Diabetic Foot Ulcers:
Clinical Evidence;
Conflicting Data Reconcilation

Dick Clarke, CHT

Diabetic Foot Ulcers

Review of published clinical research & reconciliation of conflicting data

Primary Training in Hyperbaric Medicine

Columbia, South Carolina

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Update on management of diabetic foot ulcers

Everett E, Mathioudakis N. Ann NY Acad Sci 2018

Epidemiology/Consequences

- 9.1-26.1 million DM pts ulcerate annually
- 19-34% DM pts develop ulcers in lifetime
- DFU mortality > 40% at 5 yrs.
- DFUs account for 1/3 of DM costs (US$176b)
- 20% remain unhealed at 1 yr.

"Standard of care practices"

- Vascular assessment…*evaluated for arterial insufficiency* * #
- Infection control… *Dx by inflammation & purulence* * + *cultures obtained before ABN* * #
- Glycemic control…*optimize blood glucose control* * +
- Debridement…*sharp debridement preferred* * #
- Dressing choice…*to allow moist environment & exudate control* * ^
- Wound off-loading…*pressures should be distributed off wound* * ^

*Strength of recommendation…Strong **

Level of evidence …High ^
…Moderate #
…Low +

Everett E, Mathioudakis N
Ann NY Academy Sci 2018

DFU DATA APPRAISAL

Prospective non-formally randomized; 18 HBO 10 no HBO

Diabetic gangrene all inpt. HBO "drastically reduced leg amputations"

2.8 ATA O2 "antibacterial effect" then 2.5 ATA O2 "reparative effect'"

Baroni G, *et al.* 1987
Diabetes Care 10;(1):81-86

Retrospective; 168 HBO most with soft tissue & bone infections

Mix of in-outpt. > 50 went to major amputation

Most with angiographic evidence of PVD & absent pedal pulses

Led to study of TCOMS in selection process

Davis JC, 1987
Clinics Pod Med Surg 4(2):429-437

DFU DATA APPRAISAL

Retrospective non-formally randomized pts; 62 HBO 18 no HBO

Diabetic gangrene all inpt; "significant reduction in amputation rate"

Oriani G, *et al.* 1990
J Hyper Med:5(3):171-175

10 yr retrospective 151 pts

Diabetic gangrene all inpt; "significant reduction in amputation rate"

Oriani G, *et al.* 1992
J Hyper Med:7(4):213-221

DFU DATA APPRAISAL

Hyperbaric Oxygen Therapy in Diabetic Foot

Doctor N, *et al.* J Postgrad Med 1992;38(3)

Study Design

30 DM inpatients randomly allocated - "well matched"

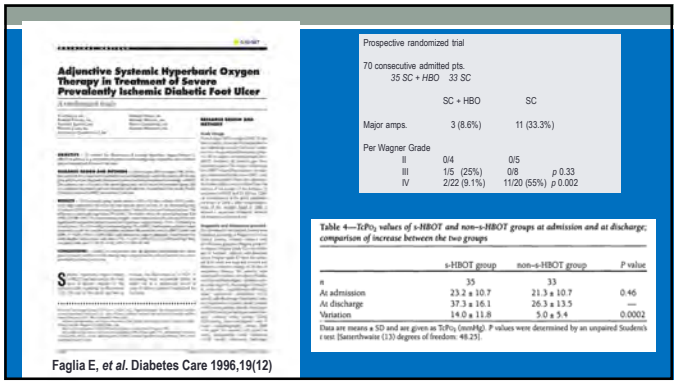
SC (I & D; Antibiotics; DM control)

SC + HBO 4 tx over 2 weeks 3.0 ATA x 45 mins

Assessed wound cultures pre-post HBO, LOS, wound response, amputation & its level

Results

Parameter	Study Group	Control Group	p
LOS (days)	40.6 (23-65)	47 (20-68)	NS
Major amps.	2	7	<0.05
Minor amps.	4	2	NS
+ Cultures Pre- Post	19/3	16/12	<0.05



