

# Clinical Evidence for Multidex

Jonathan Cayce, PhD

Clinical Research Coordinator



Improving Care. Improving Business.®

# Overview of Clinical Literature for Wound Care

- “ONLY 4% of all advanced wound dressings have a true randomized control trial”
  - *What do we learn from our failures?* at International Symposium Diabetic Foot
    - Dr. Andros, **Prof Apelqvist**, and Dr. WH van Houtum
- Most clinical evidence are **case series** and **case studies**
- Guidelines issued by ISDF
  - Clean ulcers regularly with clean water or saline, debride when possible, and dress them with a sterile inert dressing to **control excessive exudate, and maintain a moist environment in order to promote healing.**
  - Select dressings principally on the basis of **exudate control**, comfort, and **cost**
  - Conclusion: “In the absence of any specific indication, practitioners should use the dressing/application with the **lowest acquisition cost**, but which supports **moist wound healing** whilst controlling any **exudate.**”
- **Take Home: *Multidex is well positioned to compete in the wound care market with a +20 year history in treating chronic wounds***

# Overview of Clinical Literature

## Supporting Multidex

1. Silvetti 1981 – Case Series in 58 Patients with Chronic Wounds
2. Silvetti - Unpublished RCT and Mirror Lesion Studies in Pressure Ulcers
3. Silvetti and Eldibany – Poster reporting on presence of white blood cells in wound bed
4. Bonham 1999 – Multidex treatment of recalcitrant peristomal ulcers
5. Smiddy 2000 – Multidex treatment of brown recluse spider bites
6. Earles and Smiddy 2003 – Multidex treatment of diabetic foot burn injury
7. Krötzsch et al. 2005 - Multidex treatment of venous leg ulcers
8. Yurttas 2012 – Multidex treatment of Mycosis Fungoides
9. Brunette 2012 – Multidex treatment of four recalcitrant wounds
10. Palec 2012 – Multidex treatment of diabetic foot with exposed tendon
11. Hartzell et al 2014 – Treatment of tracheostomy ulcers with Multidex and Silver Alginate
12. Puerta et al. 2015 – Case series of Multidex treatment in Diabetic Foot Wounds



# Silvetti 1981: Case Series Demonstrating Efficacy of Multidex for Acute and Chronic Wounds

- Describes treatment of 58 patients with Multidex
  - Age: 6 days to 95 years
  - Wound types: pressure ulcer, traumatic wound, venous leg ulcers, diabetic wounds, 2<sup>nd</sup> and 3<sup>rd</sup> degree burns
  - Most patients **recalcitrant** to conventional treatment
- 55 of 58 patients responded to treatment
  - Three patients with failed treatment attributed to terminal condition or non compliance
- Reported quick formation of granulation tissue and epithelial proliferation
- Small to medium sized wounds healed between 4 and 8 weeks
- Larger lesions were decreased in size and successfully autographed
- No adverse events reported
- Demonstrated effectiveness of Multidex for all indicated wounds
- Silvetti *J. Dermatol. Surg. Oncol.* 7:6 June 1981; p. 501-508

# Silvetti: 510K Pressure Ulcer Clinical Study

- Original clinical study for obtaining US FDA 510K Approval
  - Target wound: **Recalcitrant** stage III and IV pressure ulcers
  - Experimental dressing: Multidex powder primary, gauze as secondary
  - Control dressing: Standard Treatment
    - Wet to dry dressing soaked in saline, Dakin's solution, or Betadine
  - Daily dressing changes until treatment discontinuation or discharge
- Mirror Lesion Study: Multidex versus Saline wet to dry(n=10)
  - Multidex treatment **decreased** wound size by **26±13.6%**
  - Saline wet to dry dressing treatment **increased** wound size by **33.6±16.6%**
  - Difference between two groups is significantly different
    - Independent t-test: p=0.013, power=0.75
- Mirror Lesion Study: Multidex versus Dakin's wet to dry (n=22)
  - Multidex treatment **decreased** wound size by **44.2±9.0%**
  - Dakin's wet to dry dressing treatment **decreased** wound size by **7.6±9.0%**
  - Difference between two groups is significantly different
    - Independent t-test: p=0.043 **power=0.86**

