & preserve lead to a resurgence in research and clinical use of amniotic tissue derived products



# SOURCES OF TISSUE BASED CUTANEOUS WOUND HEALING PRODUCTS

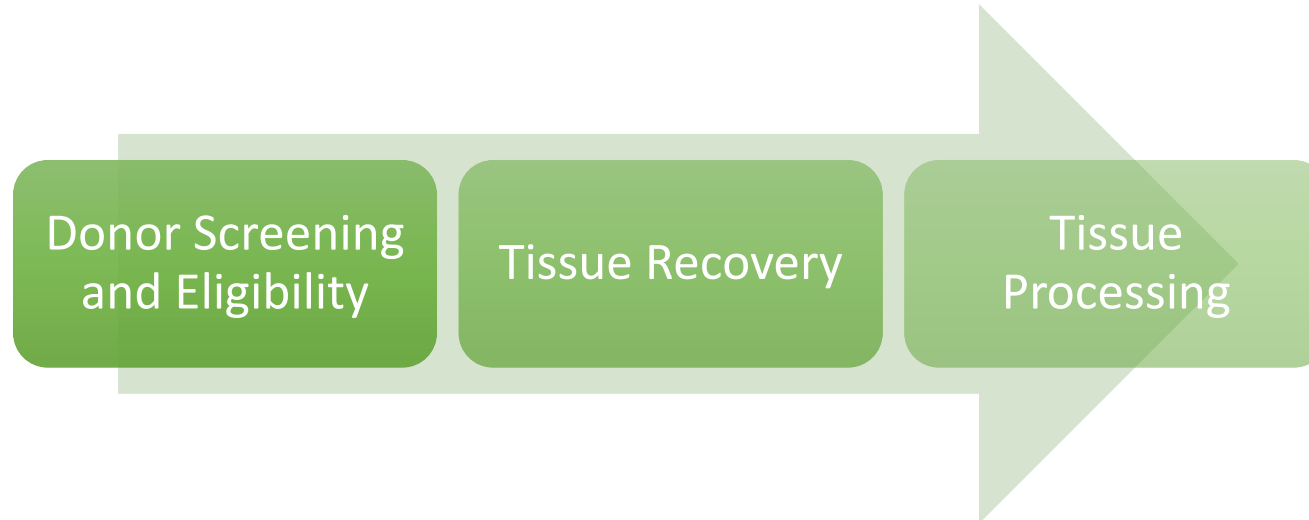


# Why amniotic tissue?

- Immune privileged material minimizes immune response and reduces potential for graft / host rejection (*general to amnion tissues*)
- Recovery performed in the OR, vertical integration, safest profile
- Tissue derived only from amniotic tissue
  - Inherent tissue composition, collagens, ECM, signaling molecules - naturally in place to assist in regeneration, protection and nutrition of fetus
  - Structural architecture maintained
  - Not side-specific in applying the tissue to the wound bed
  - Basement membrane and compact layer maintained, ECM proteins
- DryFlex® Technology renders a flexible, easily handled membrane that adheres to the wound bed due to its hydrophilic nature
- Off-the-shelf/ room temperature stable
- Terminally sterilized to SAL  $10^{-6}$
- Ethically priced