Faglia E, *et al.* Diabetes Care 1996,19(12)

Ischemic LE DFU's

Non-healing to SC > 6 weeks

All underwent dx angiography

Flow augmentation pts excluded

25 screened, 18 enrolled, 16 studied

Ulcers healed:	HBO	Sham	
At 6 weeks	5/8	1/8	NS
At 6 months	5/8	2/8	NS
At 1-year	5/8	0/8	0.026

Abidia A, *et al.* Eur J Vasc Endovasc Surg 2003(25)

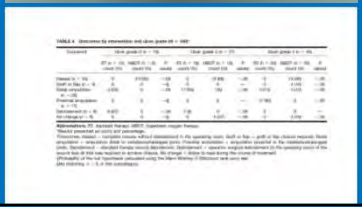
Prospective, formally randomized, long-term f/u; 17 HBO 21 no HBO

All outpt. DFU's; effective healing in setting of reversible local hypoxia

Kalani M, *et al.* 2002
J Diabetes Compls;16:153-158

RCT, although unblinded/no sham; 50 HBO 50 no HBO

Infected DFU's, all inpt; effective healing & reduced amputation rate



Duzgun AP, *et al.* 2008
J Foot Ankle Surg;47(6)

Trial Design/Primary Outcome

164 assessed; 94 enrolled
57%

SC non-responders > 2 months

DFU > 3 months (mean 10 months)
Wagner grade 2-4

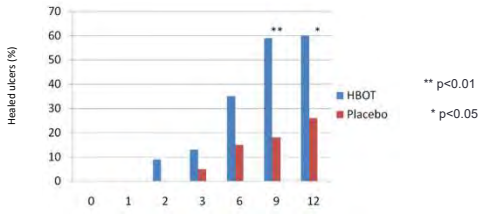
Randomized to SC + HBO vs. SC + sham

Placebo/sham controls

2.5 ATA (mask) O2 vs. air x 40 sessions

Primary outcome complete healing 1 yr.

Londahl, M *et al.* Diabetes Care 2010;33



** p<0.01

* p<0.05

Complete healing at one year:

Intention to treat analysis: ***25/48 (52%) in HBO 12/42 (29%) Sham P < 0.03 NNT 4***

Per protocol analysis: ***23/38 (61%) in HBO 10/37 (27%) Sham P < 0.009 NNT 3***

Londahl M, *et al.* 2010
Diabetes Care;33:998-1003

Specialized Wound Care

We know that having a wound that won't close can be worrisome and affect your quality of life. We can help.
Here's what you can expect when you come to one of our wound centers:

Expertise

Our wound care teams have specialized training in managing and assessing wounds of all types. With access to an ongoing national database that tracks wound treatments and outcomes, we have access to the latest and best therapies.

Quality Outcomes

We have consistently excellent outcomes for wound healing.

We successfully close 94 percent of the wounds we treat, higher than the national healing rate of 91 percent
We're skilled at treating even the most complex cases
We prevent limb loss on a daily basis
We heal wounds faster than the national average – often in fewer than 30 days

OPTIMAL MANAGEMENT OF DIABETIC ULCERS OF THE LOWER EXTREMITY

Valerie Palmer, RN, ACHRN, CWCN, CWS, CMBS, FACCWS, UHMSADS
Director of Operations and Compliance
National Baromedical Services, Inc.

NO FINANCIAL CONFLICT OF INTEREST TO DISCLOSE

2021 CDC NATIONAL DIABETES STATISTICS REPORT

- 38.1 Million adults 18 years or older in U.S. have diabetes
- 14.7% of adults 18 years or older in U.S. population have diabetes
- 8th Leading cause of death in U.S.