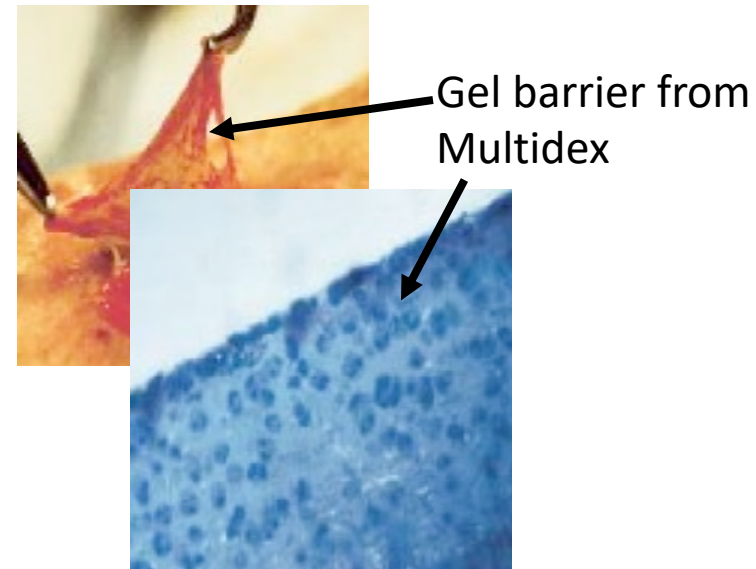


# 510K Pressure Ulcer Clinical Study Continued

- Independent Lesion Study: Multidex (n=38) versus Saline (n=18) and Dakin's (n=18)
  - Multidex treatment **decreased** wound size by **43.8±3.9%**
  - Dakin's wet to dry dressing treatment **decreased** wound size by **2.8±11.6%**
  - Saline wet to dry dressing treatment **increased** wound size by **33.6±16.6%**
  - Difference between Multidex and two control groups are significantly different
    - Dakin's Solution: p=0.026
    - Saline: p=0.0046
    - **Study power: 0.95**
- Independent Lesion Study: Multidex (n=63, wounds=154) versus Betadine (n=55, wounds 162)
  - Study reported wounds treated with **Multidex healed 3 times faster** than control dressing (Betadine)
  - Linear regression identified significant difference with a p value < 0.01
  - Data analysis performed by independent Biostatistician
- Four studies demonstrate that Multidex is **effective** at treating recalcitrant pressure ulcers
  - Results of study allowed 510K approval

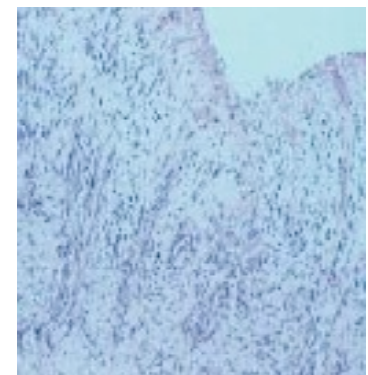
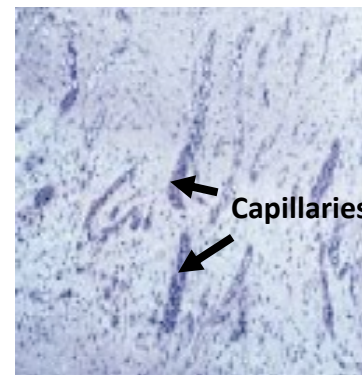
# Silvetti: Presence of white blood cells in wound bed demonstrate Multidex promotes ideal wound healing environment

- Follow on report to Boyden chamber test demonstrating attraction of neutrophils to Multidex
- Compared biopsies from patients treated with Multidex to those treated with wet to dry dressings
- Clear difference between wounds treated with Multidex compared to wet to dry dressings
  - Pathology of biopsies demonstrated increased presence of leukocytes, fibroblast, and endothelial cells in patients treated with Multidex