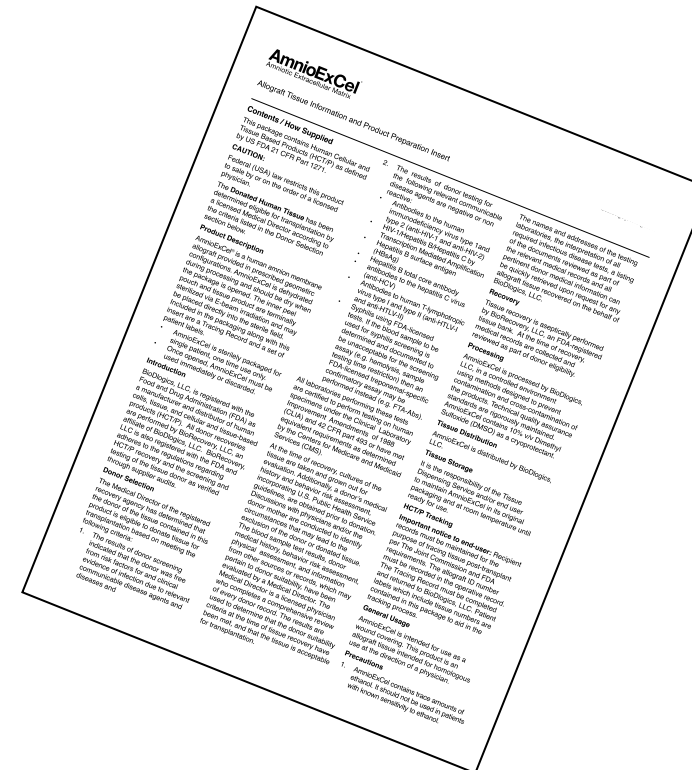


# Tissue Recovery, Processing and Distribution



# DONOR ELIGIBILITY

- Donor free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases.
- The results of donor testing for the relevant communicable disease agents are negative or non-reactive.

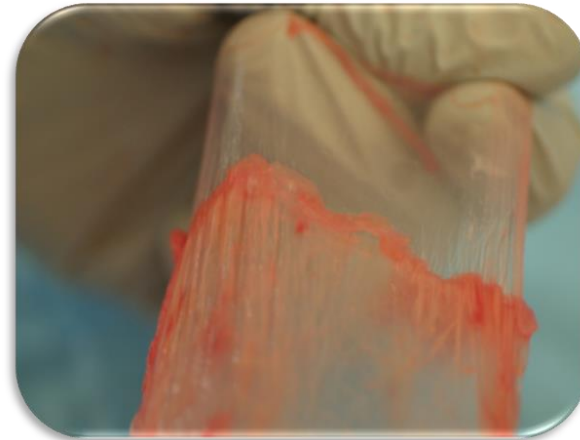


# Tissue Recovery



- All tissues recovered are **donated under consent** and acquired at the time of **scheduled elective cesarean sections**.

- Recovery technicians **aseptically receive tissue** directly from physician.
- Primary blunt dissection of the membranes completed under sterile conditions.



# The Process

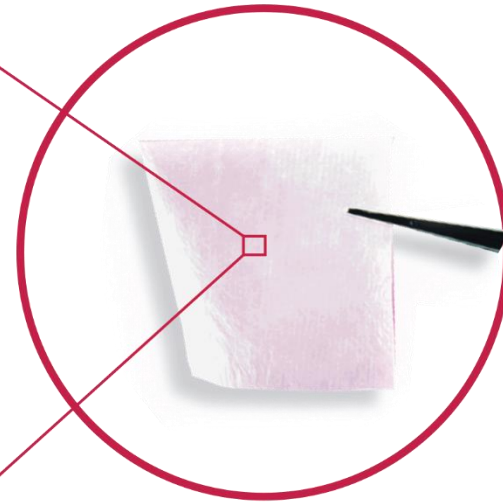
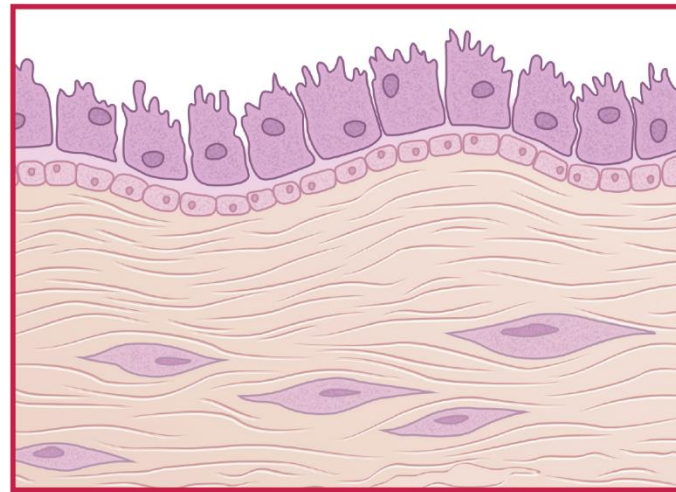
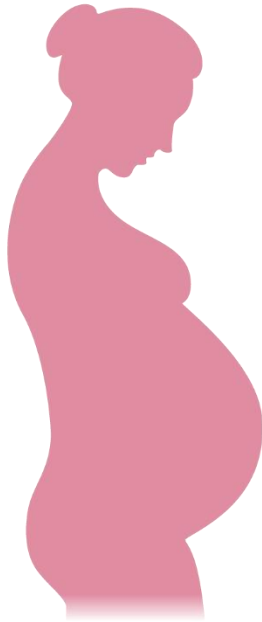
The processing for AMNIOEXCEL includes:

- Tissue delivered to facility within 2 hours to begin processing helps preserve key components
- Removal of the chorion from the amnion layer
- Gently cleansing the amnion layer
- Chemical dehydration
- Cut to one of 11 sizes
- Packaged and gamma sterilized



# The Result

An allogeneic membrane made from the amniotic membrane



# AMNIOEXCEL CLINICAL EVIDENCE



- Snyder RJ, Shimozaki K, Tallis A, Kerzner M, Reyzelman A, Lintzeris D, Bell D, Rutan RL, and Rosenblum B  
**A Prospective, Randomized and Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft (DAMA) compared to Standard of Care (SOC) for the Closure of Chronic Diabetic Foot Ulcers**
- *Wounds 2016; in press*



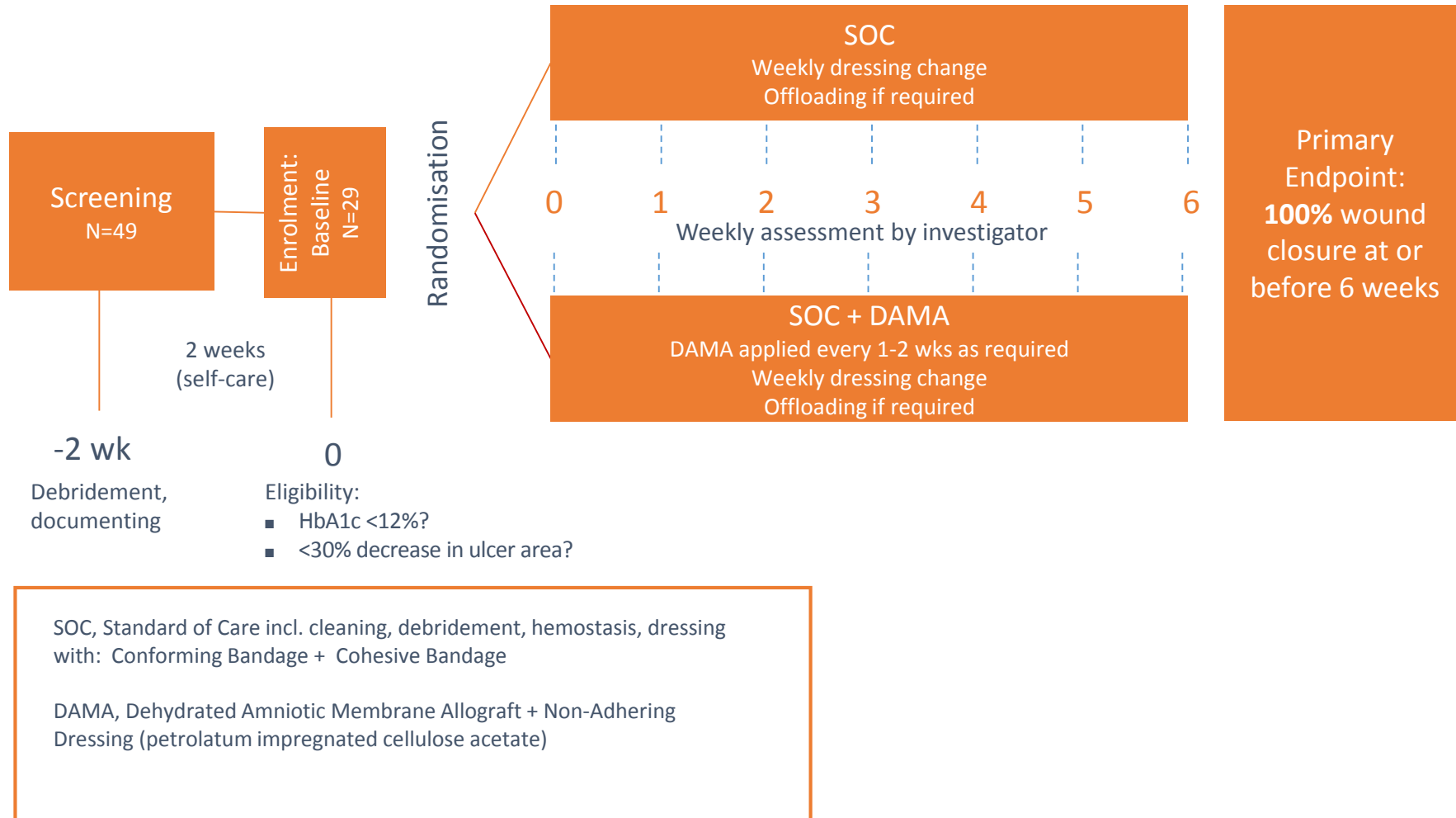
# Study Design

Prospective, randomized, multicenter, open-label, parallel group study:

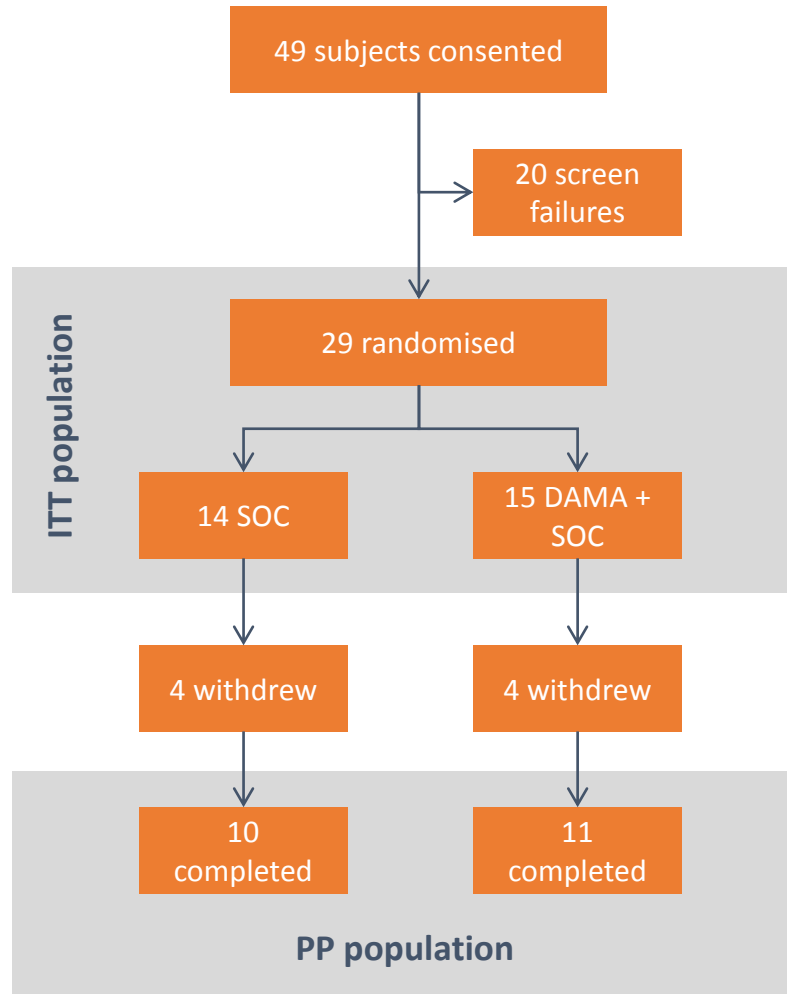
Characteristic	
Prospective	Investigators begin enrolling subjects and collecting baseline information, before the subjects have developed any of the outcomes of interest.
Randomized	Randomly allocated, without bias, to a treatment group. e.g. like the flip of a coin (but more sophisticated)
Multicenter	<ul style="list-style-type: none"><li>■ Rob Snyder, Barry University, Miami FL</li><li>■ Ken Shimosaki, Pacific Wound Center, Stockton CA</li><li>■ Art Tallis, Associated Foot &amp; Ankle Specialists, Phoenix AZ</li><li>■ Mike Kerzner, Duke University Medical Center, Durham NC</li><li>■ Alex Reyzelman, Center for Clinical Research, San Francisco CA</li><li>■ Dimitrios Lintzeris, Wayne Memorial Wound Care Center, Goldsboro NC</li><li>■ Desmond Bell, First Coast Cardiovascular Institute, Jacksonville FL</li><li>■ Barry Rosenblum, Beth Israel Deaconess Hospital, Plymouth MA</li></ul>
Open Label	No attempt was made to blind Investigators to treatment assignment
Parallel Group	Subjects in both groups received their assigned treatment and data was collected during the same time period