2021 CDC NATIONAL DIABETES STATISTICS REPORT

- 60%-70% diabetics have nervous system damage
- Severe nervous system damage increases chance of ulceration
- > 60% non-traumatic lower limb amputations occur in people with diabetes

INTERNATIONAL DIABETES FEDERATION GLOBAL POSITION STATEMENT

- Global prevalence 537 million adults in 2021
- Predicted to reach 783 million by 2045
- $966 billion USD spent yearly globally to treat diabetes
- 1 in every 6 people with diabetes will develop foot ulcer
- 85% diabetes related amputations are preceded by foot ulcers
- 49% - 85% of amputations are preventable
- Requires well-organized diabetic multidisciplinary team

So, just how do you evaluate and treat a diabetic ulcer of the lower extremity?

Just like you do any other lower extremity ulcer!

SYSTEMIC FACTORS AFFECTING WOUND HEALING

- **Diabetes**
- **Tobacco use**
- **Malnutrition**
- **Hereditary disorder**
- **Alcohol use**
- **Malignancy**
- **Renal failure**
- **Autoimmune**
- **Chemotherapy**
- **Steroids**
- **Extremes of age**
- **Systemic infection**

LOCAL FACTORS AFFECTING WOUND HEALING

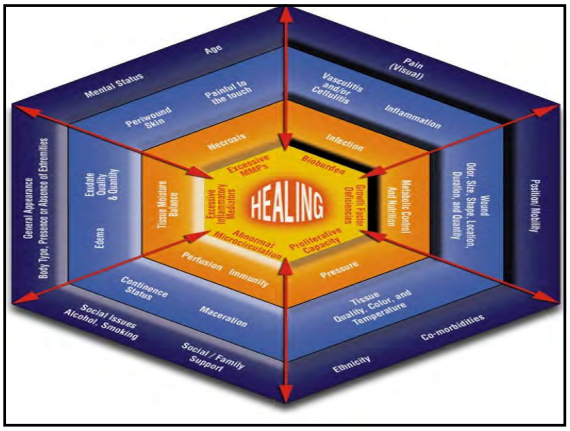
- **Ischemia**
- **Edema**
- **Infection**
- **Scarring**
- **Radiation injury**
- **Topical steroids**
- **Local toxins**
- **Trauma/Pressure**
- **Foreign bodies**
- **Local malignancy**

Why Diabetics Don't Heal

- High levels of matrixmetalloproteinases (MMP-9)
- Low levels of growth factors (Cullen et. al: Wound Rep Reg 10: 2002)
- If hypoxic:
  1. Poor collagen production
  2. Impaired resistance & response to local infection
  3. Limited angiogenesis
  4. Decreased fibroblast replication

CHRONIC WOUNDS HAVE:

- Inhibitors or blockers of growth factor action
- Inadequate quantities of growth factors
- Primary inadequate response to available growth factors
- Have 30 X more MMP activity than acute wounds



DIAGNOSIS OF DELAYED WOUND HEALING

Evaluation of:

1. **V**ascular status
2. **I**nfection (local or systemic)
3. **I**mmune system
4. **N**utritional status
5. **M**echanical factors
6. **M**alignancy (exclude)

VASCULAR EVALUATION History

- Diabetes
- DVT
- Tobacco use
- Radiation
- Local toxins (Spider bite)
- Collagen vascular disease
- Scarring
- Claudication
- Rest Pain

VASCULAR EVALUATION Examination

- Pulses (palpable/audible)
- Skin color (dependent rubor/hyperpigmentation)
- Rate of capillary refill (< 3 sec)
- Edema (even trace amounts)
- Hair (minor finding)

VASCULAR EVALUATION Diagnostic Testing

- CBC (anemia)
- TCOM
- Arterial doppler
- Venous doppler
- Tissue biopsy
- Collagen vascular Screening
- Arteriogram
- MRA
- MRV
- CTA
- CTV

NUTRITIONAL EVALUATION

- Physical examination
- Total protein
- Albumin
- PreAlbumin
- CBC (anemia)
- Glucose (blood sugar, HgbA1C 6.5% or <)