**Multidex**

**Wet to Dry**



Density level indicative of fibrosis in the section

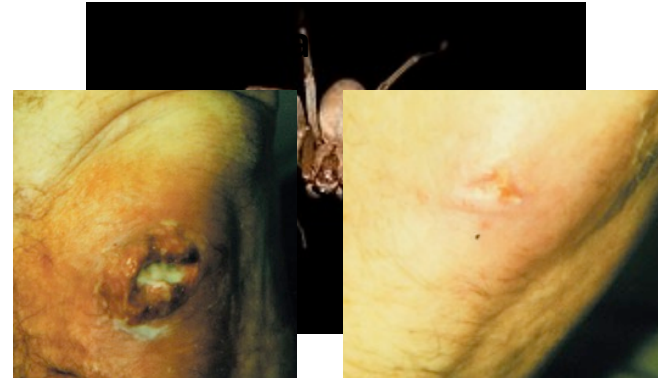
# Bonham and Schaffer: Recalcitrant Peristomal Ulcer

- Reports on treatment of peristomal ulcers with 13 month history and 3 months of failed treatment
- 75 year old women with history of cancer
  - Received a cystectomy and ileal conduit for urinary system cancer
  - Hypertension, arthritis, gastrointestinal bleeding, cerebral stroke
  - Ulcers developed 5 years after surgery
- Failed treatment:
  - Hyperbaric oxygen
  - Calcium Alginate dressing
  - Stomadhesive Powder (Convatec)
  - Aquacel (Convatec)
  - Medifil Collagen
- Multidex treatment replaced Medifil collagen after 3 months of failed treatment
  - Patient received nutritional supplement
- Wound resolved at 12 months with wound grafting



# Smiddy: Treatment of Brown Recluse Spider Bites with Multidex

- Brown Recluse Spider
  - Highly venomous spider located in Midwest and Southeast United States
  - Hemotoxic venom can cause severe necrotic ulcers
- Study enrolled 6 patients with Brown Recluse Spider bites with skin necrosis
  - Multidex with a secondary dressing
  - Hypobaric oxygen treatment for 90 minutes
  - Daily dressing changes
- Protocol resulted in rapid resolution of necrotic lesions
- No patient required antibiotics, dapsons, or surgery



Day 0

7 HBO Sessions

## Case 2



Day 0

6 HBO Sessions

# Earles and Smiddy: Treatment of Diabetic Burn Patient using HBO, Enzymatic Debridement, and Maltodextrin

- Case Study on 46 yr Male Diabetic Patient
  - 2<sup>nd</sup> degree burn on plantar surface of left foot and toes 1 -5, with peripheral neuropathy
- Wound Management
  - HBO for 9 treatments for ischemia (13 days)
    - Dressing silver sulfadiazine and calcium alginate
  - Offloading was applied
  - Enzymatic debridement utilized for 5 days
  - Patient transitioned to Multidex treatment (64 days)
    - Powder used on granulating tissue
    - Gel used on eschar to facilitate autolytic debridement
- Case demonstrates conservative management utilizing different advanced wound care techniques to heal a diabetic wound in 9 weeks



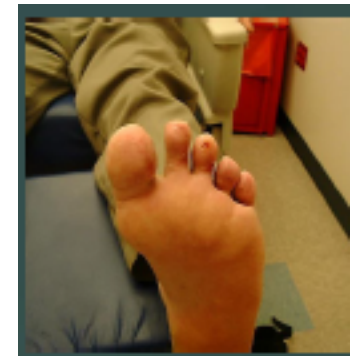
Initial Visit



Day 20:  
Multidex Initiated



Day 55: 35 Days of  
Multidex Treatment



Day 84: Wounds Healed  
64 Days of Multidex  
Treatment

# Kröttsch et al. 2005: Efficacy of Multidex for treating Venous Ulcers

- Pilot study for the treatment of Venous Ulcers with **Multidex**
  - Zinc Oxide treatment standard in Mexico
  - Mexico's health system does not allow compression therapy
  - Standard treatment is ineffective
- Multidex promotes healing of venous ulcers **without compression**
  - MDX 57% (n=11) wound closure vs. CTRL 16% (n=9)
    - (p = 0.035)
  - Wound microenvironment markers support healing seen for Multidex
    - Increased microvasculature (71.4% MDX vs. 28.6% CTRL)
    - Increased extracellular phosphatase activity (55.6% vs. 28.6%)
    - Increased cytokine IL-1 $\beta$  (50% vs. 28.6%)
  - Observed percent wound closure likely to increase with compression therapy



# Yurttas 2012 – Multidex treatment of

## Mycosis Fungoides

Week 0



Week 6 on Prot.  
(Week 8 Overall)



