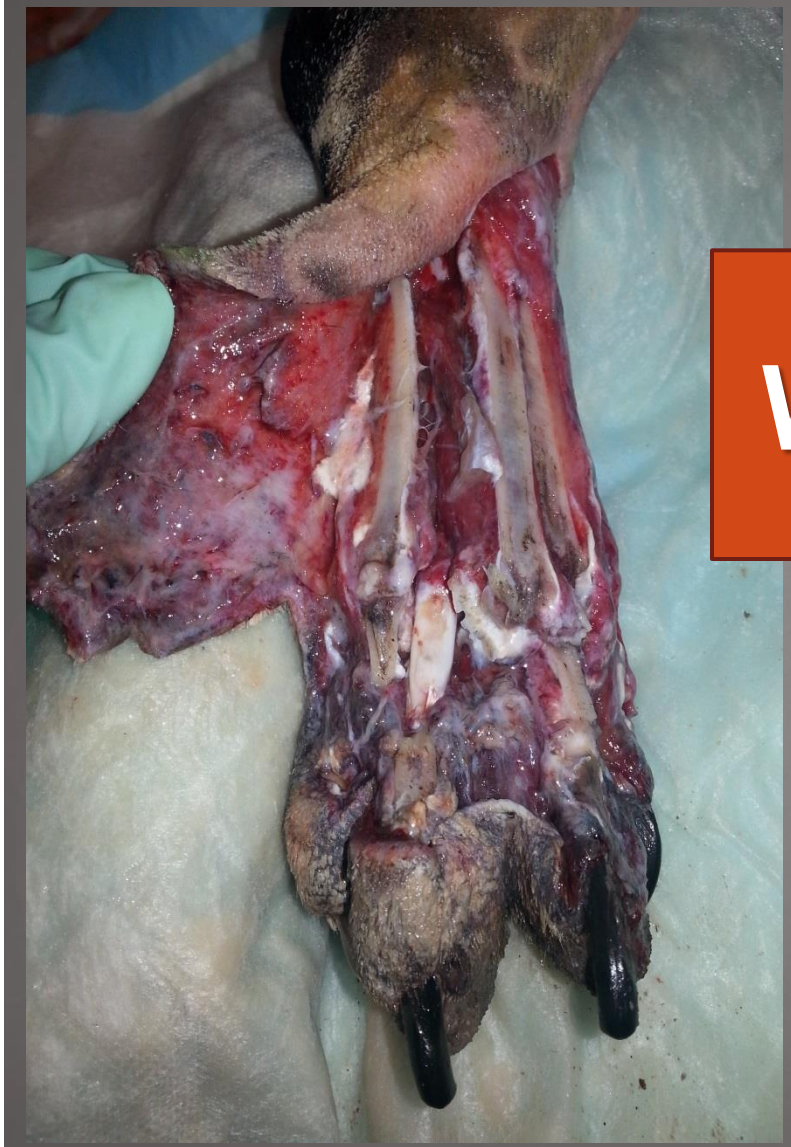


# WOUND HEALING

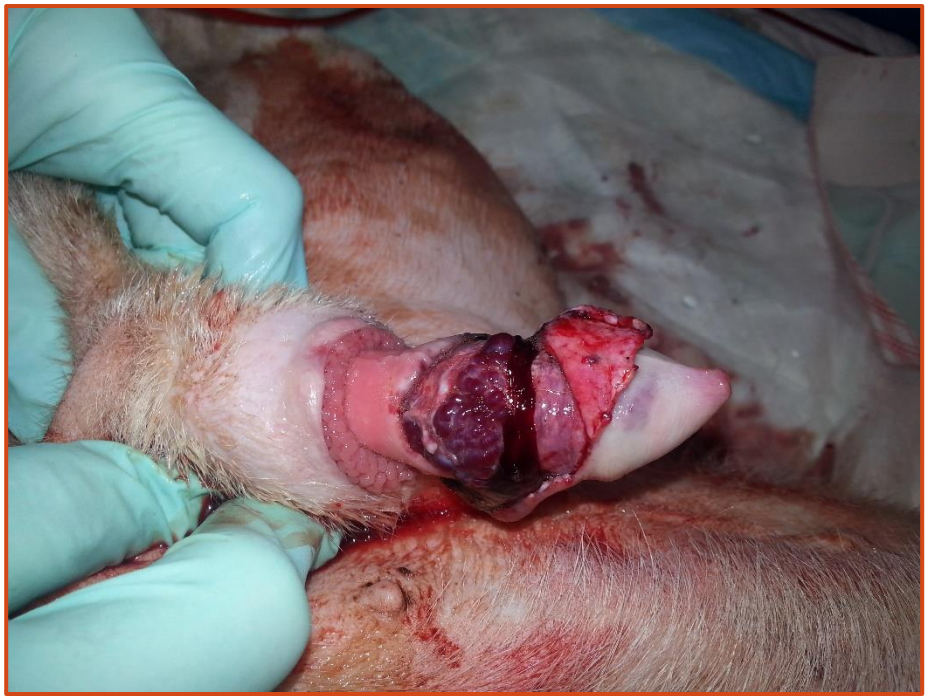
MARIANA A. PARDO

EMERGENCY AND CRITICAL CARE RESIDENT

2016

Cornell University
College of Veterinary Medicine

- Wound Classification
- Types of Wound Healing
- Stages of Healing
- Factors Affecting Healing
- Wound Management
  - Cleansing
  - Debridement
  - Dressings
  - Drains
- Techniques that Promote Healing
  - Negative Pressure Wound Therapy
  - Low Level Laser Therapy
  - Hyperbaric Oxygen Therapy



Disturbance in the normal skin anatomy and function; tissue injury resulting in the "loss of continuity of epithelium with or without the loss of underlying connective tissue"

Wound Healing Society

# Wound

# Wound Classification based on Microbial Contamination

| | |
|---|---|
| **Category I. Clean wounds** | Non-traumatic wounds not involving the respiratory, oropharyngeal, gastrointestinal or urogenital organs and with no inflammatory processes (Figure 1.). |
| **Category II. Clean-contaminated wounds** | Non-traumatic wounds where respiratory, oropharyngeal, gastrointestinal or urogenital organs are opened without spillage of contents, clean wound in which a drain is placed, small breach of the aseptic technique. |
| **Category III. Contaminated wounds** | Traumatic wounds < 4 hours old; inflammatory processes without purulent exudate; procedures that are contaminate with contents of gastrointestinal organs or infected urine; serious breach of aseptic technique. |
| **Category IIII. Dirty wounds** | Traumatic wounds > 4 hours old; inflammatory processes with purulent exudate or necrotic tissue; perforation of the gastrointestinal organs or infected urogenital organs; serious faecal contamination. |

http://www.theveterinarysurgeon.com/en_US/content/chapter-6/6-1-3-classification-of-surgical-wounds-and-infections

# Wound Classification based on Bone Fracture

| | |
|---|---|
| Grade I | Small break in the skin caused by bone penetrating through |
| Grade II | Soft tissue trauma contiguous with the fracture, often caused by external trauma (i.e., bite wound) |
| Grade III | Extensive soft tissue injury, commonly in addition to a high degree of comminution of the bone (i.e., gun shot wounds) |

Garzotto 2015

# Types of Wound Healing

| | | | |
|---|---|---|---|
| First Intention | < 12 hr | No separation wound edges<br>Minimal scar formation | Clean, recent wound |
| Second Intention | > 24 hr | Wound left open and allowed to heal from the inner layer to the outer surface | Infection, excessive trauma, tissue loss, or imprecise approximation of tissue |
| Delayed Primary Intention | > 3-4 days | Debridement of nonviable tissues and open wound management until 1ary closure is possible | Contaminated, dirty and infected traumatic wounds with extensive tissue loss and a high risk of infection |

# Stages of Primary Wound Healing

Hemostasis Stage

Inflammatory or Debridement Stage

Repair or Proliferative Stage

Maturation or Remodeling Stage

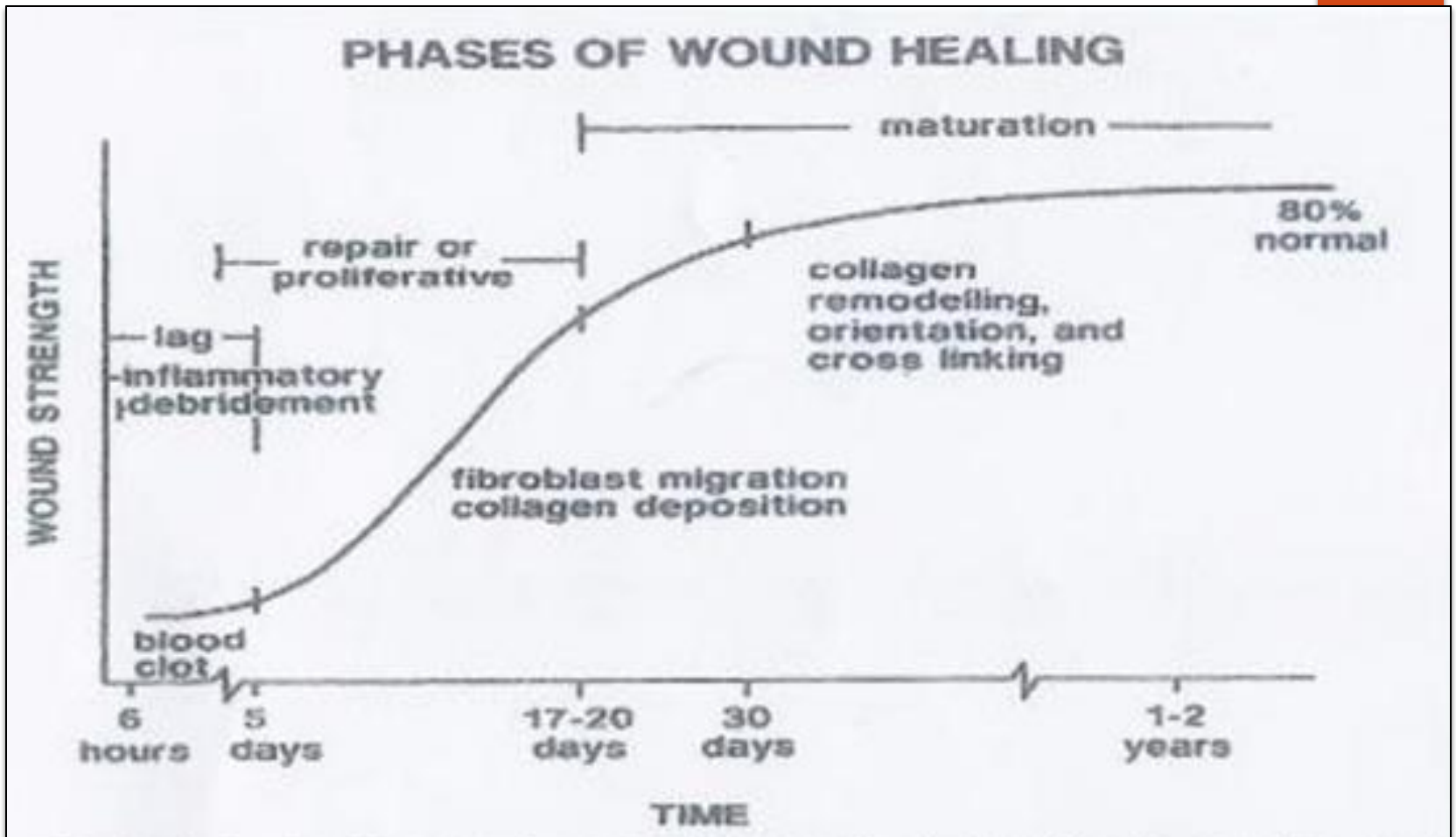
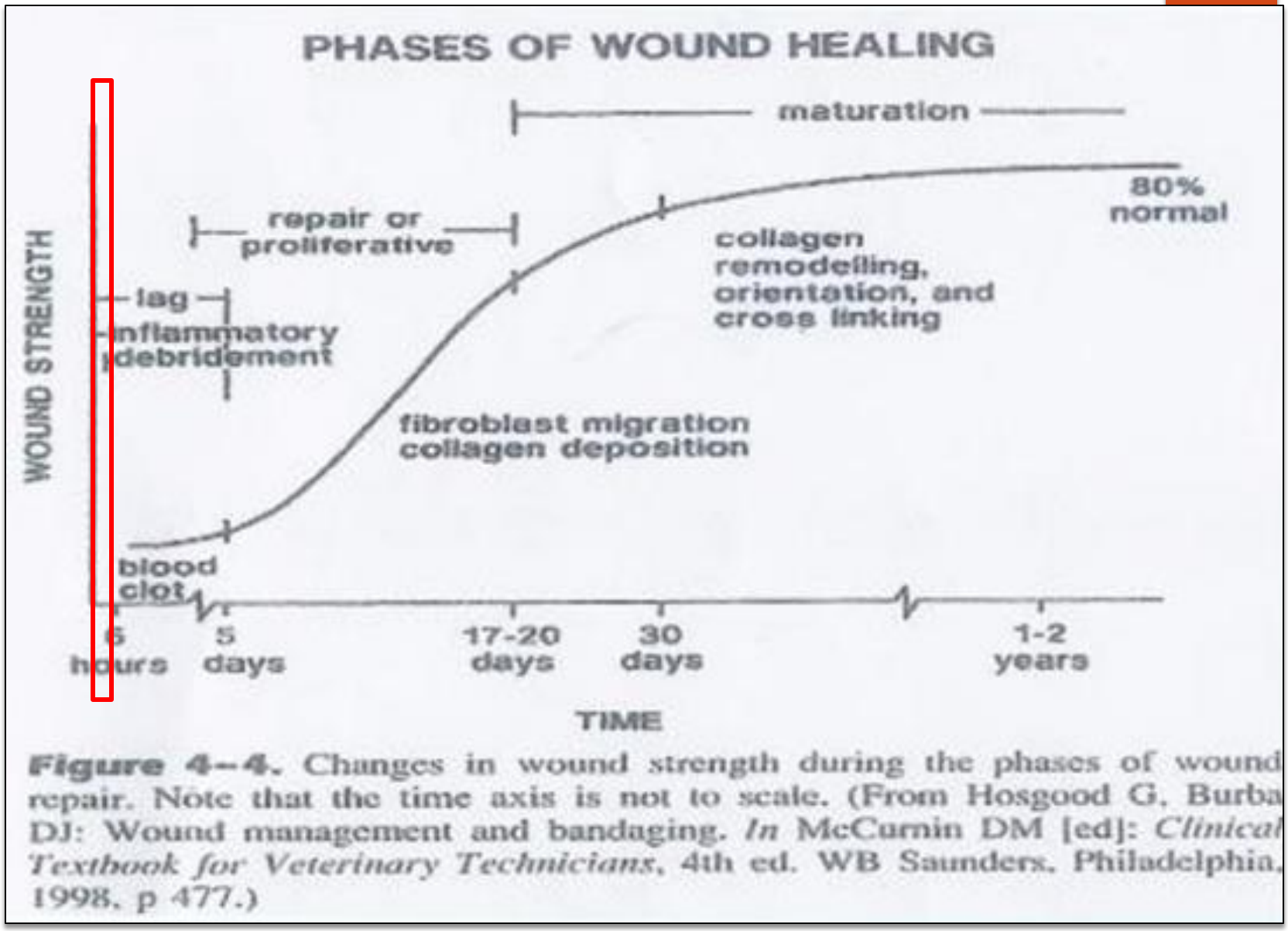



**Figure 4–4.** Changes in wound strength during the phases of wound repair. Note that the time axis is not to scale. (From Hosgood G, Burba DJ: Wound management and bandaging. *In* McCurnin DM [ed]: *Clinical Textbook for Veterinary Technicians*, 4th ed. WB Saunders, Philadelphia, 1998, p 477.)