EVALUATION OF MECHANICAL FACTORS

- Pressure
- Foreign body
- Edema

EVALUATION OF MECHANICAL FACTORS
Pressure Due To Immobilization

- CVA
- Paralysis (spinal)
- Closed head injury
- Trauma with loss of consciousness
- Surgery
- Traction

EVALUATION OF MECHANICAL FACTORS
Pressure Due To Orthotics

- Shoes
- Stockings
- Braces
- Prosthesis

EVALUATION OF MECHANICAL FACTORS
Pressure Due To Dressings

- Cast
- Splint
- Circumferential dressings
- Dressing packing

EVALUATION OF MECHANICAL FACTORS
Foreign Body

Intentional
- ORIF
- Joint implant
- IV Access
- Mesh
- Synthetic grafts

Incidental
- Retained suture
- Bone (sequestrum)
- Needle
- Retained dressing Material
- Retained fingernail or toenail fragment

EVALUATION OF MECHANICAL FACTORS
Edema

- Trauma
- CHF
- Renal failure
- Lymphedema (congenital acquired)
- Tumor
- Surgery

IMMUNE SYSTEM EVALUATION

- Collagen vascular disease
- Drugs
  - Steroids
  - Chemotherapy
- HIV
- Systemic malignancy

EVALUATION FOR MALIGNANCY

- "Think of It"
  - Primary malignancy
  - Secondary malignancy
- Biopsy
  - Incisional
  - Excisional
- Location
  - Especially lower leg or arm
  - History of "almost healing"

EVALUATION FOR INFECTION

- Soft Tissue "bioburden"
  - Swab culture
  - Wound biopsy (gold standard)
  - (> 100,000 Organisms per gram of tissue)
- Bone infection
  - Clinical inspection
  - Bone biopsy
  - Plain X-Ray
  - CT scan
  - MRI scan
  - Labeled WBC scan

TREATMENT OF DELAYED WOUND HEALING

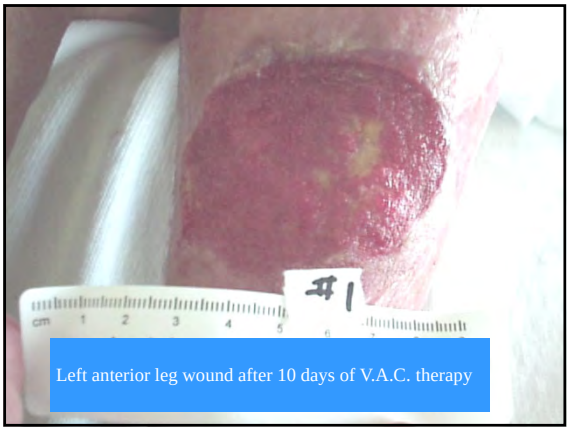
- Surgery
  - Debridement
  - Revascularization
  - Skin graft
  - Flap
  - Amputation
- Edema reduction
- Hyperbaric oxygen therapy
- Pressure relief
- Nutritional supplements
- Removal of foreign bodies
- Resolution of infection
- Excise malignancy
- Medical adjunctive care
- Local care of wound
  - Topical care
  - Dressing care

(SURGERY) SKIN GRAFTS AND FLAPS

- Split thickness skin graft
  - Requires a uniform, granulating, infection Free bed
- Skin and Skin/Muscle flaps
  - To cover non-vascularized wounds (bare bone)
  - To cover pressure areas (sacral, ischial, trochanteric pressure ulcers)
  - To cover exposed, non-infected, foreign body (prosthesis)