# Study Design: Study overview



# Study consort statement



Reasons for Screen failure	N
Wound closed >30% during lead-in	4
Ulcer infection	4
Ulcer <1cm <sup>2</sup> in area	2
Protocol deviations	2
Failed >1 Eligibility Criteria	8

Reasons for Withdrawal	SOC Alone	DAMA +SOC
Withdrew Consent	2	0
Ulcer infection	1	1
Protocol Violation	1	2
Lost to Follow Up	0	1

# Study demographics

		SOC Alone	DAMA +SOC	P value
N		14	15	
Age [Mean years ± SD (range)]		58.6±6.97 (48-71)	57.9±12.49 (34-85)	0.855
N Male (%)		13 (92.9)	12 (80)	0.597
Race	N Caucasian (%)	11 (78.6)	8 (53.3)	0.245
	N Black (%)	2 (14.3)	3 (20.0)	1.000
	N Am Indian (%)	0 (0)	1 (6.7)	1.000
	N Other (%)	1 (7.1)	3 (20.0)	0.597
Ethnicity	N Hispanic (%)	2 (14.3)	4 (26.7)	0.651
Weight [Mean lb. ± SD (range)]		242.4±53.14 (166 - 345)	234.47±38.18 (180 - 292)	0.648
Height [Mean in. ± SD (range)]		69.86±4.43 (61 – 75)	68.9±5.57 (52.5 – 75)	0.638
BMI [Mean ± SD (range)]		35.06±8.14 (24.9 – 55.7)	34.88±5.97 (28.2 – 50.2)	0.944

# Baseline Ulcer Characteristics

		SOC Alone	DAMA +SOC	P value
Lower Extremity with Target Ulcer [N (%) Right foot]		8 (57.1)	10 (66.7)	0.597
Side of Foot (N (%) Plantar)		9 (64.3)	10 (66.7)	1.000
Position to Midline	N Midline (%)	2 (14.3)	2 (13.3)	0.842
	N Lateral (%)	6 (42.9)	5 (33.3)	
	N Medial (%)	6 (42.9)	8 (53.3)	
Ulcer Part of Foot	N Forefoot (%)	6 (42.9)	9 (60.0)	0.572
	N Hindfoot (%)	3 (21.4)	2 (13.3)	
	N Medial (%)	6 (42.9)	8 (53.3)	
	N Metatarsals (%)	1 (7.1)	0	
	N Phalanges (%)	0	1 (6.7)	
Ulcer Width [cm, Mean ± SD (range)]		1.9 ± 0.92 (0.7-4.5)	1.8 ± 0.9 (0.7-3.5)	0.769
Ulcer Length [cm, Mean ± SD (range)]		3.4 ± 3.28 (0.9-13.2)	2.2 ± 1.56 (1-5.7)	0.214
Ulcer Area [cm <sup>2</sup> , Mean ± SD (range)]		6.9 ± 6.75 (1.1-21.1)	4.7 ± 5.43 (1.2-16.5)	0.340

# Secondary Endpoints



## Rate of Complete Wound Closure:

Both ITT and PP with  $p < 0.0001$  DAMA+SOC vs SOC alone



## Change from Baseline in re-epithelialization:

ITT with  $p = 0.285$ , DAMA+SOC vs SOC alone



## Change from Baseline in granulation:

ITT with  $p = 0.092$ , DAMA+SOC vs SOC alone



## Number of applications of DAMA:

- 15 subjects received 65 pieces (Mean  $4.33 \pm 1.7$  pieces)
- 5 subjects whose wounds closed received 23 pieces (Mean  $4.6 \pm 1.34$  pieces) vs
- Wounds that did not close ( $n = 10$ ) received 42 pieces ( $4.2 \pm 1.93$  pieces)