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# Hemostasis Stage

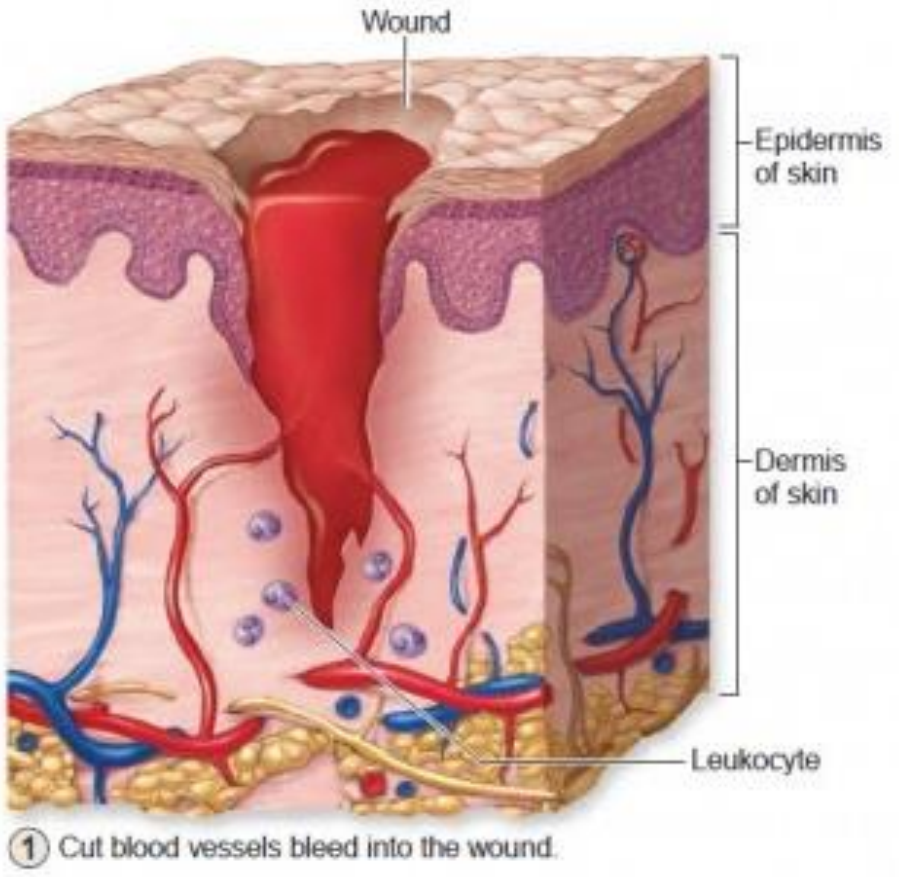
0-6 hours

Platelet Aggregation

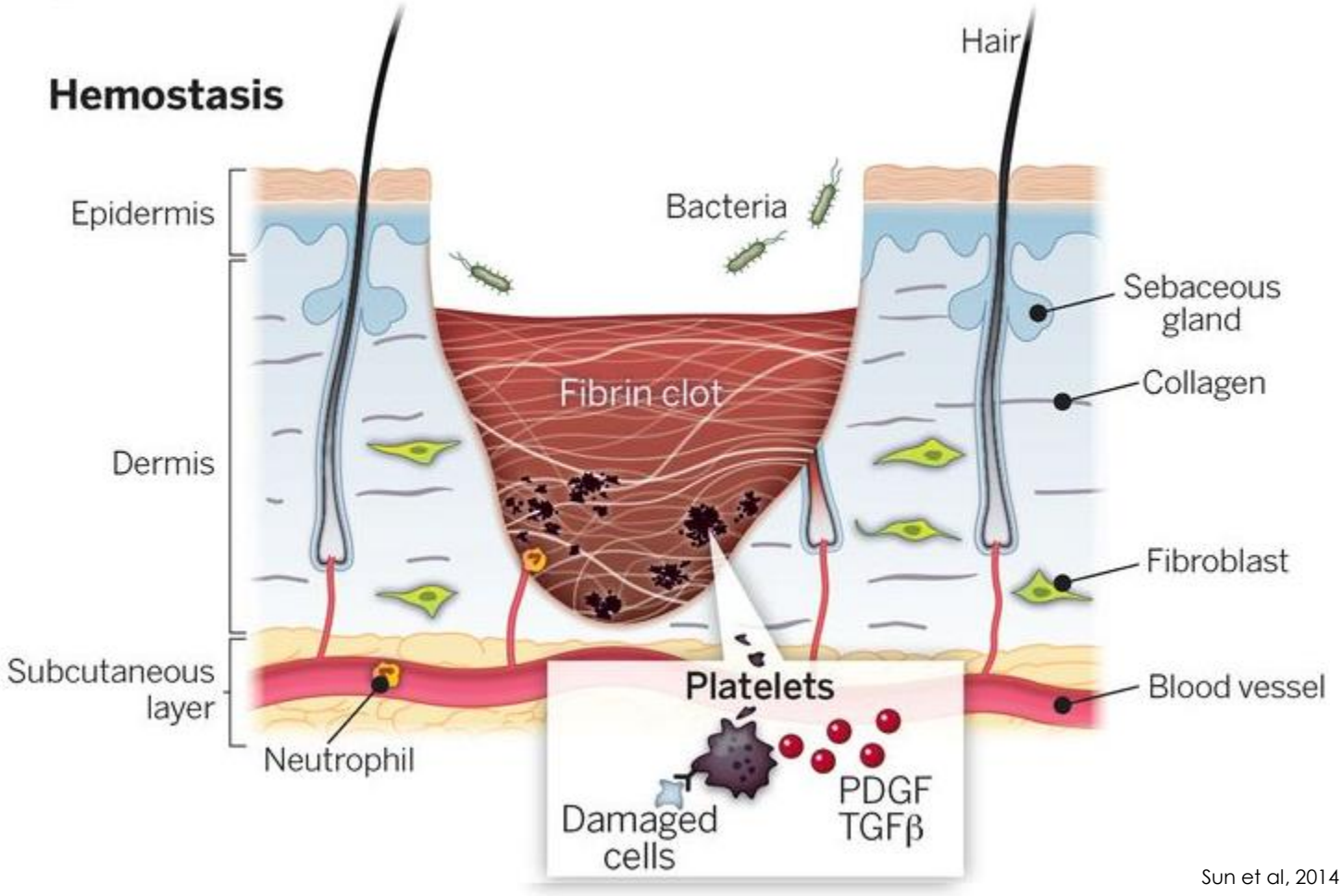
Platelet Degranulation

Vasoconstriction

Fibrin Clot




http://biology-forums.com/index.php?action=gallery;sa=view;id=15063



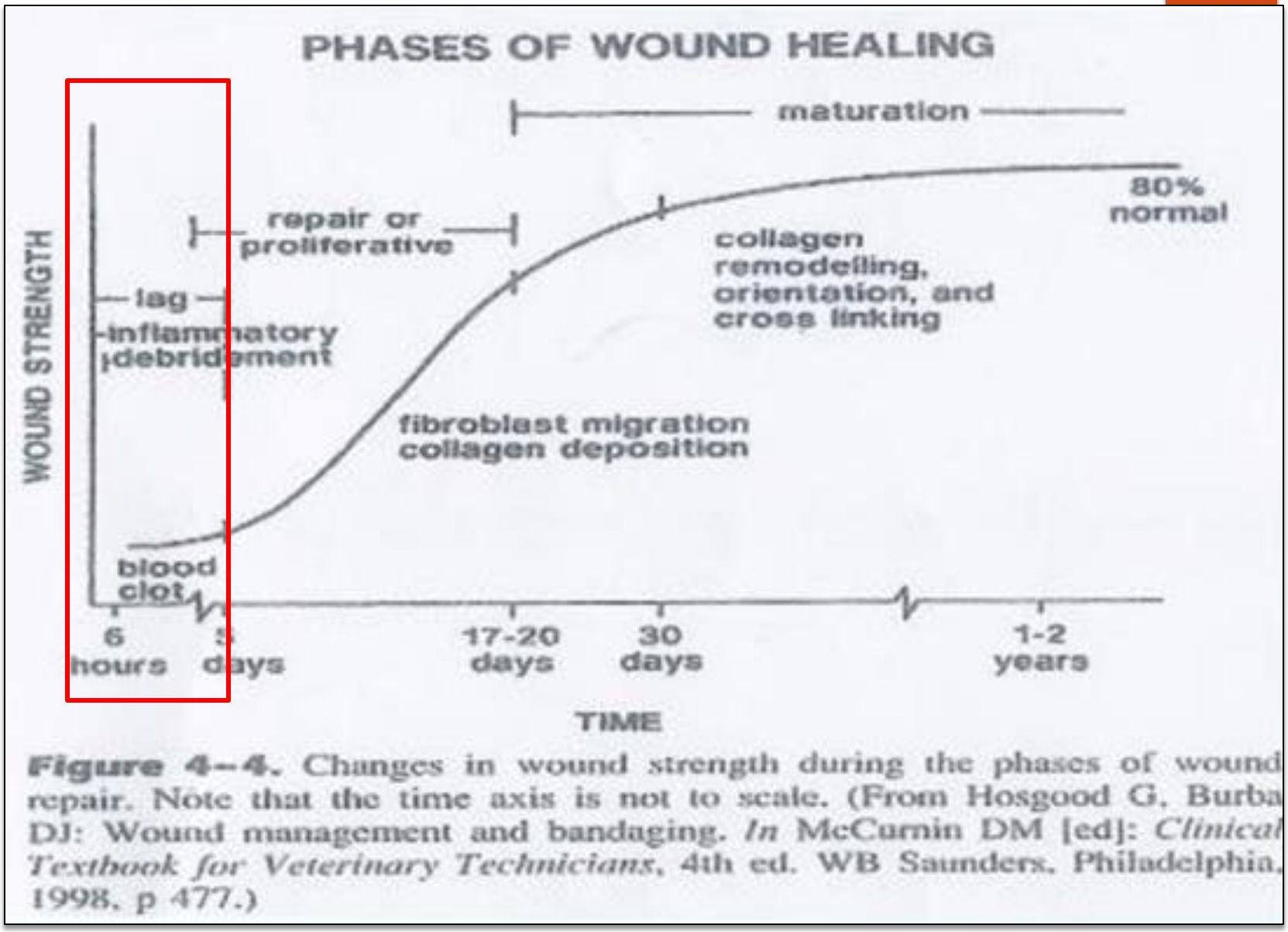

Sun et al, 2014

# Platelet-Mediated Growth Factors

**Table 3. Platelet-Mediated Growth Factors Involved in Wound Healing**

| Cytokine | Purpose/Function |
|---|---|
| Epidermal growth factors (EGF) | Mitosis and migration of keratinocytes; stimulates wound re-epithelialization; angiogenesis |
| Fibroblast growth factor (FGF) | Mitosis and migration of keratinocytes and fibroblasts; stimulates collagen formation; angiogenesis |
| Insulin-like growth factors (IGF-1, IGF-2) | Mitosis of keratinocytes and fibroblasts |
| Keratinocyte growth factor (KGF) | Mitosis of keratinocytes; activation of monocytes |
| Platelet-derived growth factor (PDGF) | Chemoattractant for fibroblasts and other cells; cell proliferation; wound contraction |
| Transforming growth factor-$\alpha$ (TGF-$\alpha$) | Mitosis and migration of keratinocytes; regulation of inflammatory cells |
| Transforming growth factor-$\beta$ (TGF-$\beta$) | Chemoattractant for fibroblasts and macrophages; migration of keratinocytes; fibroblast matrix synthesis and remodeling |

Strodtbeck, 2001

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# Inflammatory or Debridement Stage