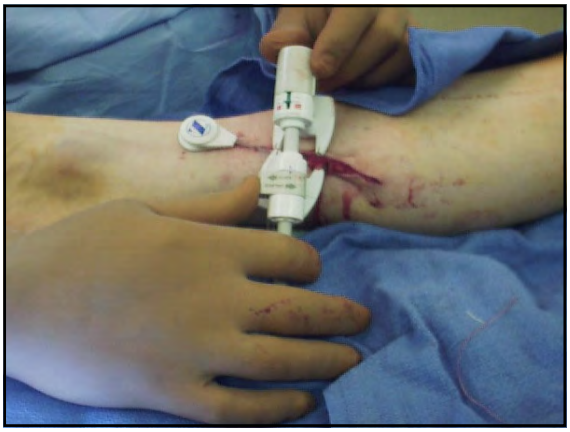
(SURGERY) SKIN GRAFTS AND FLAPS

- Skin stretching device
- Epidermal autograft (CelluTome®)
  - Donor site less painful than STSG
  - Donor site heals in 3-4 days and care be reharvested
  - Good for patients with large wounds
  - Requires no anesthesia
  - Epidermal grafts take on characteristics of recipient site
  - Can be used on patients with scleroderma or pyoderma gangrenosum



Left anterior leg wound after 10 days of V.A.C. therapy


Left anterior leg wound 6 days post-op split thickness skin graft



EFFECTS OF EDEMA

- CIRCULATION
  - Arterial and venous
- MECHANICAL
  - Distracts wound edges
- NUTRITION
  - Protein loss in excessive swelling/ drainage

EDEMA REDUCTION

- Compression
  - Multi-layer compression wraps
  - Unna's boot
  - Compression stockings
  - Sequential pressure devices
  - Ace wrap/short stretch ace
- Elevation (as tolerated)
- Negative pressure wound therapy
- Diuretics

COMPRESSION

- Must be appropriate to arterial circulatory status
- ABI of <0.7 or TCOM of lower extremity <40 mmHg calls for modification of compression strength

COMPRESSION

All patients/caregivers must be instructed on the signs/symptoms of vascular (arterial) compression/compromise and its immediate treatment

Hyperbaric oxygen is not a primary treatment for chronic diabetic foot wounds:

IT IS ADJUNCTIVE THERAPY

CMS CRITERIA

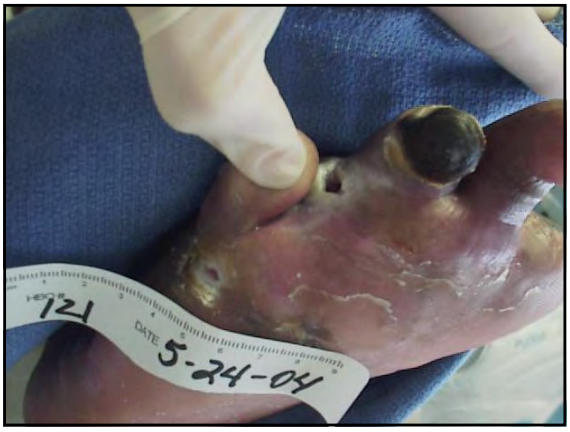
- Diabetic Ulcer
  - Type I or II diabetes
  - Lower extremity ulcer as a result of diabetes
  - Wagner grade 3 or greater
  - 30 days of failed standard wound care

EVALUATION AND TREATMENT MUST ALSO INCLUDE:

1. Appropriate debridement
2. Offloading/pressure relief
3. Optimizing nutritional status
4. Optimizing vascular status
5. Appropriate antibiotics
6. Wound dressings to maintain a moist granulating bed

Patient #121

- 45 year old black male
- Adult onset diabetes mellitus
- History of left BKA
- 10/4/99 Right femoral-distal peroneal bypass with insitu saphenous vein
- 9/23/03 presented to wound center with two diabetic, neuropathic Wagner III ulcers to right foot
- No osteomyelitis
- Previous bypass left no revascularization options
- Began HBO for a total of 40 treatments



PRESSURE RELIEF

- Beds
  - Water beds
  - Egg crate topper
  - Reactive surface beds (low air loss)
  - Clinitron
- Cushions (Foam, Felt)
- Crutches
- Rolling walker
- Turning/Repositioning
- Orthotics
  - Shoes
  - Total contact cast (Gold standard)
  - Active offloading walker
  - Specialty splints

NUTRITION

Probably the most neglected parameter in wound healing, especially in nursing home patients.