Week 2 of Failed  
Treatment



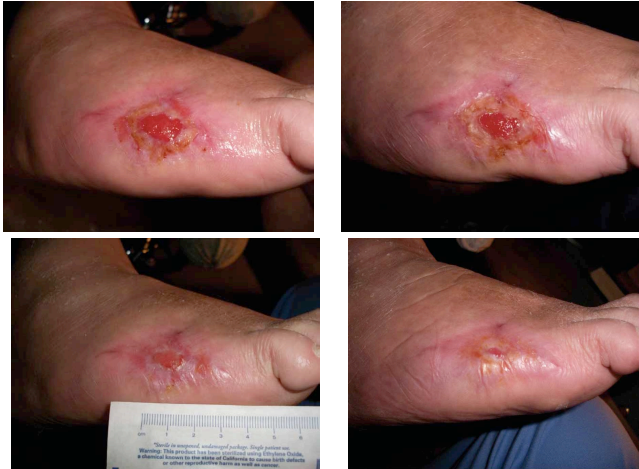
Week 12 on Prot.  
(Week 14 Overall)



- Mycosis Fungoides
  - Complication of Stage IV Lymphoma
  - Extreme pain, copious exudate, bleeding and malodour
  - Unique wound where other treatment had failed
  - Multidex used with a variety of interventions to resolve a wound initially treated as palliative care
- Treatment Protocol
  - Jetox used for debridement, Multidex placed on wound, and NPWT for 9 weeks
  - At week 9 NPWT discontinued
  - Week 15 patient discharged with Multidex treatment
- Healed in 20 weeks on protocol

# Brunette 2012 – Multidex treatment of four recalcitrant wounds

## Case 1: Diabetic Foot Wound



## Case 4: Chronic Surgical Wound (Squamous Cell Cancer)



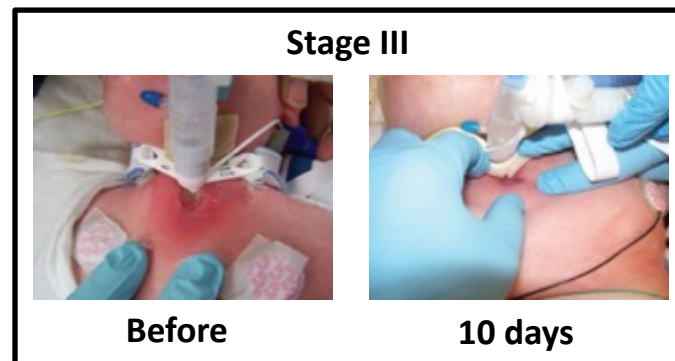
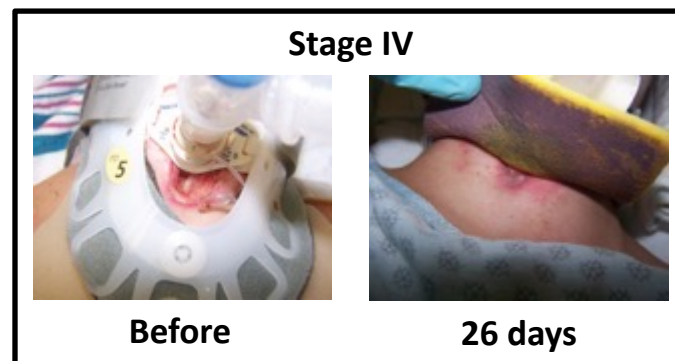
- **Case 1: Diabetic foot wound**
  - Initial treatment: Treated with NPWT until granulated then silver alginate
    - Silver alginate allowed biofilm to develop
  - Transitioned to Multidex Powder
    - Biofilm became thinner and easier to debride
    - Wound healed within 10 weeks
- **Case 2: Dehisced chest wound following Aortic Valve Replacement**
  - Silver alginate caused wound measurements to increase and tunnel
  - Transitioned to Multidex and wound healed within 2 weeks
- **Case 3: Traumatic wound**
  - Collagenase ointment used initially
    - Swelling and purulent drainage, managed by silver fabric
  - Transitioned to silver alginate
    - Wound closed to pinpoint but with undermining
    - Reopened, wound decreased in size but stalled
  - Multidex treatment healed wound within 4 weeks
- **Case 4: Chronic surgical wound on ankle following removal of skin cancer (1 year history)**
  - Silver Alginate and unna boot to treat wound and edema
    - Wound increased in size and wound edges became discolored (4 days treatment)
  - Multidex initiation and unna boot discontinued
    - Wound healed within 8 weeks