6 hours – 5 days

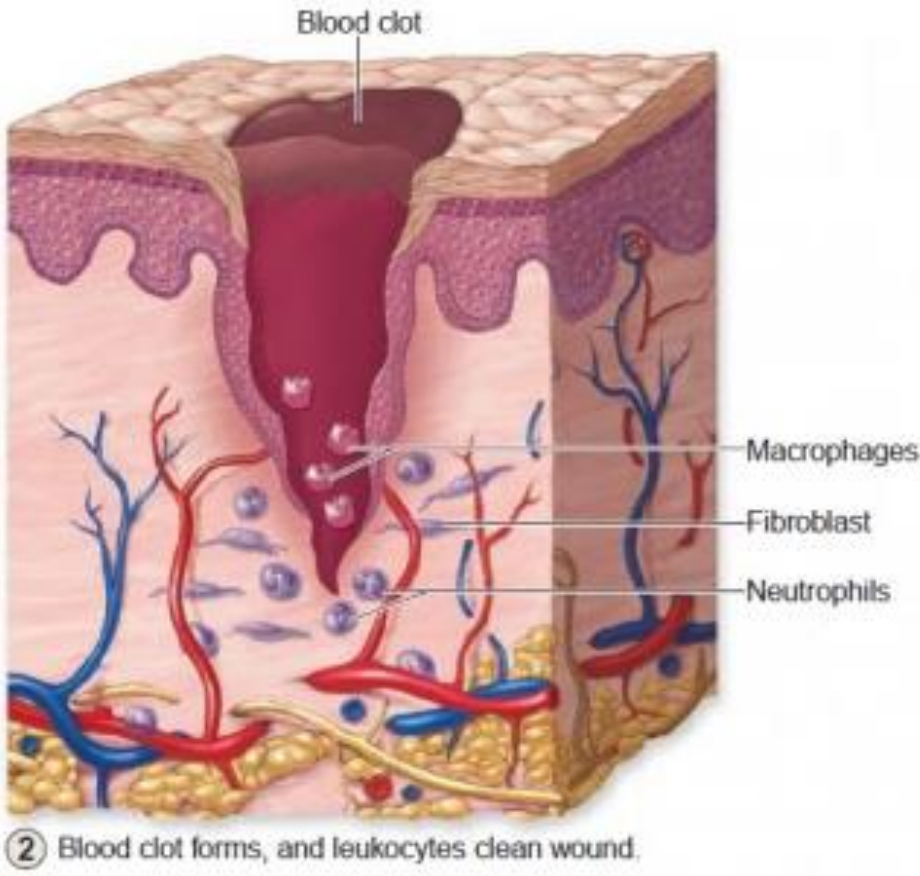
Neutrophil Infiltration

Monocyte Infiltration

Differentiation to Macrophages

Increased Endothelium Permeability and Perfusion

Wound Debridement

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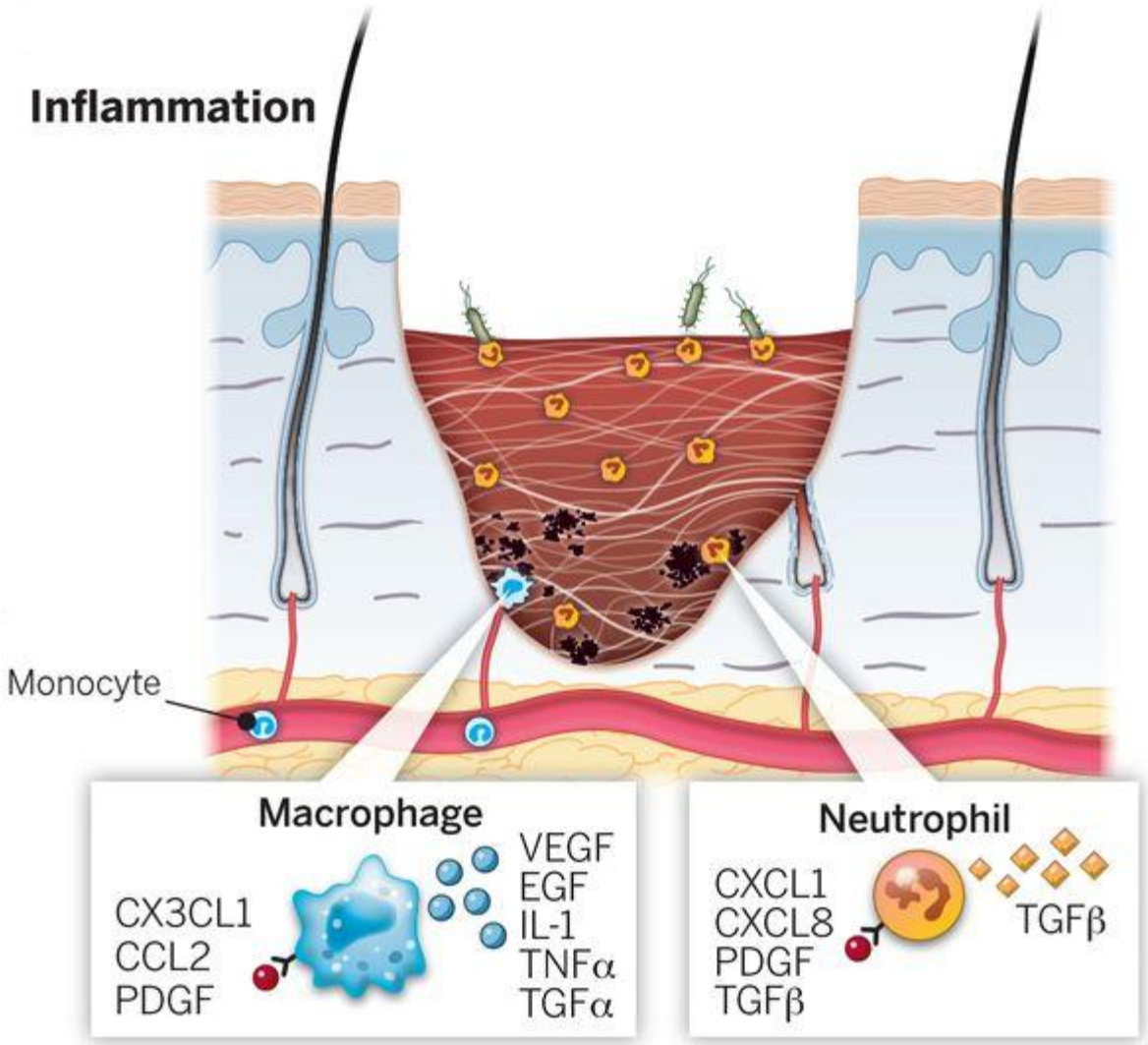
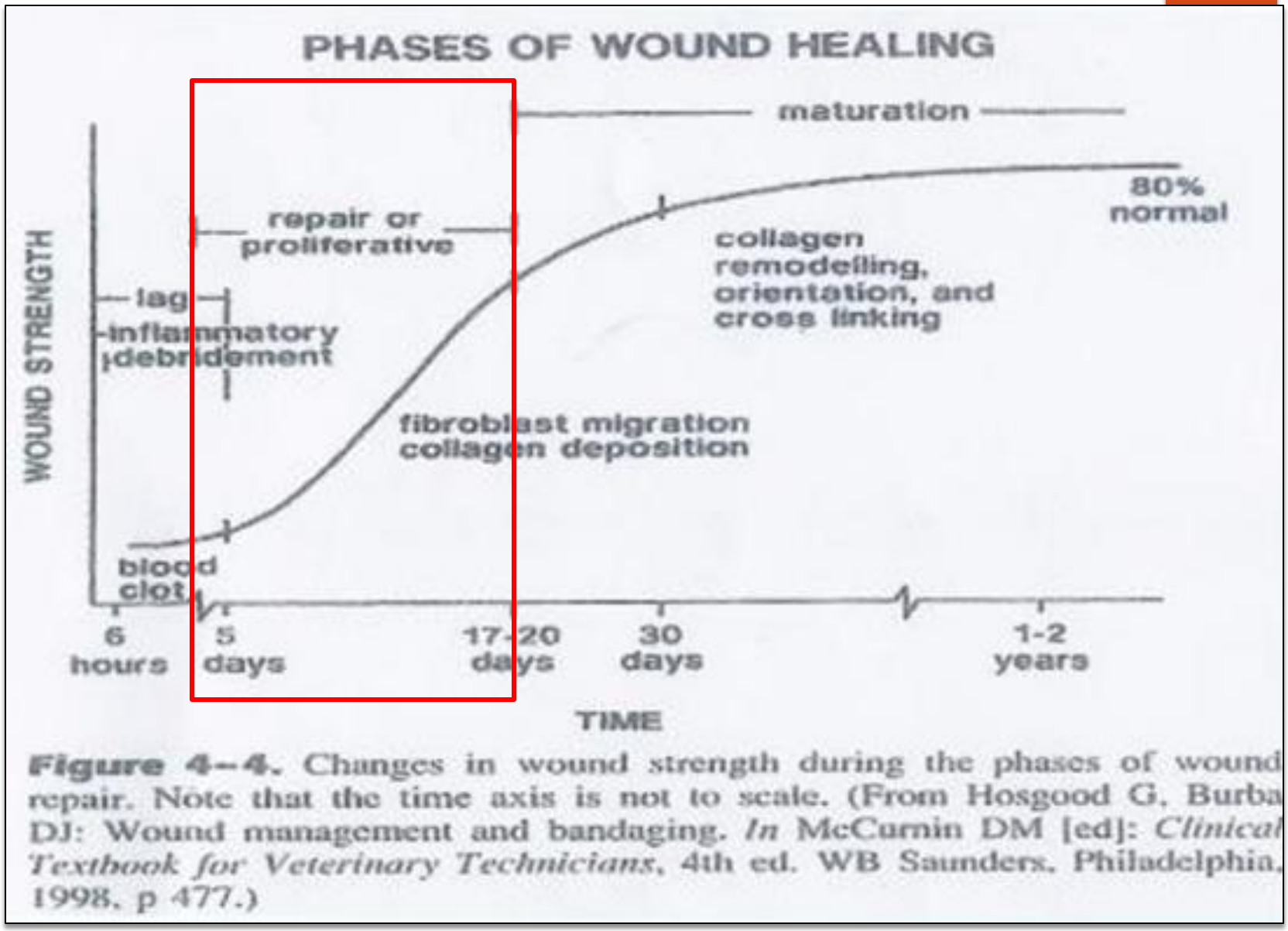



Sun et al, 2014

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# Repair or Proliferative Stage

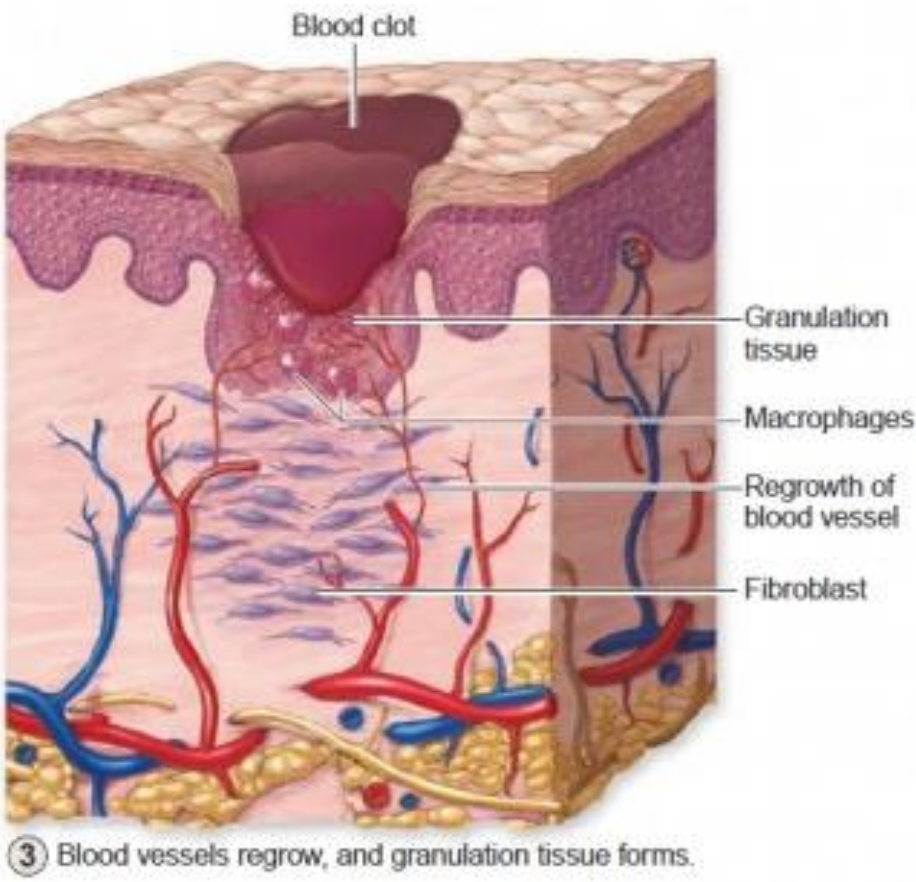
5 - 21 days

Angiogenesis

Re-epithelialization

Collagen Synthesis

Extracellular Matrix Formation

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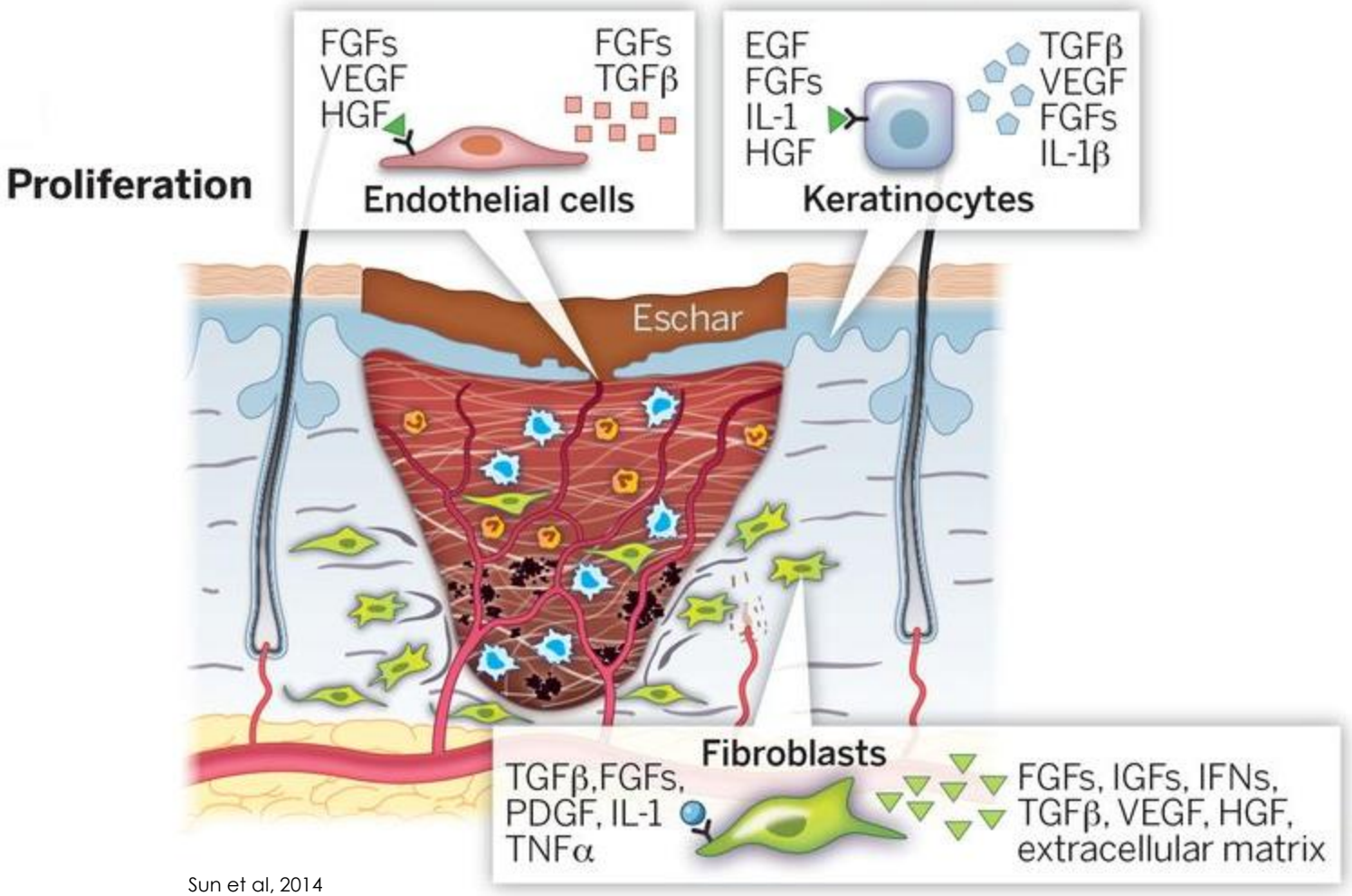
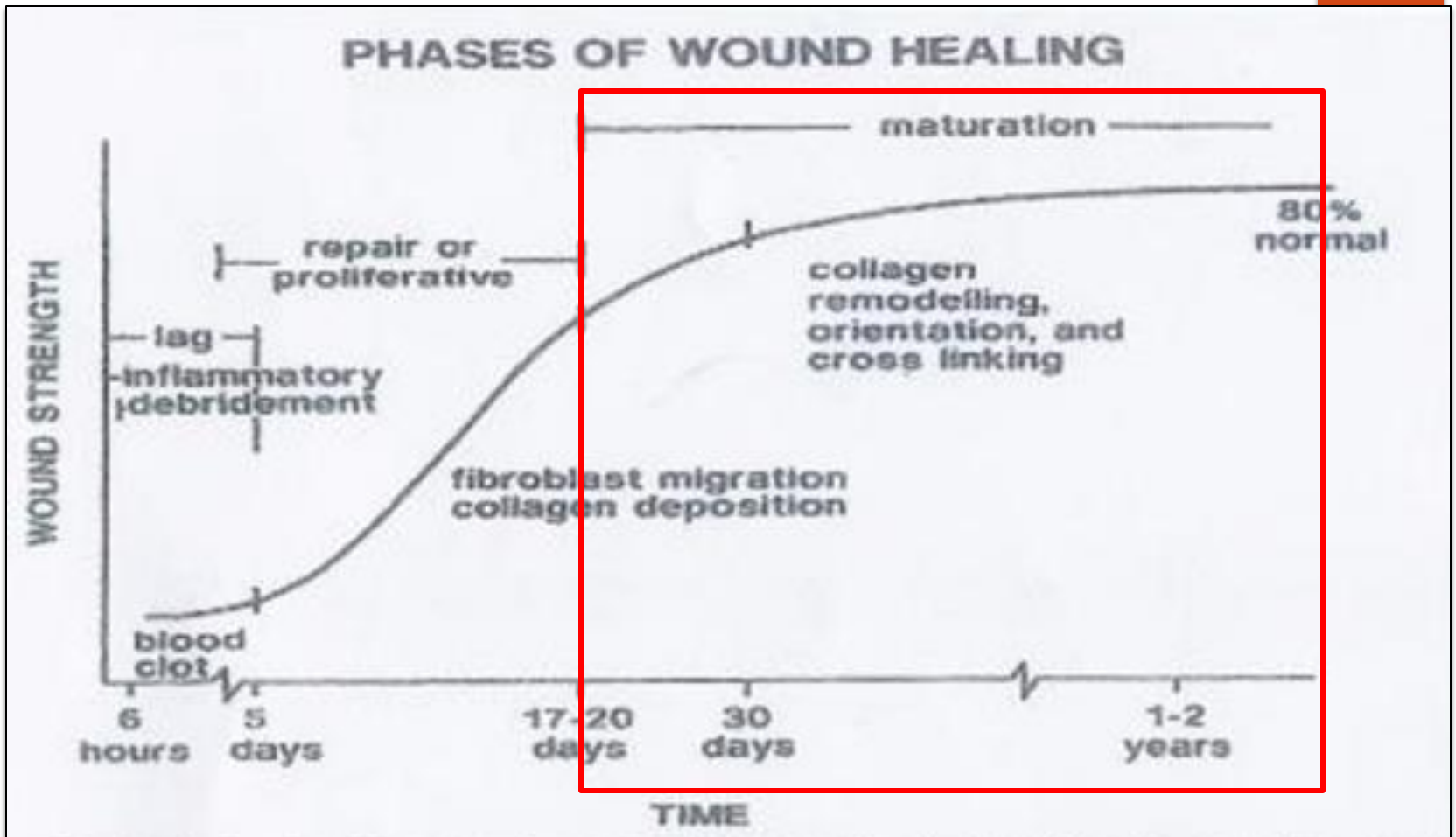