NUTRITION TREATMENT

- Maximize glucose control in diabetics:
  - Medication
  - Diet
- Vitamins/Minerals
- Anabolic steroids
- Maximize protein in diet (especially L-Arginine)

L-ARGININE

- Main substrate nitric oxide pathway
- Precursor to endothelial-derived nitric oxide
- Nitric Oxide:
  - Vasodilator (helps pain from PVD)
  - Non-specific immunity
  - Supports collagen production
  - Enhance wound tensile strength

ARGINADE – 4.5 g L-ARGININE

JUVEN – 7.0 g L-ARGININE
1.5 g HMB
(B-HYDROXY – B METHYLBUTYRATE)
7.0 g GLUTAMINE

REMOVAL OF FOREIGN BODY ASSOCIATED WITH WOUNDS

Unintentional Foreign Bodies

- Sewing needles
- Pebbles
- Bullets
- Thorns
- Retained dressings (packing, foam sponges)
- Gouty tophi

REMOVAL OF FOREIGN BODY ASSOCIATED WITH WOUNDS

Intentional Foreign Bodies

- ORIF orthopedic devices (exposed)
- Prosthetic devices
- Retained, non-absorbable suture (infected)

TREATMENT OF INFECTION

- Debride non-viable tissue
  - Soft tissue/Bone
    - Excisional
    - Enzymatic
    - Curettage
    - Amputation
- Antibiotics (culture guided)
  (6 weeks for osteomyelitis)
- Topical antibiotics

TREATMENT OF MALIGNANCY

- Surgical excision (with skin margins clear)
- Moh's chemosurgery
- Radiation therapy
- Topical chemotherapy (5-FU)

MEDICAL ADJUNCTIVE CARE

- Anticoagulation
- RBC wall deformation
- Control gout (foreign body)
- Maximize control Of CHF & HTN
  - Circulation
- Maximize control of diabetes
- Maximize control of autoimmune and/or collagen vascular diseases

GUIDING PRINCIPLES FOR LOCAL WOUND CARE

- Many wounds will improve if **anything** is done regularly
- Choice of topicals (and treatment) must be driven by **diagnosis** and not by what product is on the shelf

GUIDING PRINCIPLES, CONTINUED

- Topical agents will **NOT** defeat:
  1. Failure to relieve pressure
  2. Inadequate Circulation
  3. Malnutrition
  4. Unrelieved edema
- Cost **IS** a factor

LOCAL WOUND CARE

- Topical Antibiotics/Antibacterials
- Debriding agents
- Stimulating agents
- Enzyme (MMP) inactivators (Protease modulating dressings)

(LOCAL CARE) TOPICAL ANTIBIOTICS/ANTIMICROBIALS

- Antibiotic ointments/Gels (Mupirocin, Bacitracin, Neomycin)
- Sodium hypochlorite (Anasept, Vashe)
- Silver compounds
- Iodine compounds

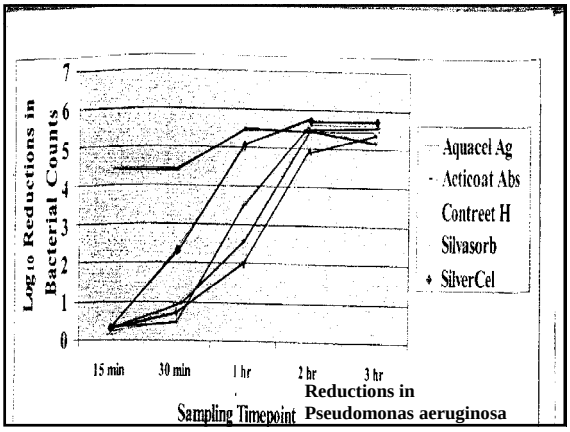
SILVER

- EXISTS IN TWO FORMS:
  1. Elemental or metallic Ag(0)
  2. Ionic silver/Silver cation Ag(I) or Ag+