# Palec 2012 – Multidex treatment of diabetic foot with exposed tendon

- Diabetic bilateral foot ulcers with at least 1 year history.
  - 2 ulcers on left and 1 ulcer on right later ankle with slough
- Initial Treatment
  - Medical grade honey for wound debridement and compression for edema
  - Weekly sharp debridement
- 7 Weeks: Right wound reduced in size with left wounds becoming larger
  - Tendon exposed on left ankle
  - Infected with *Strep* and *Enterobacter cloacae*, treated with oral antibiotics
  - Treatment transitioned to living bilayered skin substitute
- 10 Weeks: Left ankle wounds increased redness, drainage, wound area, and tendon exposure
  - Treatment transitioned to silver alginate, foam, and compression
    - Copious drainage and eventual hospitalization for IV antibiotics
    - Tendon required debridement
- Multidex treatment initiated and silver dressing discontinued
  - Wound size decreased in size weekly
  - Full covering of tendon within 2 months of treatment initiation
- **Take home point: Medical honey, living bi-layered skin substitute, and silver alginate all failed to treat wound over 17 week period. Multidex dressing allowed wound to heal within 2 months (8 weeks)!**

# Hartzell et al 2014 – Treatment of tracheostomy ulcers with Multidex and Silver Alginate

- Case series that described treatment protocol for tracheostomy ulcers utilizing Multidex and Silver Alginate Foam Dressings
- Case series included 11 patients
  - Age range: 0.3 – 15.6 years
  - Wounds: Stage 2 = 6, Stage 3 = 4, Stage 4 = 1
  - 9 patients received Multidex and Silver dressing, remaining 2 received only Multidex
- Protocol was credited with evoking rapid wound healing
  - Wound healing duration
    - Mean: 12.8 days
    - Median: 10 days
    - Range: 6 – 28 days
  - Authors indicated remarkable anecdotal decrease in wound treatment duration compared to prior protocol
    - Prior protocol utilized gauze, foam barrier, ointments
- Hartzell et al. *Respiratory care*, 2014, respcare-02822



# Puerta 2015 – Case Series Reporting on Efficacy of Multidex for Treating the Diabetic Foot

- Challenges:
  - Limited resources and education
    - Employment typically requires feet
    - Socialized medicine with limited resources
  - Warm, humid, and moist climate year round creating difficult condition to heal diabetic foot wounds
- Need:
  - Cost effective wound treatment protocol for these wounds

Diabetes Prevalence <sup>1</sup>	
Cases of DM (20-79 years) in thousands	202.2
Undiagnosed cases of DM (20-79 years)	56.2
Prevalence	8.4%
Related deaths to DM (20-79 years)	1,397
Related deaths in people under 60 years	42.1
Cost per person with DM (USD)	1,096.20

Panama Diabetes Sociodemographics <sup>2</sup>	
Urban\Rural\Indigenous	52%\46%\2%
Female\Male	67%\43%
Monthly Income < 600 USD	81.7%
Monthly Income > 600 USD	18%
High School Education or Less	78%

Average Weather Data for Panama <sup>3</sup>	
High Temp.	30 °C
Humidity Range	72 – 91%
Number of Rainy Days	263

1 - International Diabetes Federation. Atlas 6th ed. update 2014

2 – McDonald et al. *Diabet. Metabolic. Syndrome* 2013

3 – [weatherbase.com/weather/weather.php3?s=760887](http://weatherbase.com/weather/weather.php3?s=760887)