# Conclusions



There is a significant **advantage** to using DAMA



**45%** of wounds closing within 6 weeks for patients adhering to protocol.  
**35%** of wounds closing within 6 weeks for the ITT population



**NONE** of the Standard of Care (SOC) subject's wounds were closed at 6 weeks



The use of DAMA was **not significantly associated** any increase in **adverse** events



Robust **clinical trial** design and data analysis



## Case 1

52 yo male with right post I & D of right dorsum foot wound with history of abscess with strep. Previous treatment had included NPWT. Wound initially measuring 8.9 cm x 1.3 cm x 0.2 cm. Wound healed in 12 weeks with 5 applications of DAMA.



6-2-14

Wound initially measured 8.9 cm x 1.3 cm x 0.2cm. First DAMA application.



7-14-14

Wound measured 3.9 cm x 1.3 cm x 0.1cm with 4th DAMA application.



7-28-14

Fifth application of DAMA. Wound measured 2.5 cm x 0.5 cm x 0.1cm.



9-28-14

Wound healed in 12 weeks with 5 applications.



## Case 2

66 yo male with a right 4th toe amputated due to PVD. History of treatments include antibiotics and NPWT. DAMA was applied with no off-loading. Wound healed in less than 28 days after only 2 applications of DAMA.



6-2-14  
Baseline measurement was 0.3  
cm x 0.9 cm x 0.2 cm.  
First application of DAMA.



6-16-14  
Second application of DAMA.  
Wound measured 1.0 cm x 0.5 cm x  
0.4 cm.



6-30-14  
Third application of DAMA was  
scheduled,  
however the wound was healed.

### Case 3

64 yo female with right plantar diabetic foot ulcer below 5th metatarsal. Patient initially wore surgical shoe then Roll on Total Contact Cast (TCC)



6-2-14

First application of DAMA. Baseline measurement was 2.8 cm x 2.7 cm x 0.3 cm with sharp debridement .



6-16-14

Second application of DAMA. Wound measured 1.7 cm x 1.7 cm x 0.2 cm. Roll on TCC System was applied.



6/30/14

Third DAMA application. Wound measured 1.4 cm x 1.5 cm x 0.2 cm. Roll on TCC System was applied.



7-14-14

Fourth DAMA application. Wound measured 0.5 cm x 0.5 cm x 0.1cm. Wound was cleansed, DAMA applied, cellulose acetate and coated with a petrolatum emulsion,\*\*\* and Roll on TCC System were applied. Roll on TCC System was scheduled for removal and reapplication on 7-21-14.



7-28-14

Wound healed in 9 weeks after 4 applications of DAMA and Roll on TCC System starting on 6-8-14. The patient had the wound for 38 weeks prior to DAMA..