Sun et al, 2014

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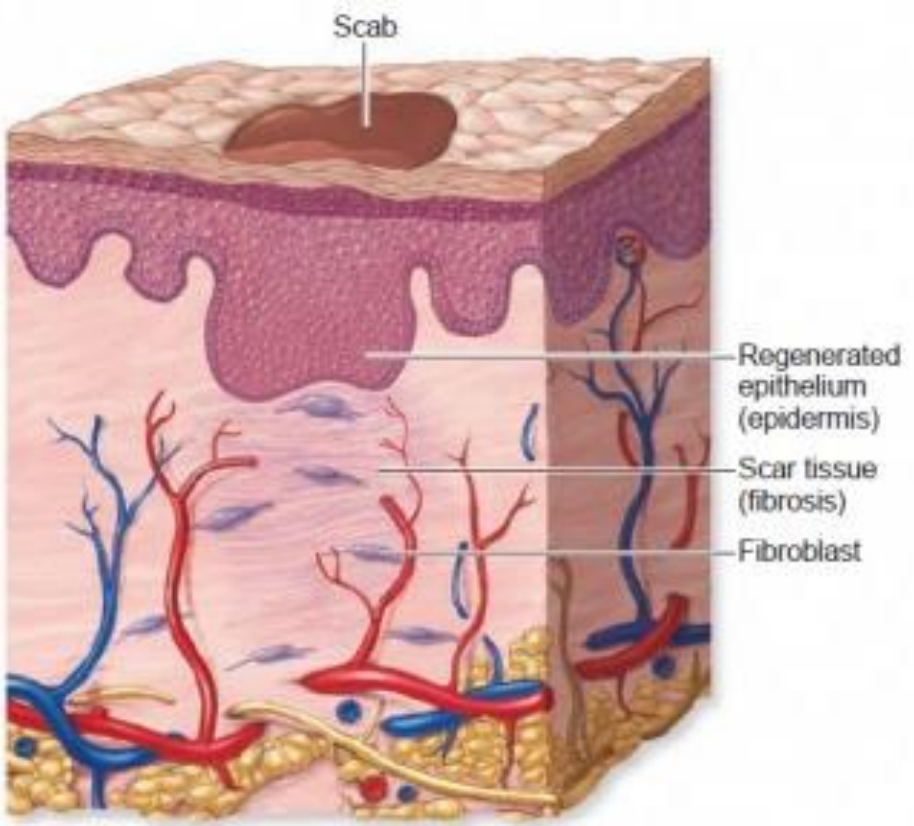
# Maturation Stage

21 days to months

Collagen Cross-Linking

Vascular Maturation

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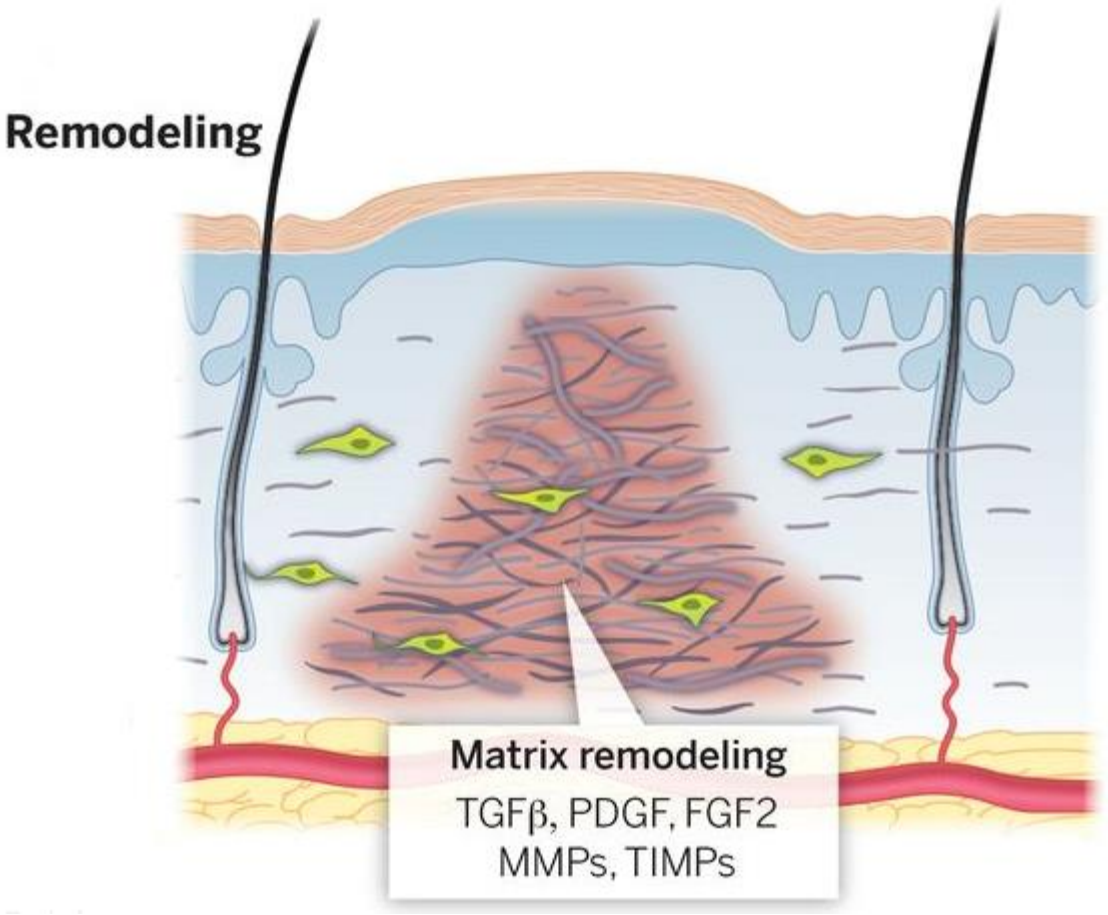



Sun et al, 2014

# Factors Affecting Wound Healing

| Wound-specific variables | Systemic variables | Medications and exposures | Diseases and conditions |
|---|---|---|---|
| Body site | Nutrition | Cancer chemotherapeutic agents | Diabetes |
| Infection | Age | Nonsteroidal anti inflammatory agents | Autoimmune diseases |
| Vascular supply | Sex | Glucocorticoids | Venous stasis |
| Oxygenation | Psychological stress | Radiation therapy | Predisposition to keloids |
| Mechanical stress | Immobility | Smoking | Some genetic skin diseases |
| Desiccation | | Alcohol and recreational drugs | Immunocompromised state (AIDS, cancer) |
| Edema | | | Obesity, vasculitis, neuropathy, some infectious diseases |

**Table 1. Factors that affect wound healing.**

Sun et al, 2014

# Factors Affecting Wound Healing

**Iatrogenic:**

- Hypotonic solutions (water)
- Highly concentrated antiseptic solutions: cytotoxic
- Removal of granulation tissue

# Factors Affecting Wound Healing

Veterinary Surgery 44 (2015) 2–8

## Prospective Surgical Site Infection Surveillance in Dogs

Ryen Turk[1], Bsc, Msc, Ameet Singh[2], DVM, DVSc, Diplomate ACVS, and
J. Scott Weese[1], DVM, DVSc, Diplomate ACVIM

[1] Department of Pathobiology and [2] Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Canada

**Table 6** Multivariable Analysis of Risk Factors Contributing to Surgical Site Infection (SSI) in Dogs (n = 846)

| | SSI Odds ratio | SSI Confidence Interval | SSI *P*-Value | Surgical Site abnormality Odds ratio | Surgical Site abnormality Confidence Interval | Surgical Site abnormality *P* value |
|---|---|---|---|---|---|---|
| TPLO | 1.37 | 0.50–3.79 | .542 | 1.52 | 0.61–3.84 | .372 |
| Implant | 5.61 | 2.01–15.63 | .001 | 1.46 | 0.69–3.07 | .323 |
| Hypotension | 27.67 | 2.14–358.32 | .011 | 8.64 | 0.074–100.45 | .085 |
| Class (Clean:dirty) | 14.60 | 1.31–162.15 | .029 | 4.77 | 0.51–44.29 | .170 |
| Class (Clean:clean contaminated) | 2.15 | 0.66–7.00 | .204 | 1.30 | 0.60–2.84 | .504 |

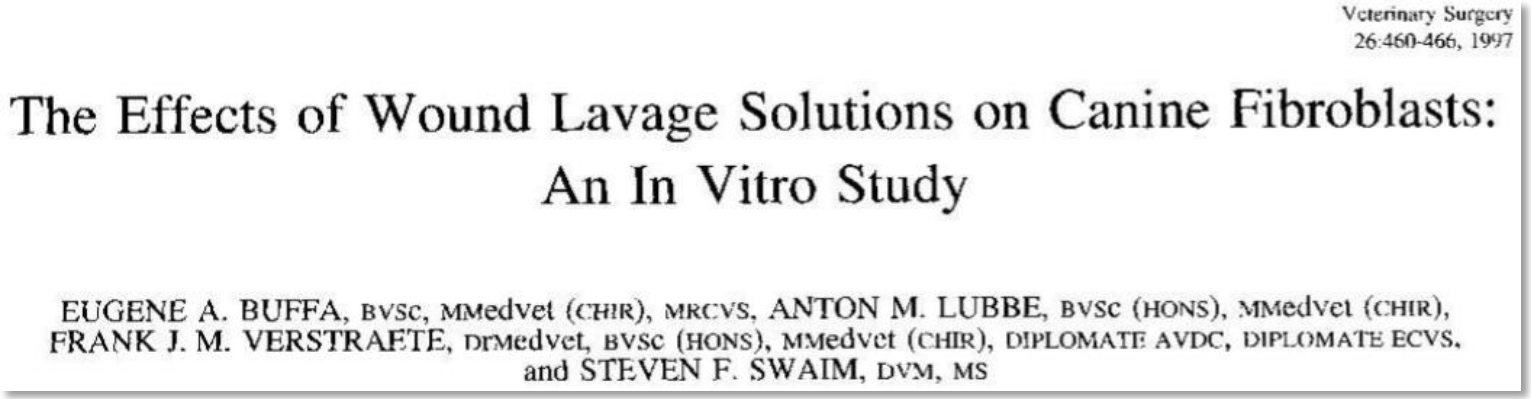
# Wound Cleansing

- Delivery
  - Solution
  - Pressure
  - Continuous vs Pulsatile
- Volume
- Additives
  - Antibiotics
  - Antiseptics


Barnes et al, 2014

http://origin.library.constantcontact.com/download/get/file/1113340357784192/Wound+Flushing+Techniques+Reviewed+Mueller+050414.pdf

# Wound Cleansing: Solution



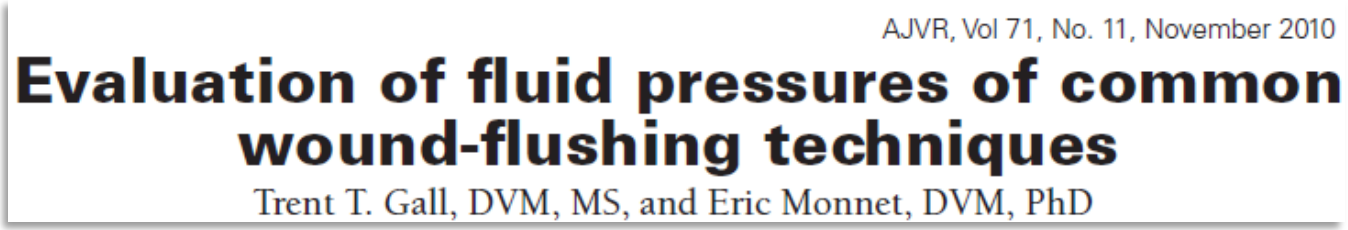
Veterinary Surgery
26:460-466, 1997

The Effects of Wound Lavage Solutions on Canine Fibroblasts: An In Vitro Study

EUGENE A. BUFFA, BVSc, MMedVet (CHIR), MRCVS, ANTON M. LUBBE, BVSc (HONS), MMedVet (CHIR), FRANK J. M. VERSTRAETE, DrMedVet, BVSc (HONS), MMedVet (CHIR), DIPLOMATE AVDC, DIPLOMATE ECVS, and STEVEN F. SWAIM, DVM, MS

- Tap Water: alkaline pH, hypotonic, cytotoxic trace elements produced severe fibroblast injury at all time points (0.5, 1, 2.5, 5,10 minutes)
- Normal Saline: acidic pH, lack of a buffering system produced fibroblast injury at 10 min
- LRS: ideal lavage solution

# Wound Cleansing: Pressure



AJVR, Vol 71, No. 11, November 2010

**Evaluation of fluid pressures of common wound-flushing techniques**

Trent T. Gall, DVM, MS, and Eric Monnet, DVM, PhD

- Solution bottles with holes on cap do not provide adequate flushing pressure
- 35 ml syringe w/any size needle will produce >7-8 psi, which can damage tissues
- Ideal method: 1L fluid bag pressurized to 300 mmHg generates 7-8 psi

# Wound Cleansing: Volume

American Journal of Infection Control 42 (2014) 525-9

## Surgical wound irrigation: A call for evidence-based standardization of practice

Sue Barnes RN, BSN, CIC [a], Maureen Spencer RN, MEd, CIC [b], Denise Graham [c], Helen Boehm Johnson MD [d,*]

- 50 to 100 mL per centimeter of laceration length or square centimeter of a wound
- Heavy contamination and debris may require larger volumes

# Wound Cleansing: Antibiotics

American Journal of Infection Control 42 (2014) 525-9

## Surgical wound irrigation: A call for evidence-based standardization of practice

Sue Barnes RN, BSN, CIC [a], Maureen Spencer RN, MEd, CIC [b], Denise Graham [c], Helen Boehm Johnson MD [d,*]

- Antibiotics in irrigation solutions do NOT appear to significantly improve clinical outcomes
- May lead to anaphylaxis, bacterial resistance, systemic absorption and toxicity
- Increased cost

# Wound Cleansing: Antiseptics

Veterinary Surgery, 17, 6, 291–295, 1988

## Effects of Chlorhexidine Diacetate and Povidone-Iodine on Wound Healing in Dogs

ISIS R. SANCHEZ, DVM, MS, STEVEN F. SWAIM, DVM, MS, KENNETH E. NUSBAUM, DVM, PhD, ANNE S. HALE, DVM, RALPH A. HENDERSON, DVM, MS, DiplomateACVS, and JOHN A. McGUIRE, PhD

- 0.05% chlorhexidine was bactericidal vs 1% iodine which was not
- Chlorhexidine > healing and contraction compared to iodine

Veterinary Surgery, 21, 2, 107–112, 1992

## Effects of Four Preparations of 0.05% Chlorhexidine Diacetate on Wound Healing in Dogs

SCOTT LOZIER, DVM, MS, ERIC POPE, DVM, MS, Diplomate ACVS, and JOHN BERG, DVM, PhD

- 0.05% chlorhexidine in sterile water, saline and LRS =100% bacterial kill
- No significant differences in wound contraction or epithelialization

# Wound Debridement

- Surgical Debridement: selective, fast, revitalizing the wound
- Mechanical Debridement: non-selective, can damage granulation tissue and wound bed
- Autolytic Debridement: selective, slow, promotes natural endogenous debridement
- Enzymatic Debridement: selective, uses exogenous enzymes for debridement

# Wound Dressings

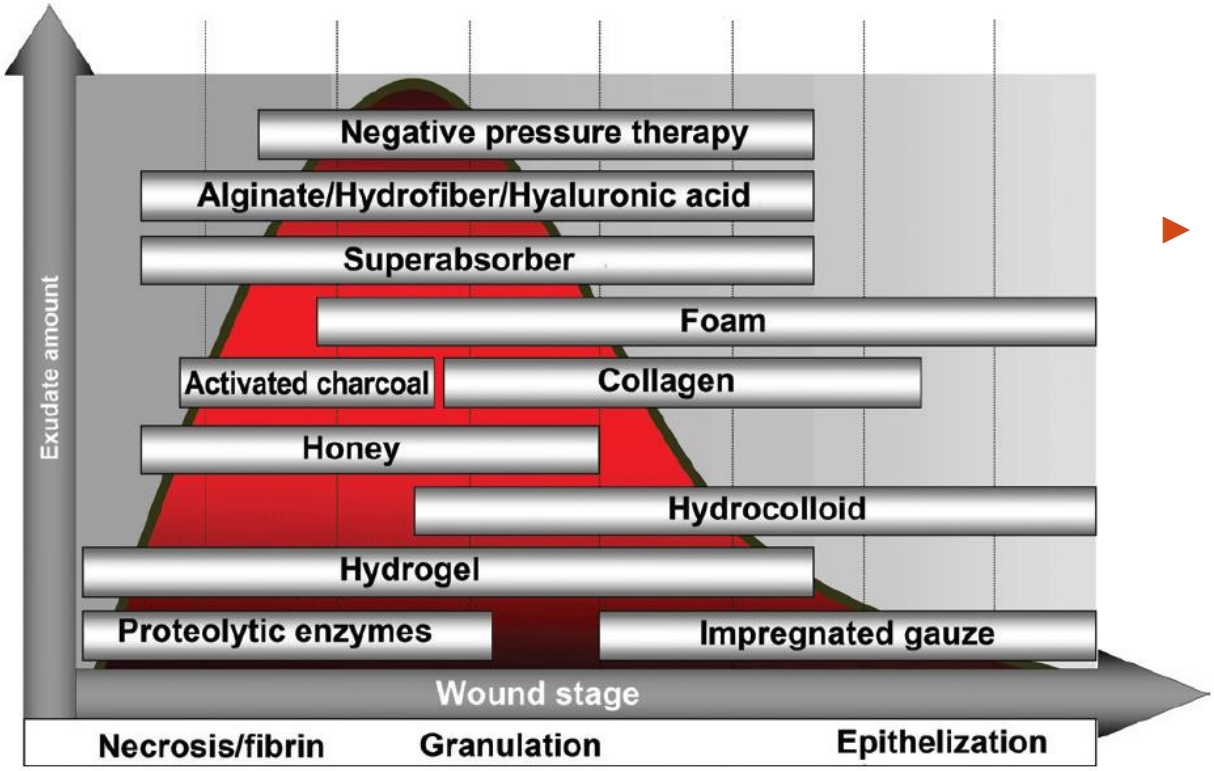



Figure 1 Phase- and exudate-dependent use of wound products for the treatment of patients with chronic wounds.