SILVER

- The biologically active form of silver is the ionic (silver cation)
- **ALL** silver products have to produce the **same** biologically active ingredient to be effective: **Ag+**

If there is any difference in the various silver products it has to be in the dressing, **not** the active agent

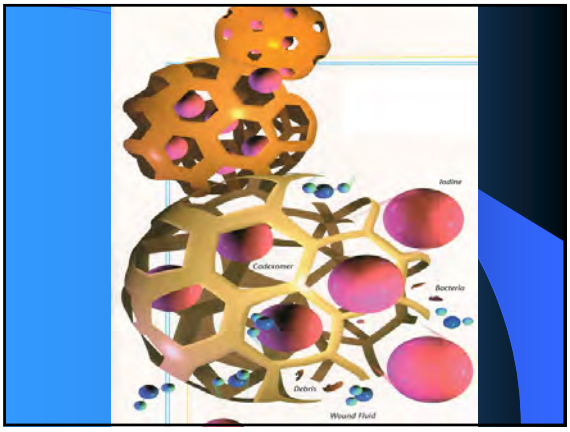


TOPICAL IODINE IS AVAILABLE IN TWO FORMS:

- **Povidone iodine (10%)**
- **Cadexomer iodine**

CADEXOMER IODINE

- **3 dimensional starch lattice formed into spherical microbeads (0.9% Iodine in starch lattice)**

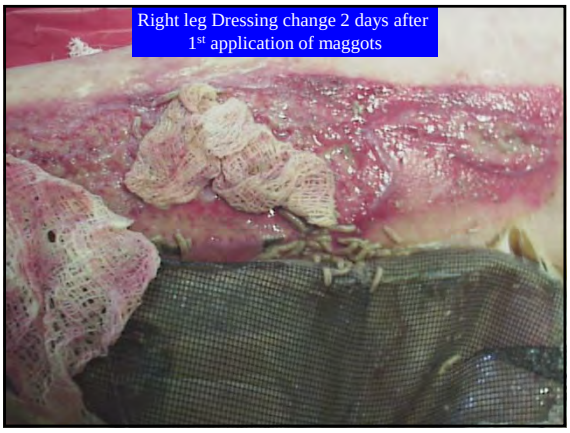


THE LATTICE:

- Has a high absorption capacity
- Absorption increases the size of the lattice, releasing the iodine at 1 part per million, until the reservoir is exhausted

(LOCAL CARE) DEBRIDING AGENTS

- Collagenase/Santyl
- Maggots
- Medical grade honey ?
- Sharp debridement (remains the quickest & most effective means)



(LOCAL CARE)
STIMULATORY AGENTS

- Balsam Of Peru (Vasolex)
- Growth factors
  - Platelet derived (Regranex, black box warning >3 tubes)
  - Cultured human neonatal skin (Apligraf & Dermagraft)
  - Allograft (Theraskin, Graft Jacket, Epifix)
  - Porcine xenograft (Oasis Matrix)
  - Bovine xenograft (Primatrix)

(LOCAL CARE)
ENZYME INACTIVATORS
(PROTEASE MODULATING DRESSING)

MMPs:

- Play a key role in wound healing
- Protein degrading enzymes that require calcium for conformation and zinc to be active
- Degrade growth factors, matrix protein, & protease inhibitors
- 24 Identified

INDICATIONS FOR PROTEASE MODULATING DRESSING

- To protect endogenous GF
- To prepare wound bed for application of exogenous GF
- To protect previously applied GF (Apligraf, Dermagraft, Regranex)

PROMOGRAN

- Protease Modulating Matrix
- Bovine Collagen
- Oxidized Regenerated Cellulose
- Can bind growth factors but they remain biologically active as the Promogran is resorbed

QUESTIONS?

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