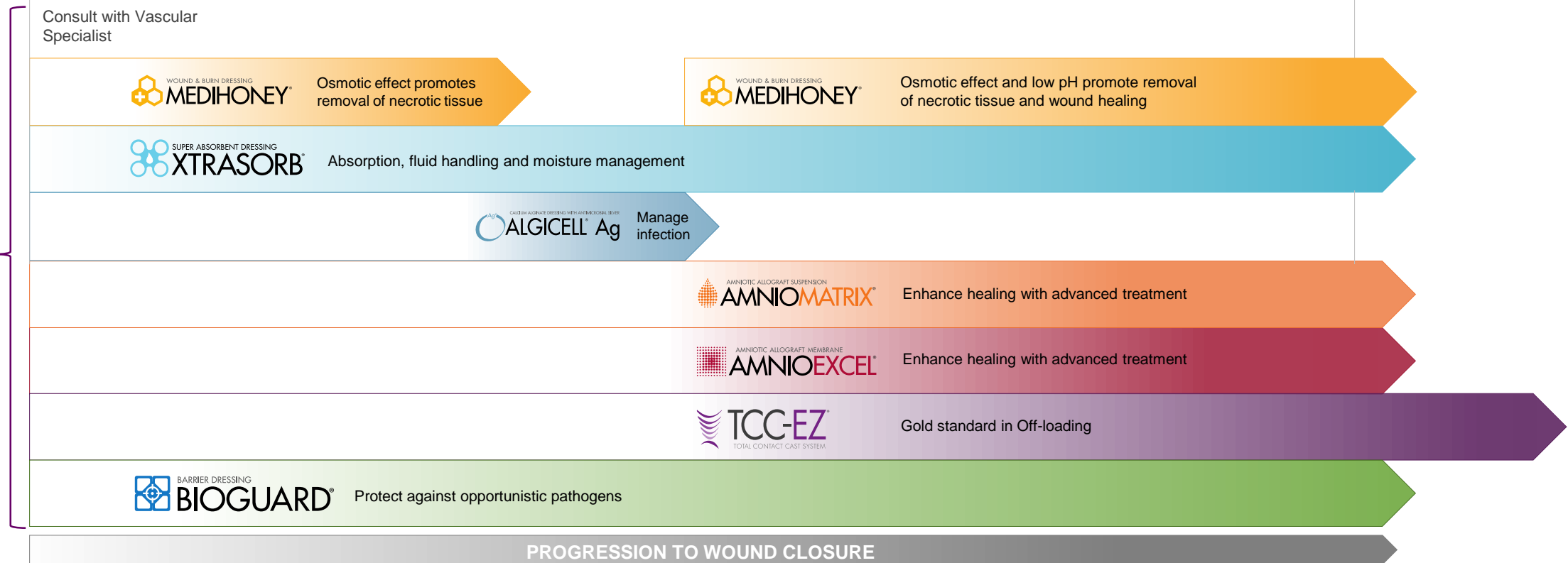


# Diabetic Foot Ulcer Wound Care and Off-loading Protocol

VIP PRINCIPLES: **V**ascular Management / **I**nfection Control and Prevention / **P**ressure Relief \*

<b>GOALS</b>	<p>Ensure Adequate Vascular Status</p> 	<p>Debridement</p> 	<p>Infection Control and Prevention</p> 	<p>Protect from Maceration and Contamination</p> 	<p>Off-Loading: Prevent Pressure and Shearing Forces</p> 	<p>Healing</p> 	<p>Completely Closed Wound</p> 
<b>BARRIERS</b>	Age, co-morbidities, obesity, nutrition, surgical candidacy	Necrotic Tissue, Elevated pH	Bioburden/Biofilm	Excessive wound exudate/MMPs	Patient adherence and activity level	Failure of the wound to progress	

## SOLUTIONS



# TCC-EZ<sup>®</sup> Makes the Choice Easy

TCC-EZ<sup>®</sup> offers the **GOLD Standard** of care with a patented, easy to apply, roll on system. The result is now an application can be completed in **under 10 minutes** while providing greater patient comfort.

- Easy 3-step process: Prep, Roll & Apply
- Takes about ¼ the amount of time of traditional systems
- Ease & consistency of application helps to decrease potential of causing tissue damage
- Requires minimal training time
- Light-weight woven design offers a more comfortable fit