Dissemond et al, 2014

- Appropriate dressing should be chosen dependent on:
  - Healing phase
  - Exudate amount

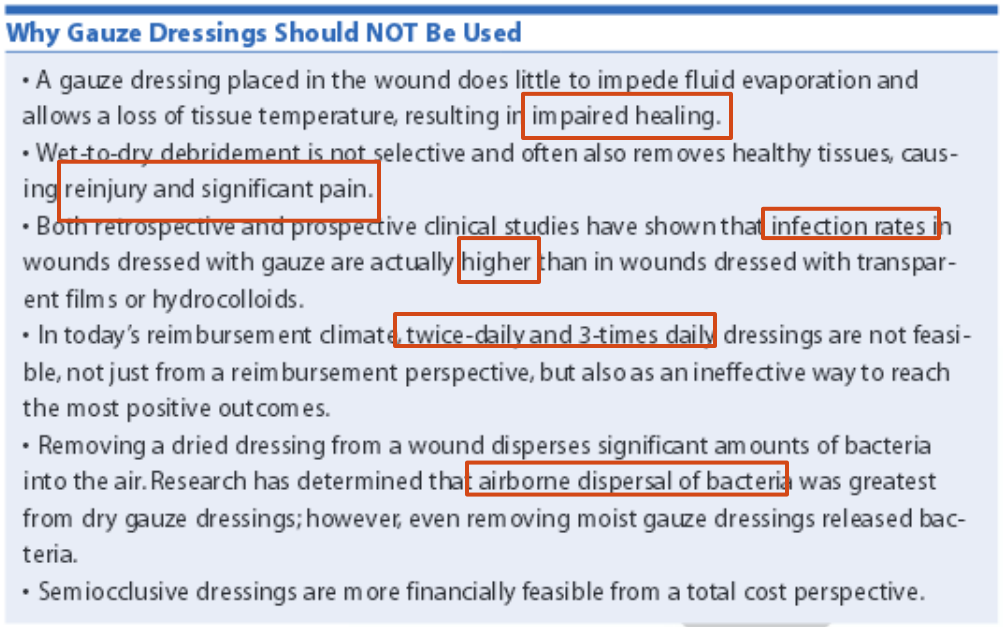
# Wet-to-Dry Dressings

ADVANCES IN SKIN & WOUND CARE • MARCH/APRIL 2002

## Hanging Wet-to-Dry Dressings Out to Dry

**Liza G. Ovington, PhD, CWS** • President • Ovington & Associates, Inc, Pittsburgh, PA.

- "The scientific literature supports mechanical debridement by wet-to-dry dressings ***only*** when the benefit of removing non-viable tissue from the wound bed outweighs the risks of detrimental disruption of healthy granulating tissue in the wound bed (such as when >50% nonviable tissue is present in the wound bed)." Cowen et al, 2009.

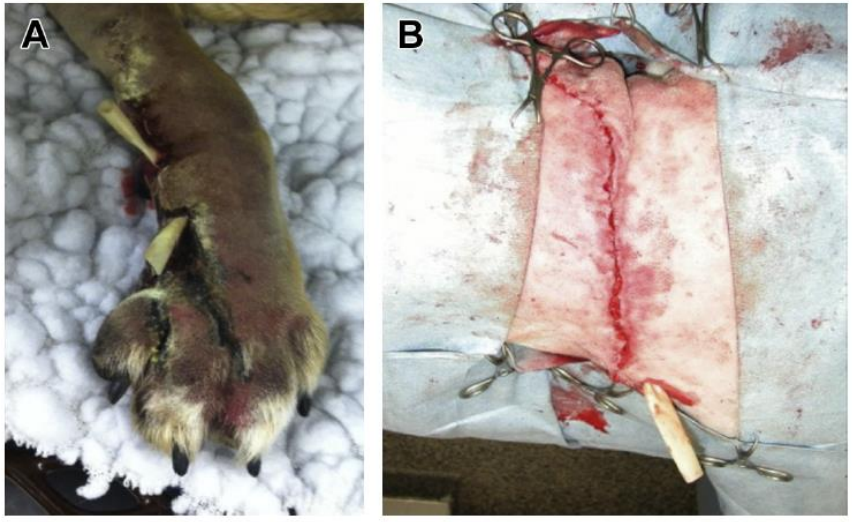


**Why Gauze Dressings Should NOT Be Used**

- A gauze dressing placed in the wound does little to impede fluid evaporation and allows a loss of tissue temperature, resulting in impaired healing.
- Wet-to-dry debridement is not selective and often also removes healthy tissues, causing reinjury and significant pain.
- Both retrospective and prospective clinical studies have shown that infection rates in wounds dressed with gauze are actually higher than in wounds dressed with transparent films or hydrocolloids.
- In today's reimbursement climate, twice-daily and 3-times daily dressings are not feasible, not just from a reimbursement perspective, but also as an ineffective way to reach the most positive outcomes.
- Removing a dried dressing from a wound disperses significant amounts of bacteria into the air. Research has determined that airborne dispersal of bacteria was greatest from dry gauze dressings; however, even removing moist gauze dressings released bacteria.
- Semiocclusive dressings are more financially feasible from a total cost perspective.

# Drains

- Classification
  - Active: Jackson-Pratt
  - Passive: Penrose
- Indications
  - Contaminated or dirty wounds
  - Large amount of dead space
- Do not place directly under wound closure
- Do not exit from the wound itself
- Most drains removed in 3-5 days




A: Incorrect placement B: Correct placement

# Drains

JAVMA, Vol 245, No. 2, July 15, 2014

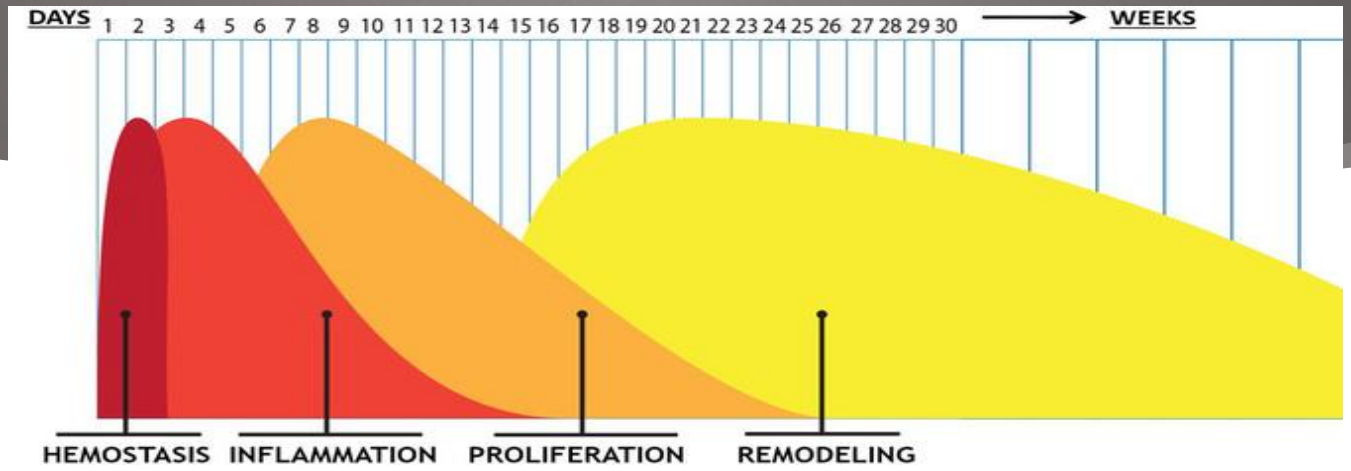
**Evaluation of fluid production and seroma formation after placement of closed suction drains in clean subcutaneous surgical wounds of dogs: 77 cases (2005–2012)**

Stephanie L. Shaver, DVM; Geraldine B. Hunt, BVSc, MVetClinStud, PhD; Scott W. Kidd, DVM

- < 0.2 mL/kg/h (4.8 mL/kg/d) at the time of drain removal were significantly less likely to form a seroma, may be a useful clinical benchmark for drain removal

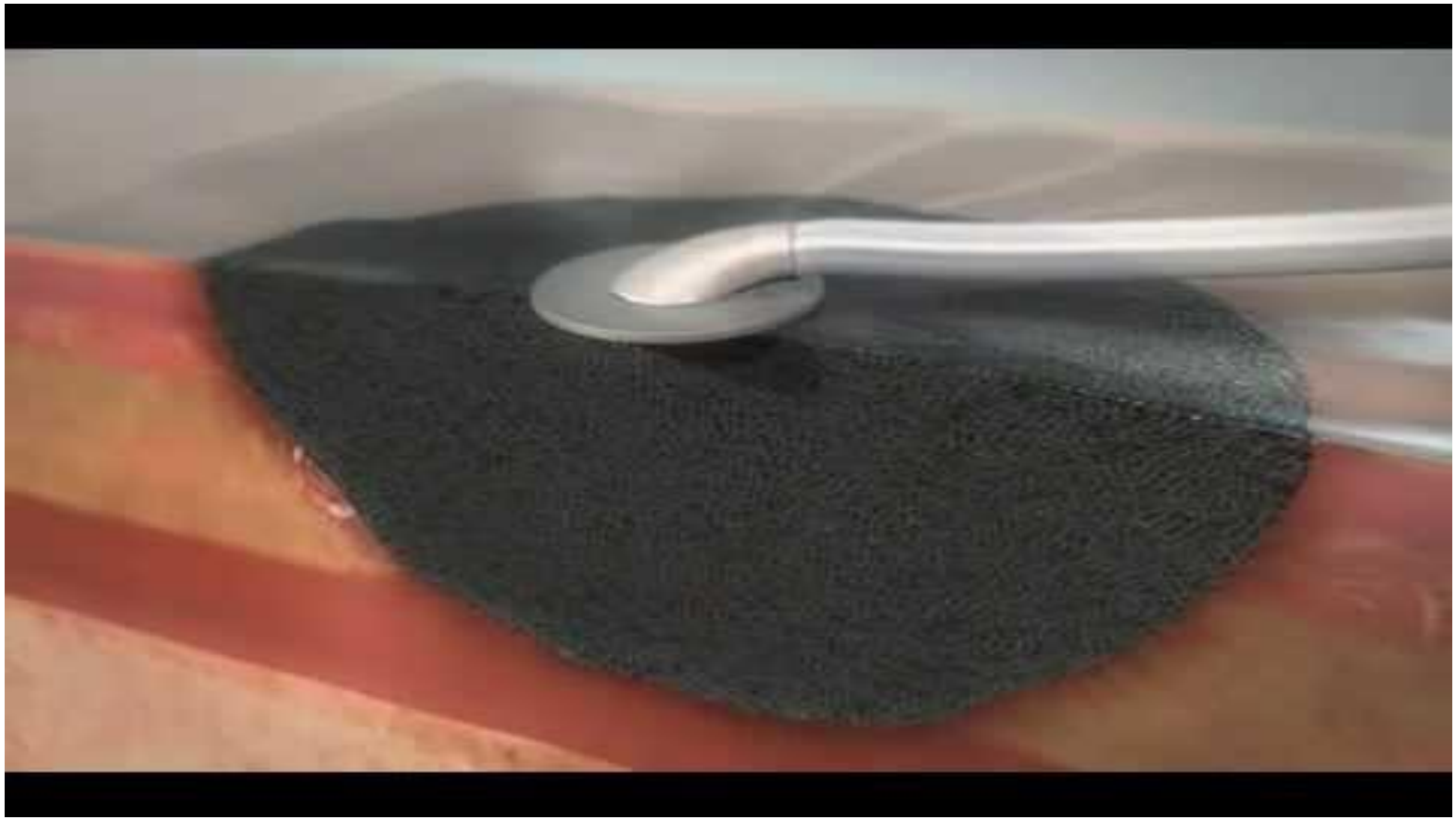
- 6.6% had surgical site infection, unknown if these had contaminated drain

# Techniques that Promote Healing




http://www.enluxtrawoundcare.com/non-healing-wounds.html

# Negative Pressure Wound Therapy



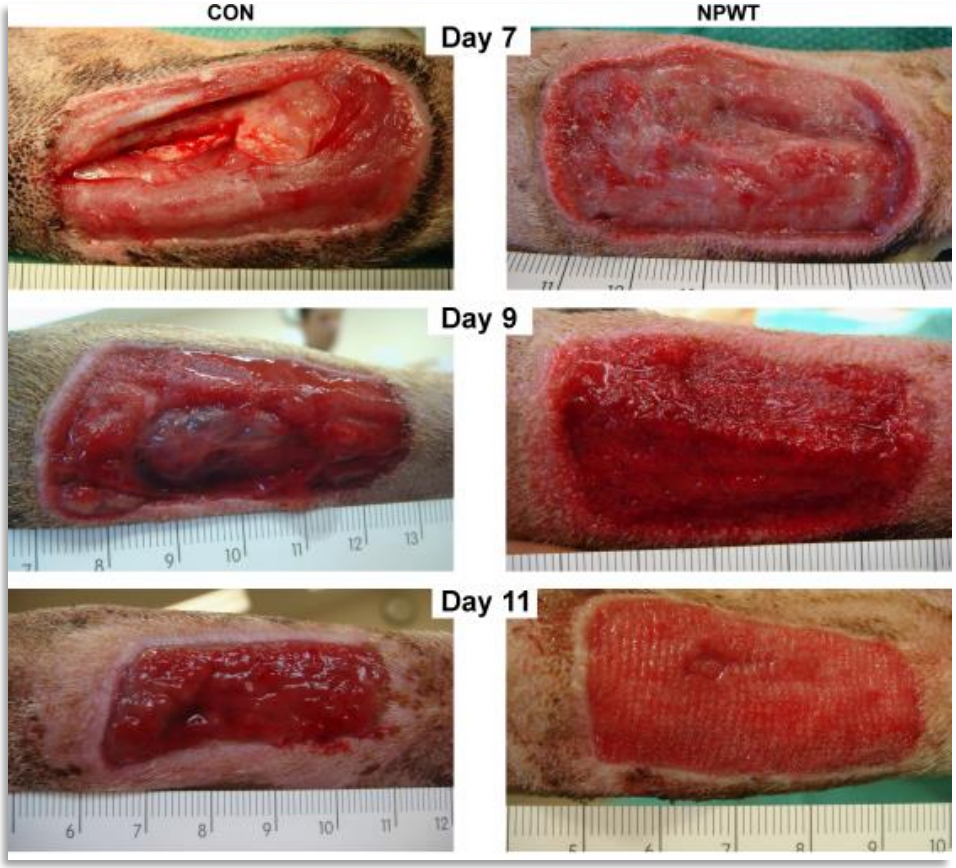
https://www.youtube.com/watch?v=MDo1dhH7Ktw