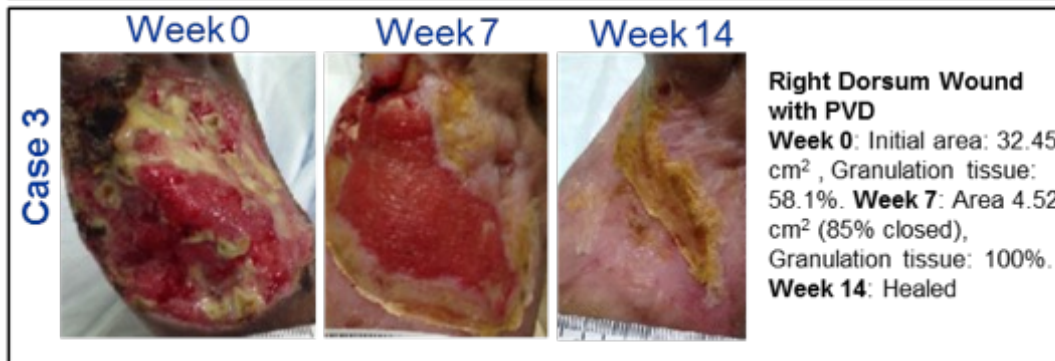
# Puerta 2015 – Importance of limb preservation following diabetic foot ulceration

- Major limb amputation is required for 7 to 20% of diabetic foot ulcer cases<sup>1</sup>
  - Within 3 to 5 years, 58% of these patients require amputation of contralateral limb<sup>2</sup>
  - 3 year Mortality rate is between 20 and 50%<sup>2</sup>
  - Morality rate is similar for some cancers<sup>3</sup>
- Major amputations are estimated to place a 67.47 million dollar burden on the Panamanian healthcare system annually
  - Estimation assumes only 7% of diabetic Panamanians require an amputation
  - Does not account for lost wages due to inability to work and reduced quality of life
- These observations indicate the importance of a cost effective limb preservation to maximize quality of life and life expectancy

# Puerta 2015 – Methods

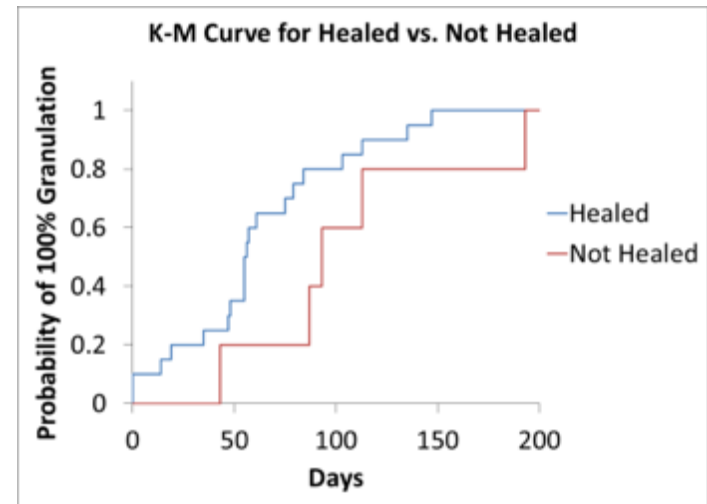
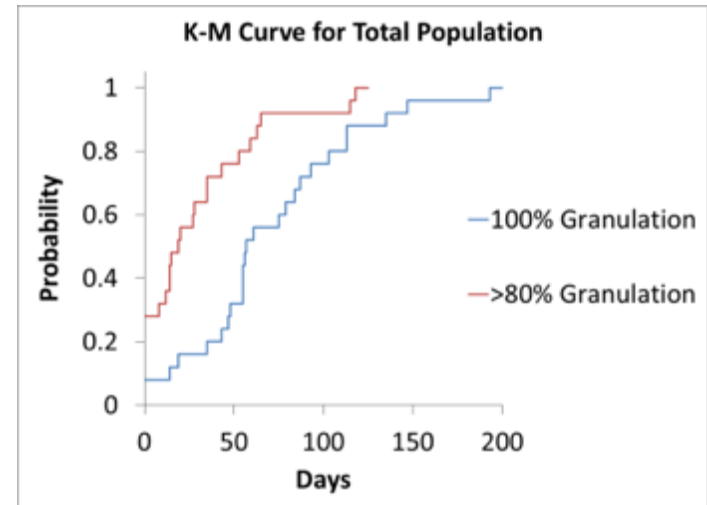
- Recruited 25 patients (26 wounds) with Wagner Stage 2 – 4 diabetic foot ulcers
  - **10 following transmetatarsal amputation in patients indicated for amputation**
- Treatment Protocol
  - **Sharp debridement** as indicated and wound cleaned with saline at weekly follow up visit
  - **Multidex** dressing applied to wound bed
    - Powder for moist/wet
    - Gel for dry wounds
  - **Cotton gauze** used as secondary dressing and appropriate **offloading** applied
  - Patients and **family members** trained to **change dressing daily**
    - Patients were placed on **supplementary nutrition**
- Wounds photographed at each follow up visit and analyzed with digital planimetry
  - Healing trajectory used to estimate weekly wound healing rate
  - Modified K-M survival curves used to quantify probability of wound healing and granulation tissue coverage over time