# Total Contact Casting Evidence



**Total Contact Casting vs Other Off-Loading Modalities**

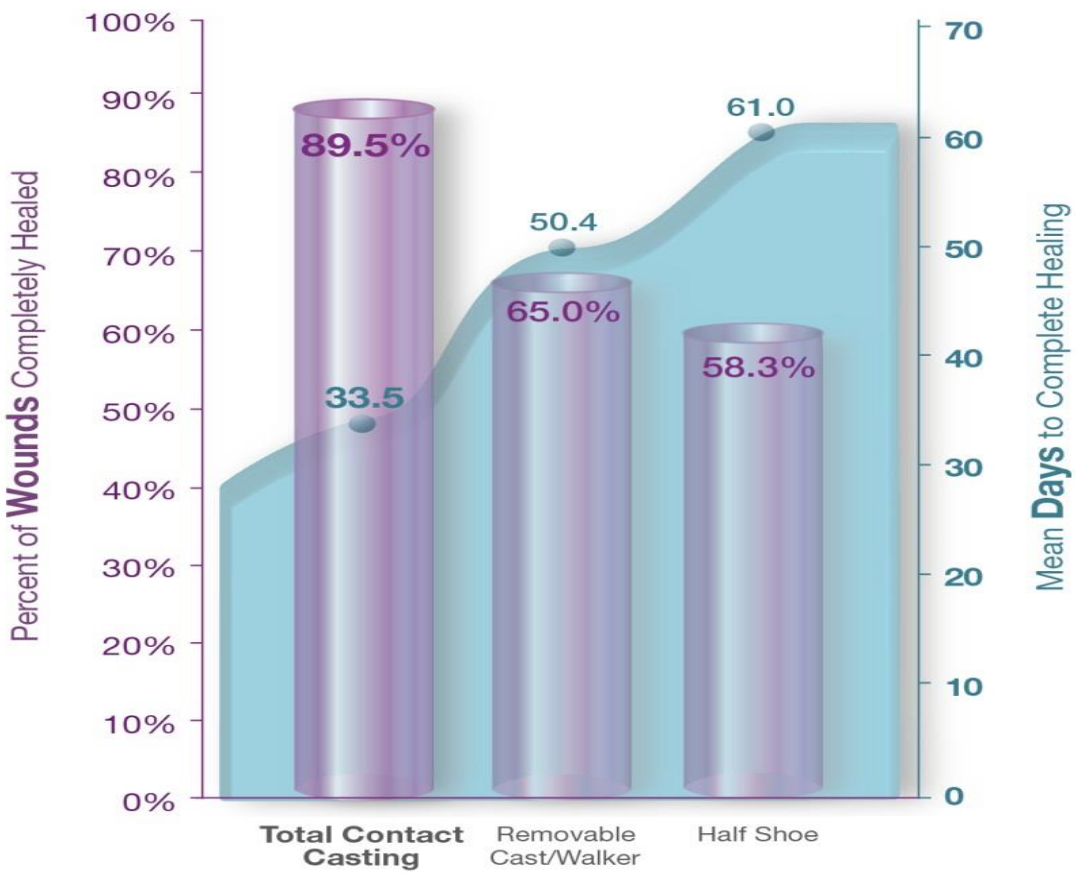


Chart Ref. 1, Armstrong 2001, RCT

TCC is supported by level I evidence. Including numerous RCTs, two meta-analyses and a Cochrane review.<sup>1-11</sup>

The 2013 Cochrane review states: “Non-removable casts provide the most effective pressure relieving intervention for the healing of diabetic foot ulcers.”

# 2006 WOUND HEALING SOCIETY GUIDELINES FOR TREATMENT OF DIABETIC ULCERS

\* No adjunctive therapies will work without appropriate off-loading



Steed DL, et al. Guidelines for the treatment of diabetic ulcers. Wound Repair Regen. 2006;14(6):680-692.



# TCC-EZ<sup>®</sup> with AMNIOEXCEL<sup>®</sup>, Perfect Partners



TCC-EZ Protects the graft: Allows the graft to do its job

1. Reduces shear on the foot that can move the graft
2. Even the smallest micromotion can disrupt the positive effects of the graft
3. Reduces pressure that can destroy the graft and epithelial tissue
4. Ensures patient compliance

# Clinical Results

## DFU treated with AMNIOEXCEL

- *Ulcer present for > 6 months, failed standard treatment*
- *Three applications of AMNIOEXCEL, applied every two weeks*
- *Off-loaded with total contact casting, TCC-EZ*
- *Full closure by week 6*



Week 0  
Initial treatment



Week 3  
After 2 treatments



Week 6  
Full Closure

Photos courtesy of Barry Rosenblum, DPM

AMNIOEXCEL is a registered trademark of BioD, LLC.

# Sample

- Male 65 with diabetes
- Treated with AWC dressings and skin substitutes 6 month prior, no effect
- Healed when off loading with TCC-EZ<sup>®</sup> in 4 months



# Welcome to 21<sup>st</sup> century wound care

- **THE FUTURE IS.....NOW**