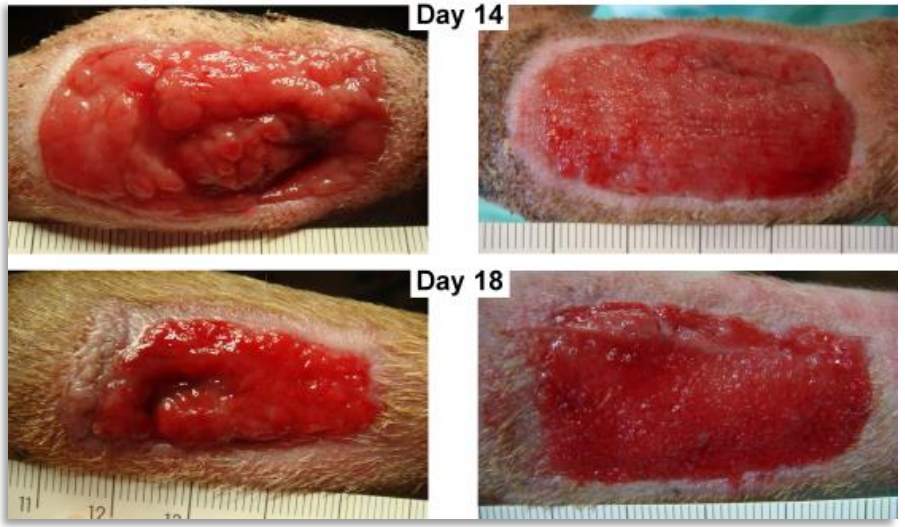
Veterinary Surgery 40 (2011) 658–669

# Effects of Negative Pressure Wound Therapy on Healing of Open Wounds in Dogs

Marco Demaria[1], DVM, Bryden J. Stanley[1], BVMS, MVetSc, Diplomate ACVS, Joe G. Hauptman[1], DVM, MS, Diplomate ACVS, Barbara A. Steficek[2], DVM, PhD, Diplomate ACVP, Michele C. Fritz[1], BSc, LVT, John M. Ryan[3], MVB, MRCVS, Nathaniel A. Lam[1], DVM, Trevor W. Moore[1], DVM, and Heather S. Hadley[1], DVM

[1]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI, [2]Diagnostic Center for Population and Animal Health, College of Veterinary Medicine, Michigan State University, East Lansing, MI and [3]Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, UK




- Graft acceptance was superior
- Fibroplasia was enhanced
- Open meshes closed faster

Veterinary Surgery 43 (2014) 380–387

# Negative Pressure Wound Therapy: Experience in 45 Dogs

Kathryn A. Pitt, BS, DVM, MS, and Bryden J. Stanley, BVMS, MVetSc, Diplomate ACVS

Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, Michigan

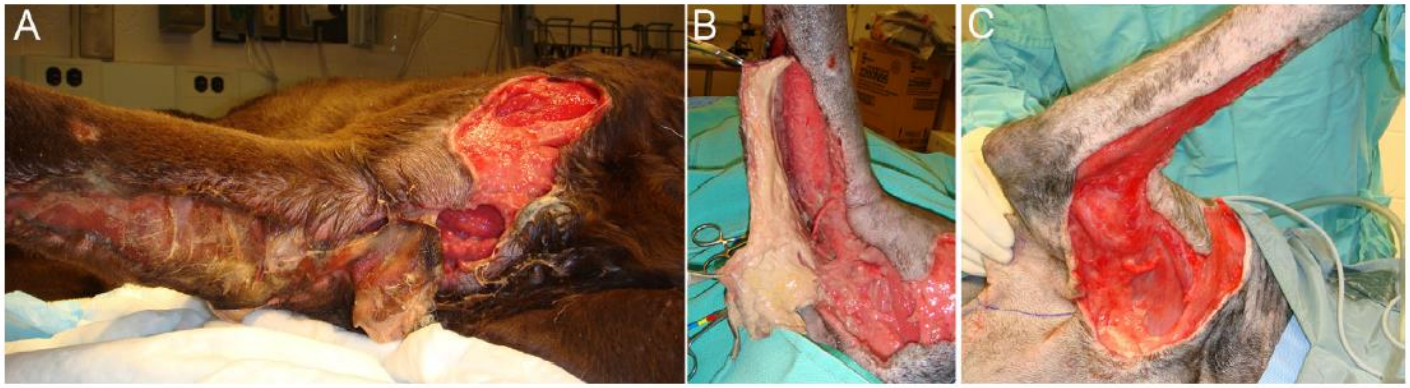
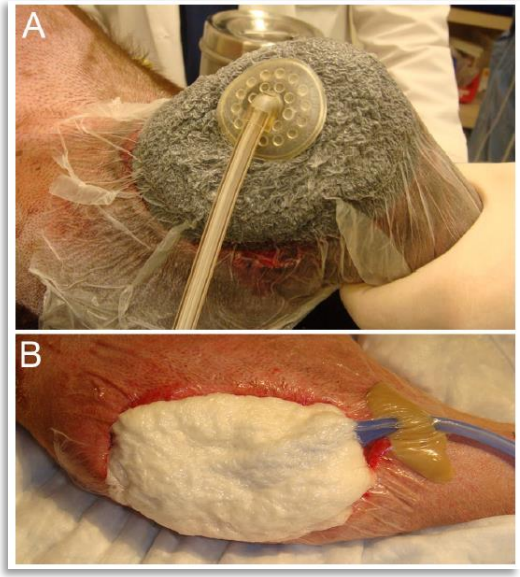
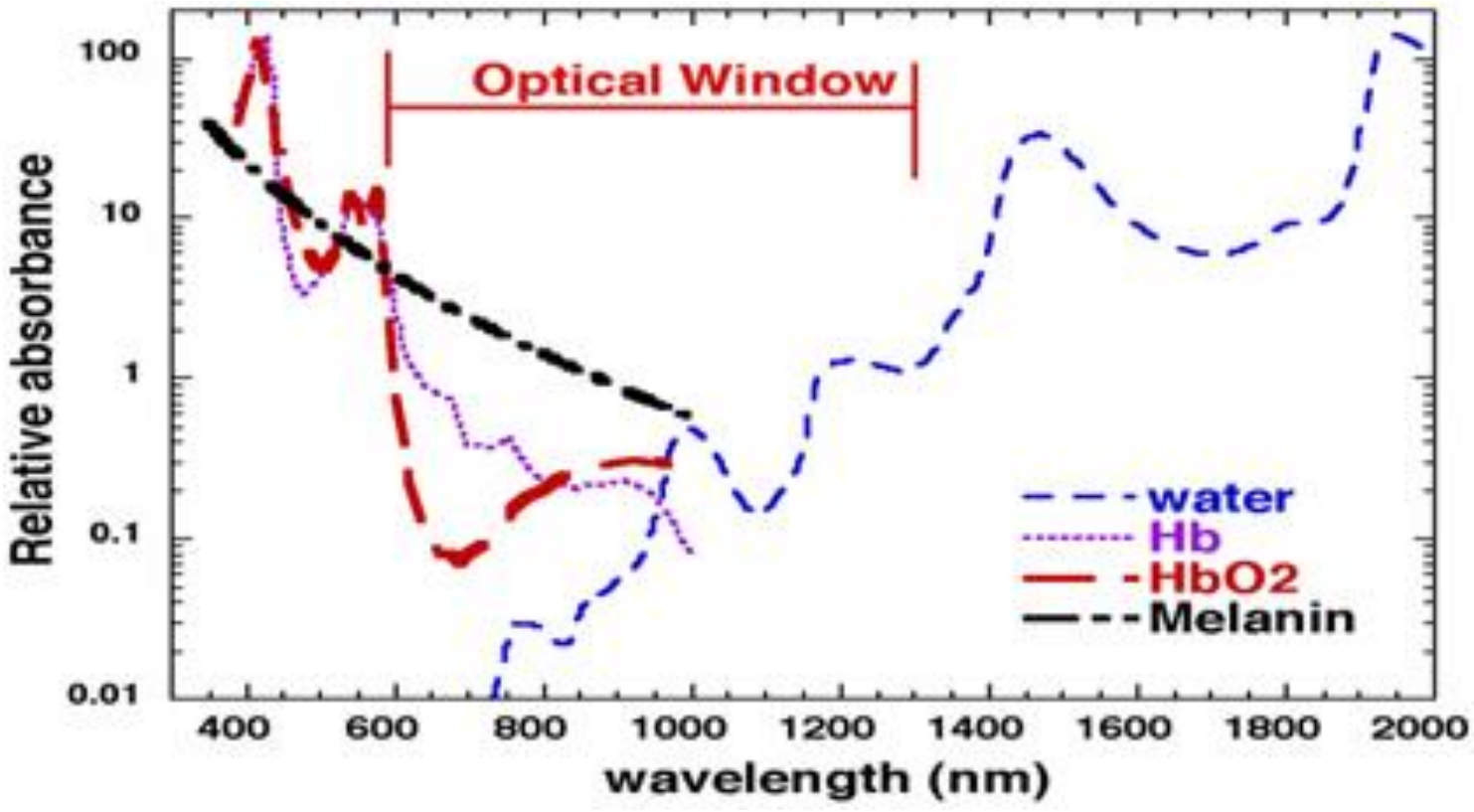



**Figure 4** (A) Necrotic wound on the right brachium and antebrachium caused by an untreated impalement in a 2-year male neutered Labrador retriever. (B) During debridement, before placement of NPWT. (C) Wound appearance after 3 days of NPWT, immediately before reconstruction. Note the early appearance of granulation tissue in the wound.



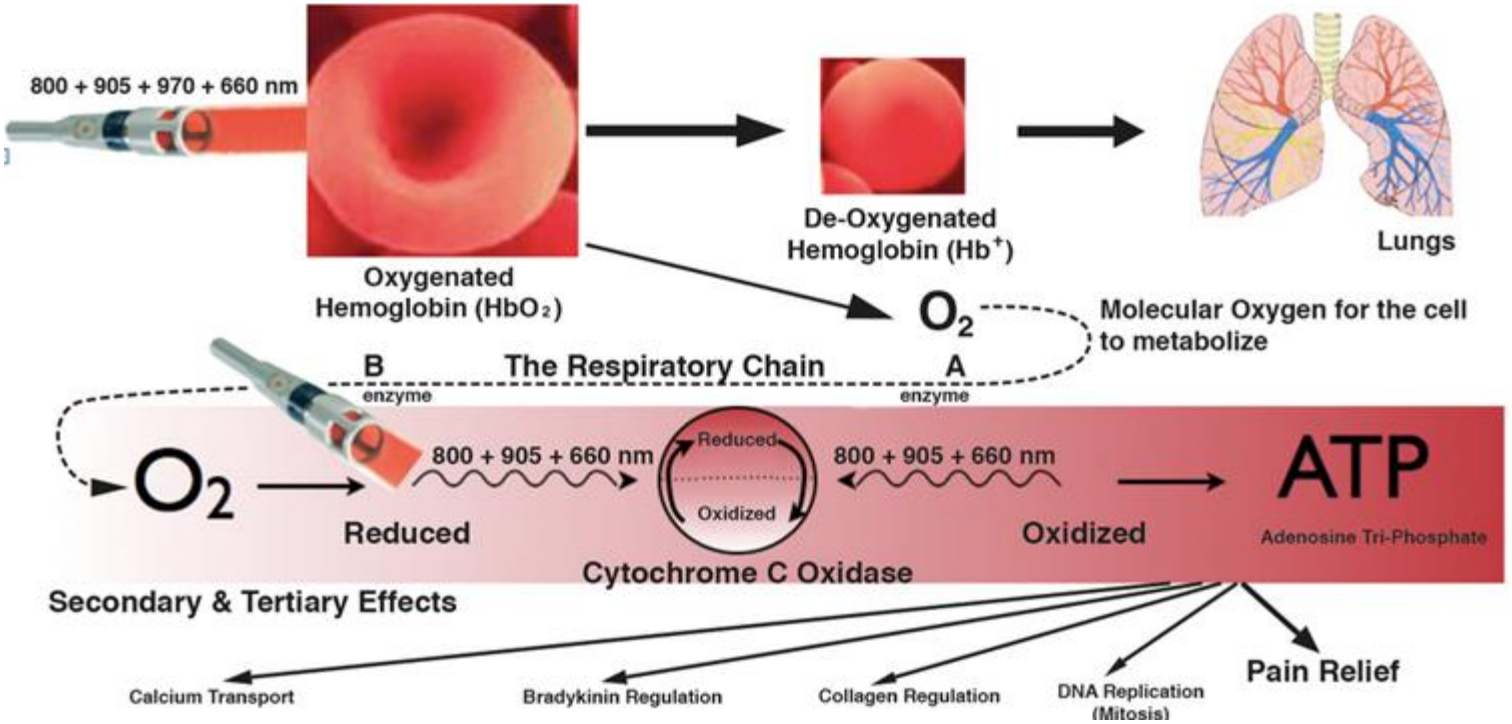

- Mean 3 days with NPWT
- NPWT wounds closed < time vs traditional management in traumatic injuries
- Changed every 3 days
- Successful at home care in 3 patients

# Low Level Laser Therapy

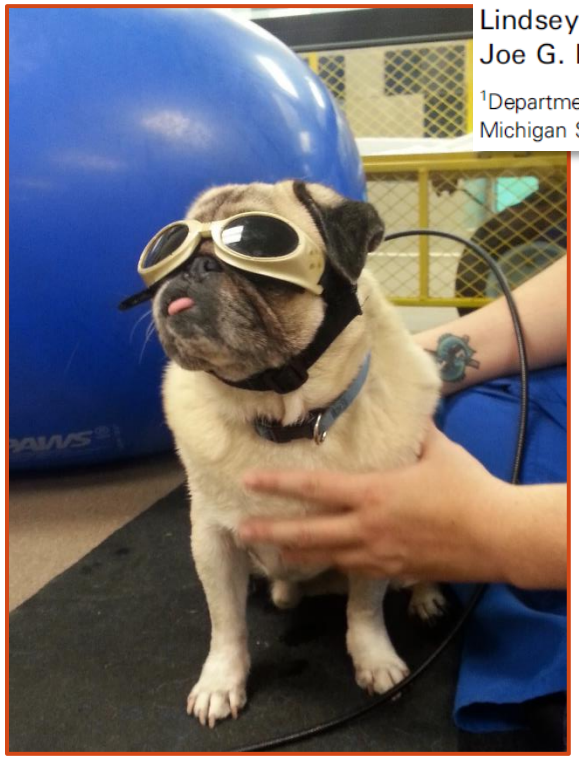



http://spie.org/newsroom/technical-articles-archive/1669-low-level-laser-therapy-an-emerging-clinical-paradigm?highlight=x2404

# Low Level Laser Therapy



# Low Level Laser Therapy



Veterinary Surgery 44 (2015) 988–996

**The Effect of Low-Level Laser Therapy on the Healing of Open Wounds in Dogs**

Lindsey M. Kurach[1], Bryden J. Stanley[1], Krista M. Gazzola[1], Michele C. Fritz[1], Barbara A. Steficek[2], Joe G. Hauptman[1], and Kristen J. Seymour[1]

[1]Department of Small Animal Clinical Sciences and [2]Diagnostic Center for Population and Animal Health, College of Veterinary Medicine, Michigan State University, East Lansing, Michigan

- No apparent beneficial effects of LLLT

*Journal of Small Animal Practice* (2012) **53**, 465–469

**Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study**

W. E. Draper, T. A. Schubert, R. M. Clemmons and S. A. Miles

- LLLT group (3-5 days) vs control group (14 days)

# Low Level Laser Therapy

*Journal of Athletic Training* 2004;39(3):223–229

## Low-Level Laser Therapy Facilitates Superficial Wound Healing in Humans: A Triple-Blind, Sham-Controlled Study

J. Ty Hopkins*; Todd A. McLoda†; Jeff G. Seegmiller‡; G. David Baxter§

- 22 healthy patients, 2 1.3 cm abrasions
- 1 wound LLLT vs sham therapy, the other wound was left untreated, daily Tx 10 days, photos daily and on day 20
- LLLT resulted in enhanced healing
- LLLT resulted in indirect healing effect on surrounding tissues

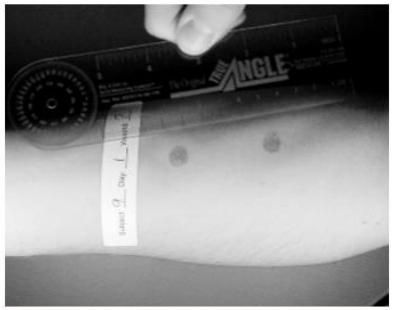


Figure 1. Experimental wounds before treatment on day 1.