# Puerta 2015 – Representative Cases



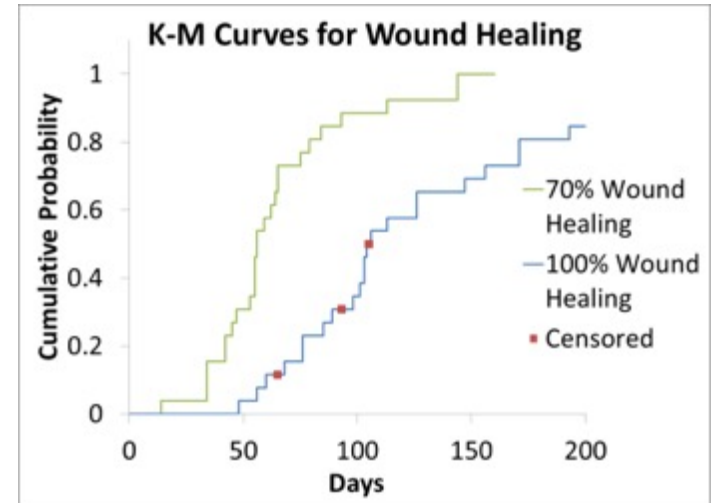
# Puerta 2015 – Efficacy of Multidex for treating diabetic foot wounds

- Complete granulation of wound bed observed in all patients
  - 100% Median: 57 days
  - 80% Median: 19 days
- Non-healing wounds were delayed in granulation tissue formation
  - Healed Median: 55.5 days
  - Non-healed Median: 93 days
  - Log-Rank p-value: 0.094



# Puerta 2015 – Efficacy of Multidex for treating diabetic foot wounds

- All wound achieved 70% wound closure
  - 70% WH Median: 56 days
  - 100% WH Median: 103 days
- Non-healing wounds (n=5) were resolved through skin grafting
  - 100% granulation and 70% reduction in wound size
- Wound healing trajectory predicts 6-7% reduction in wound size per week



# Puerta 2015 – Take home points

- A simple treatment protocol utilizing debridement, offloading, Multidex, and a gauze secondary dressing achieved effective wound healing in stage II, III, and IV diabetic foot ulcers
  - Rapid formation of granulation tissue and re-epithelialization of the wound
  - Supports claim that Multidex established an ideal moist environment that stimulates wound healing
- Resolution of 13 Metatarsal amputation wounds demonstrates ability to salvage wounds (study presented at ISDF)
  - 12 of 13 healed under protocol (remaining wound resolved with grafting)
  - Median time to wound closure was 104 days
- Similar to other advanced wound care methods
  - **NPWT**<sup>1</sup> of post amputation wounds in Diabetic Foot: 56% of population at 16 weeks
  - **Medical Grade Honey**<sup>2</sup> in non-diabetic chronic wounds: Median 100 days
- Protocol is cost effective: Potential to save \$20 million in Panama alone

# Puerta 2015 – Wound healing trajectory and KM-Survival curves explained

- Wound healing trajectory
  - Mean Percentage of wound closure vs. Time
  - Allows for wounds of different sizes to be normalized for comparison purposes
    - Calculate average percent wound healing per week
    - Compare wounds that healed versus not healed
  - Does not require complete wound healing or for the wound to meet a certain criterion
- Kaplan-Meier survival curves
  - Non-parametric statistical approach to calculate probability of a wound reaching a specific criterion (i.e. 100% wound healing, 100% granulation, 80% wound healing, etc.) as a function of time.
  - Allows for censoring of data points due to loss of patient follow up or resolution of wounds through wound grafting
  - Statistical testing can be performed to identify trends in the data