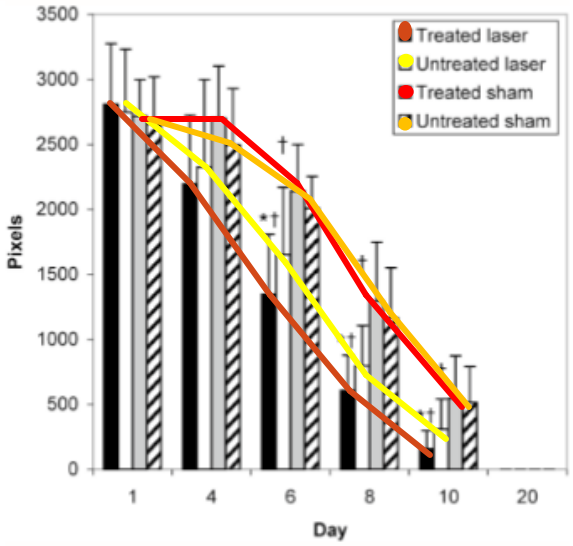



Figure 2. Average wound areas (pixels) of all groups over time. *Different from sham group for both treated and untreated wounds ($P > .05$). †Different from the untreated wound in the laser group.

# Hyperbaric Oxygen Therapy

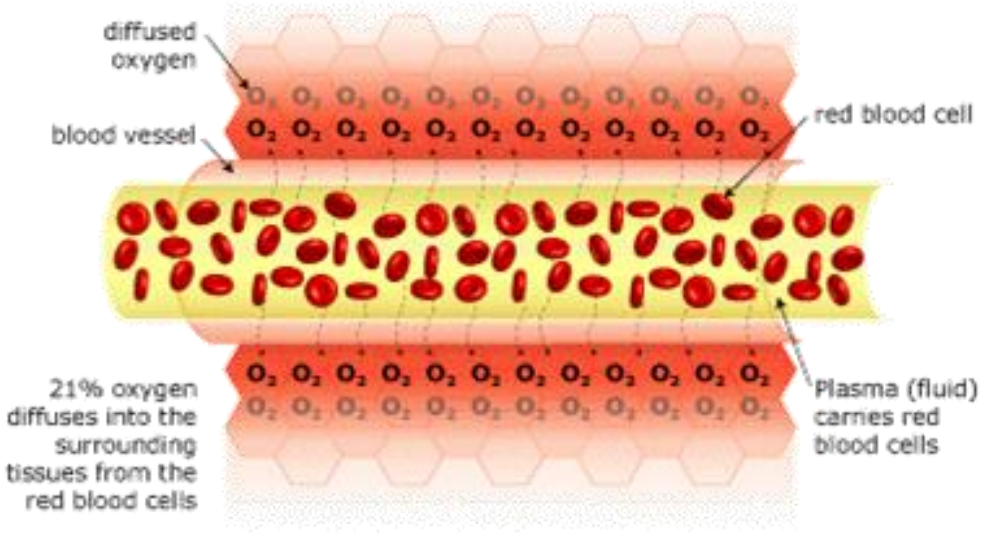
*J Vet Emerg Crit Care 2010; 20(3): 289–297)*

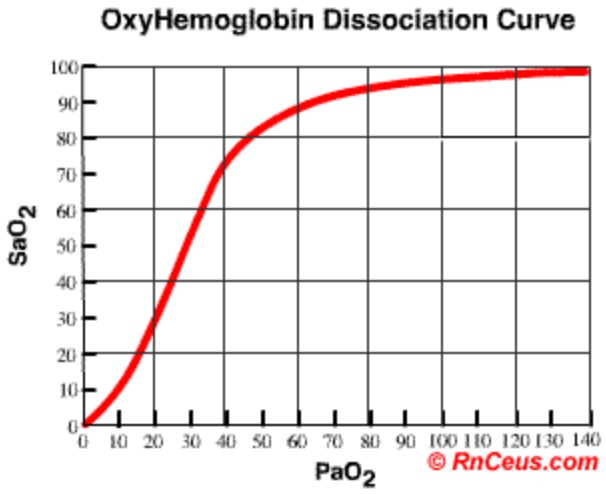
**Hyperbaric oxygen therapy. Part 2: application in disease**

Melissa L. Edwards, DVM, DACVECC

- Hyperoxygenation: ↑ from 21% to 100% $O_2$ delivery, ↑ in free $O_2$ in plasma
- Vasoconstriction: decrease in edema
- Bactericidal and AB Synergy
- Superoxide Dismutase Stimulation: antioxidant production
- Inflammation and Immune Modulation: $PaO_2$ <30 mmHg ↓ bactericidal action neutrophils
- Angiogenesis
- Increases Fibroblast, Collagen and Bone Production

# Hyperbaric Oxygen Therapy



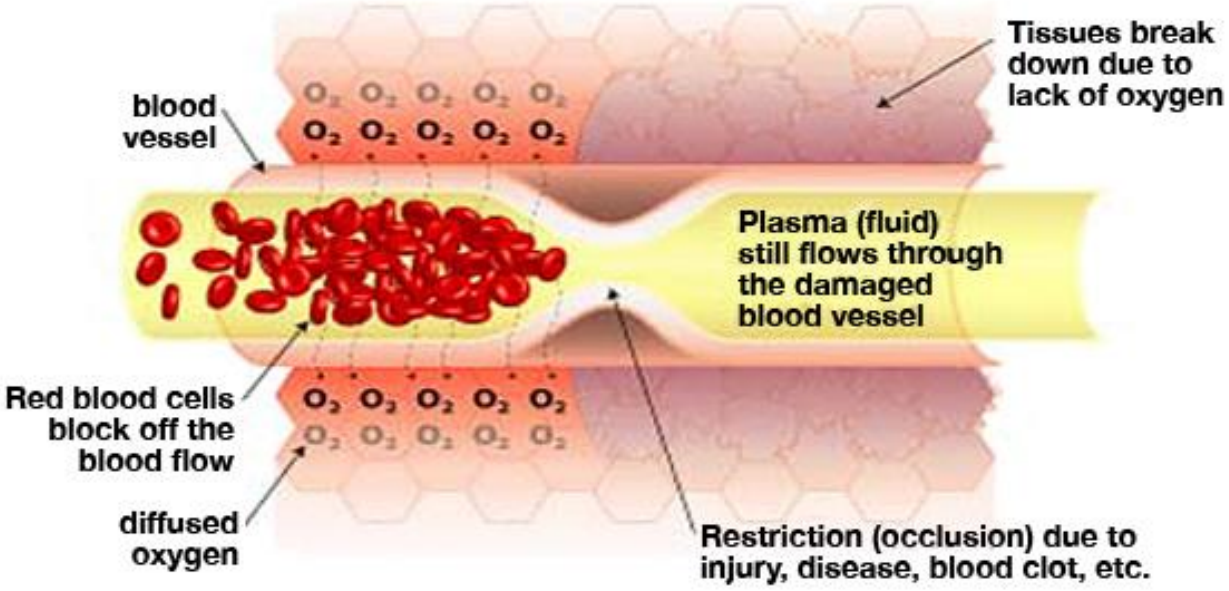




http://wesleyhyperbaric.com.au/hbot-diagrams/

**Normal Blood Flow**

Increase in normal $O_2$ delivery is limited to Hb saturation

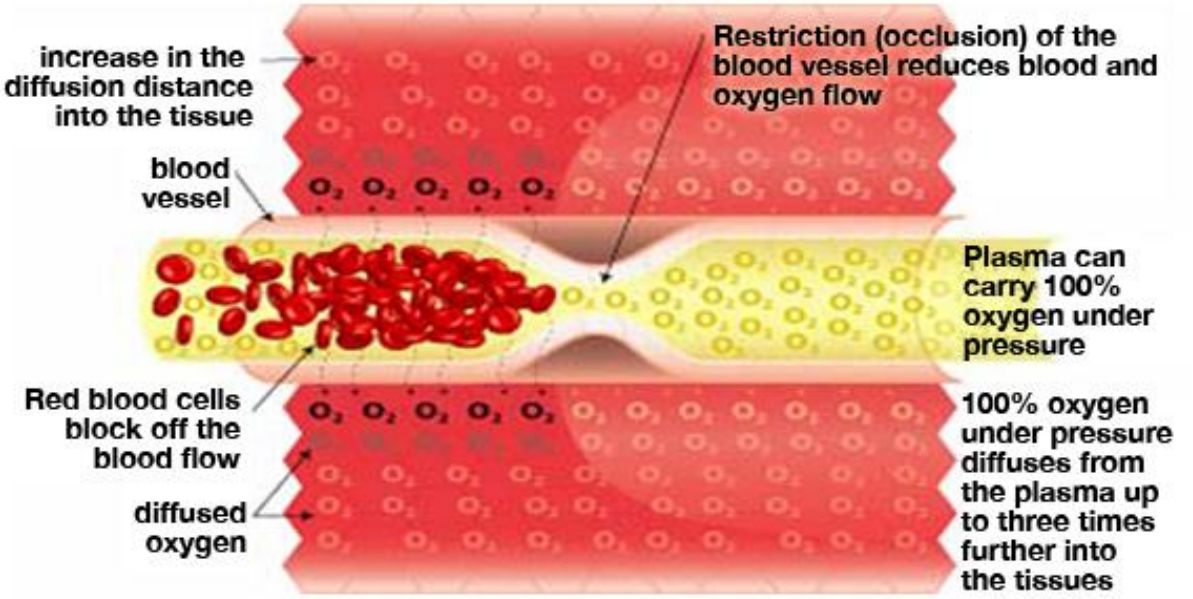
# Hyperbaric Oxygen Therapy




http://wesleyhyperbaric.com.au/hbot-diagrams/

**Compromised Blood Flow**

# Hyperbaric Oxygen Therapy

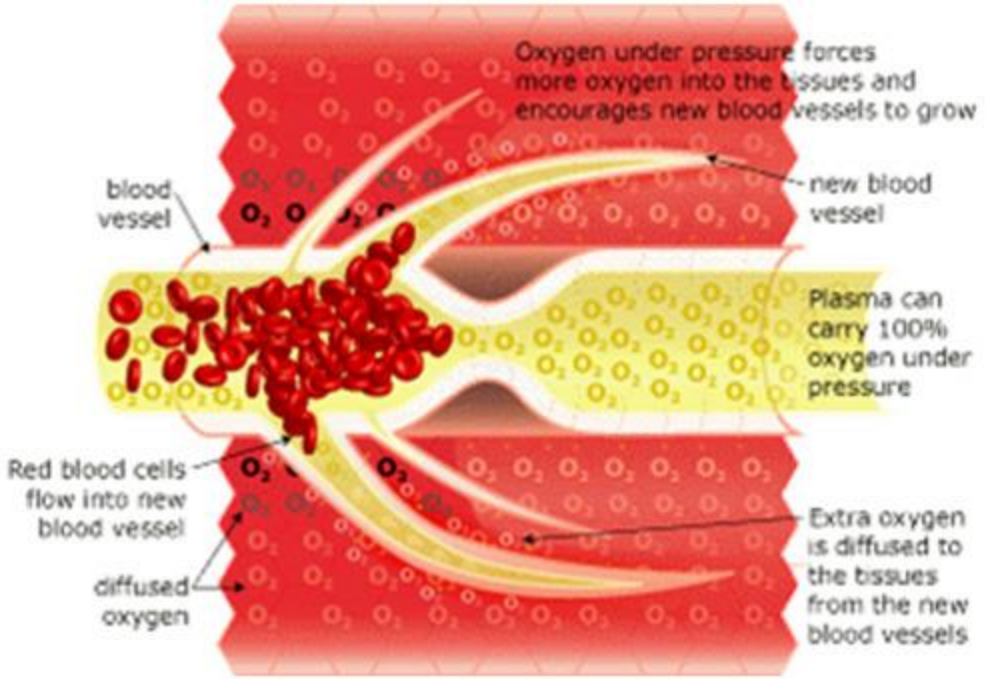



http://wesleyhyperbaric.com.au/hbot-diagrams/

**Hyperbaric Oxygen**

Increased pressure will cause more $O_2$ to go into solution, and therefore more oxygen will be transported in the plasma

# Hyperbaric Oxygen Therapy

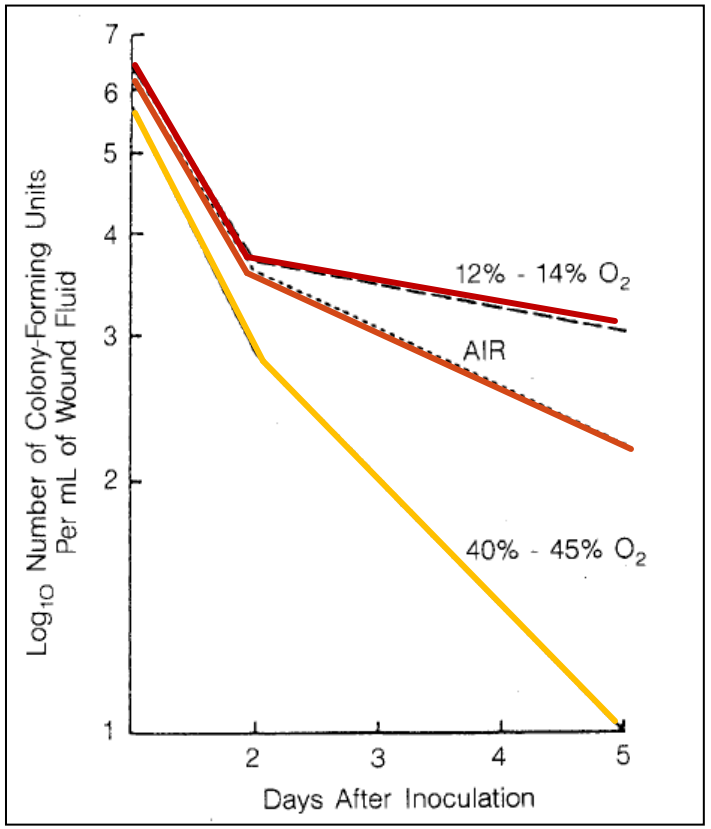



http://wesleyhyperbaric.com.au/hbot-diagrams/

**Neovascular Regeneration**

# Hyperbaric Oxygen Therapy

- Hypoxic wounds are more susceptible to infection, delayed healing
- Transcutaneous tissue $PO_2$ can be used to assess tissue oxygenation
- Hypoxia leads to ↓ ROS production, important in oxidative eradication of bacteria




Hunt 1988

Journal of the American College of Clinical Wound Specialists (2015) 6, 9–13

# Clinical Effectiveness of Hyperbaric Oxygen Therapy in Complex Wounds

Supaporn Opasanon, MD, FRCST, FICS, FACS[a,*], Warut Pongsapich, MD, Dr Med[b], Sitthichoke Taweepraditpol, MD[c], Bhoom Suktitipat, MD, PhD[d,e], Apirag Chuangsuwanich, MD[c]

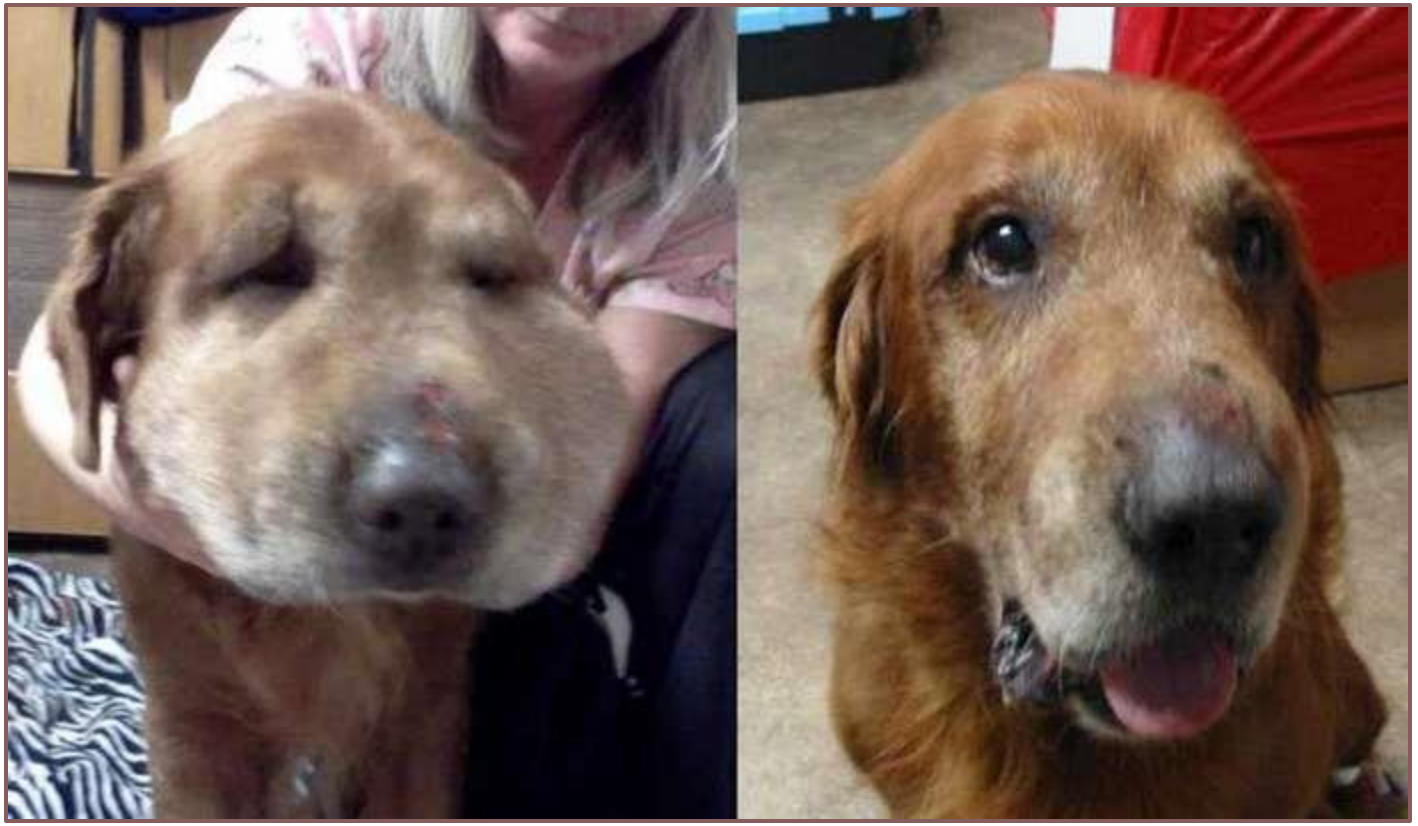
- 40 patients with complex wounds (defined as non-healing wounds, treated unsuccessfully with standard wound care for 6 months)
- HBOT Mon-Fri, for 8 weeks
- 78% healed wounds after 8 weeks
- 5 HBO treatments, wound size <29.7%
- 10 HBO treatments, wound size <17%

**Table 2** Wound Size Reduction: Comparison of the Wound Size Between Each 5 Visits. The Wound Size Reduction was Calculated as a Proportion of Wound Size Reduced From the Previous Visit.

| HBO (sessions) | Difference | *p*-Value |
|---|---|---|
| 1–5 | −29.659 | <0.001 |
| 5–10 | −16.907 | <0.001 |
| 10–15 | −8.565 | 0.141 |
| 15–20 | −12.304 | 0.022 |
| 20–25 | −5.647 | 0.224 |
| 25–30 | −9.669 | 0.012 |
| 30–35 | 3.205 | 0.591 |
| 35–40 | −18.104 | 0.073 |

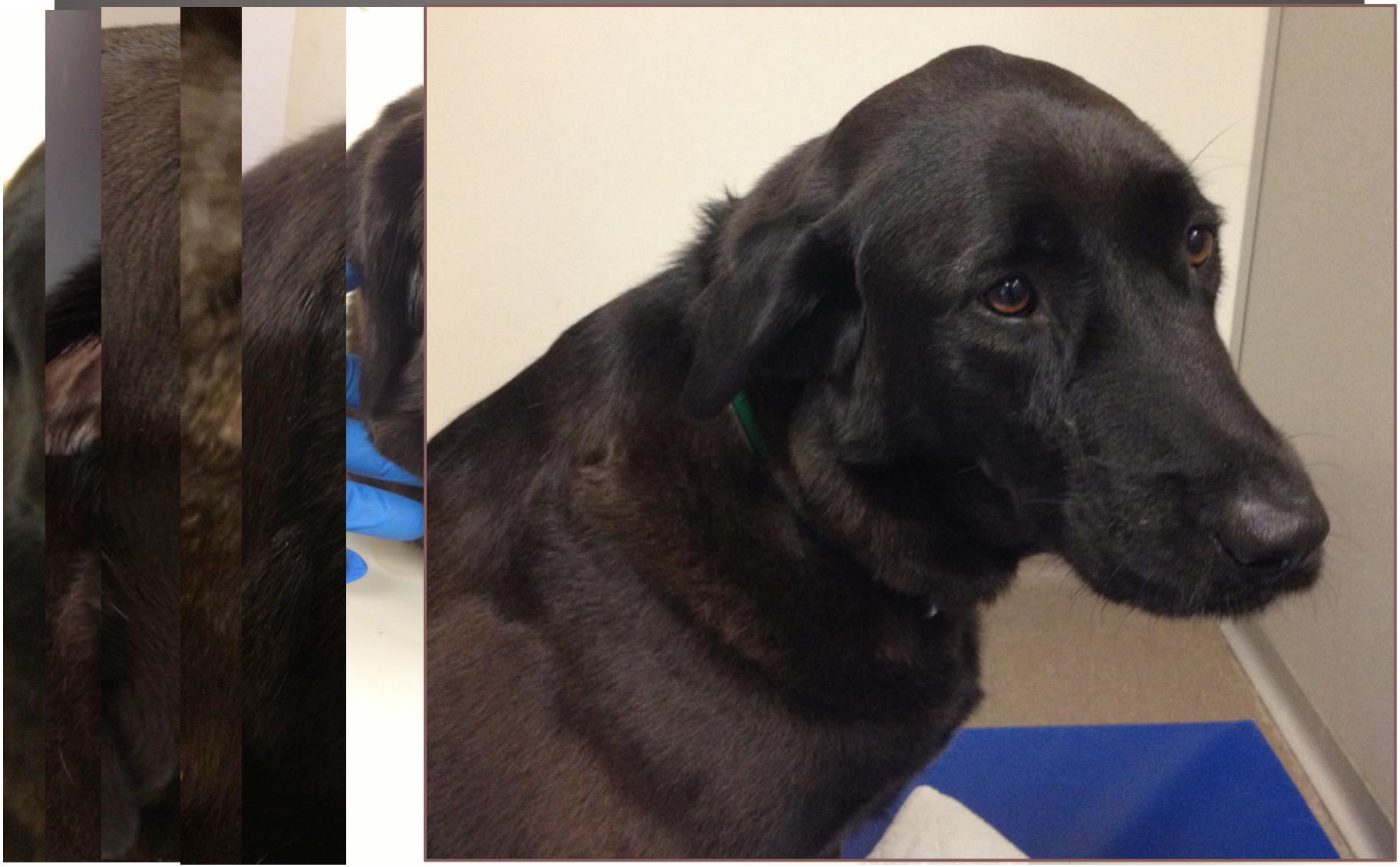
# Water Moccasin Envenomation

## 1HBOT session



Courtesy of Dr. Justin Schmalberg DVM, DACVN, CVA

# Cutaneous Pythium, HBOT over 7 months



Courtesy of Dr. Justin Schmalberg DVM, DACVN, CVA

# Conclusions

- Healing stage of the wound should be evaluated to make clinical decisions
- Wounds should not ALL receive the same management
- Complex wounds (infected, chronic, etc.) should be evaluated for enhanced healing techniques if available

# Questions

Name the 4 stages of Wound Healing

Hemostasis

Inflammation/Debridement

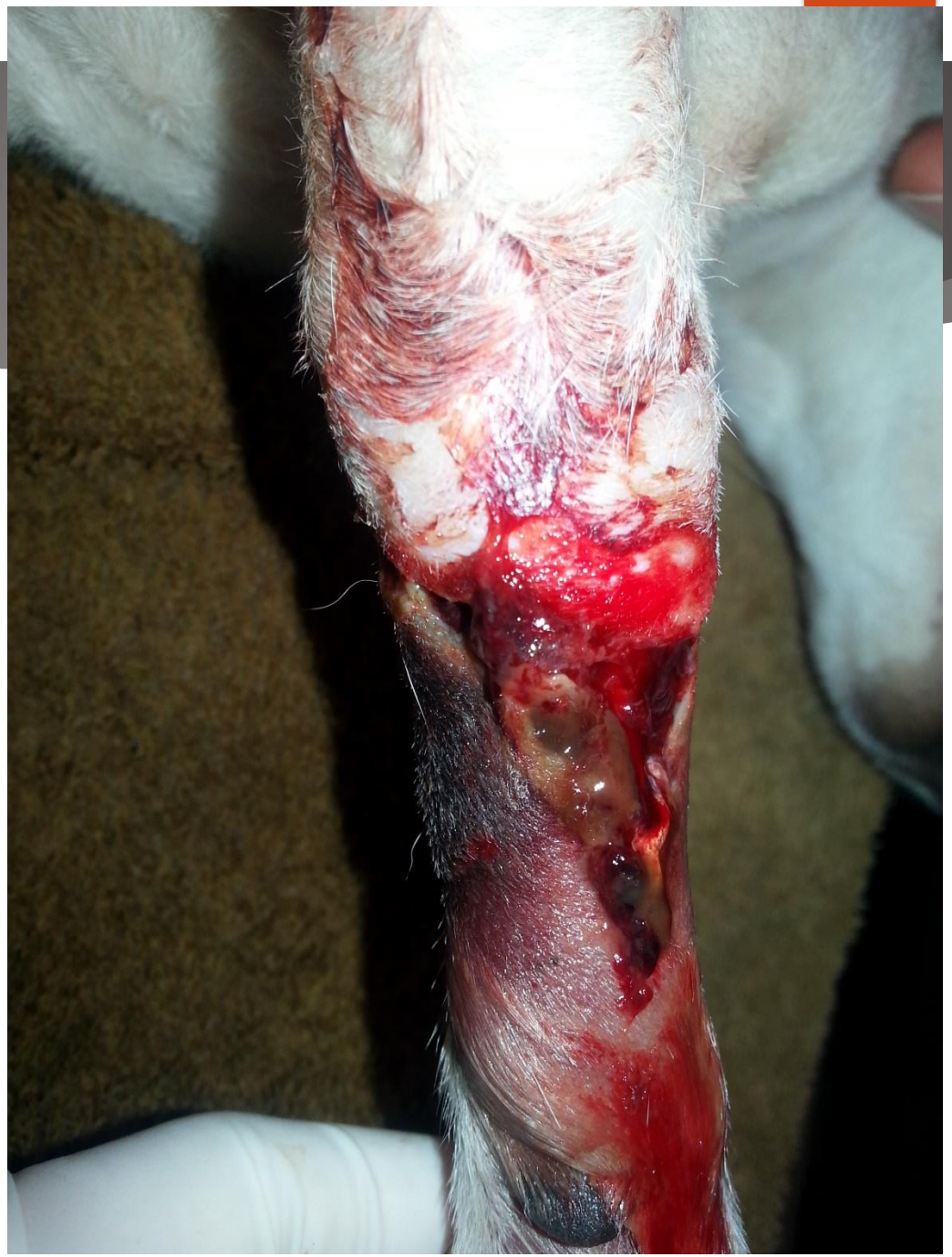
Repair/Proliferation

Maturation

# Questions

Name the Stage of Wound Healing

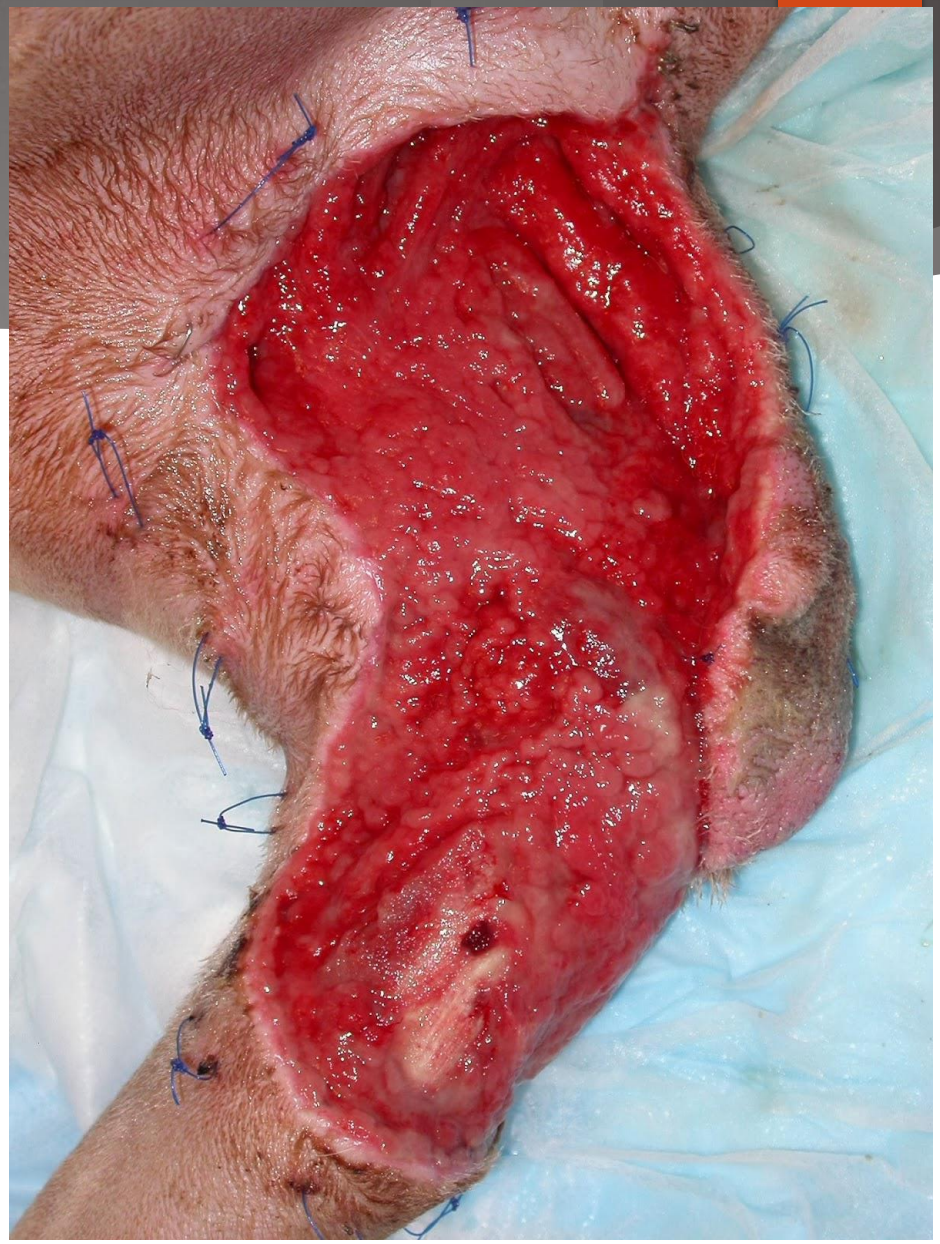
Inflammation/ Debridement



# Questions

Name the Stage of Wound Healing

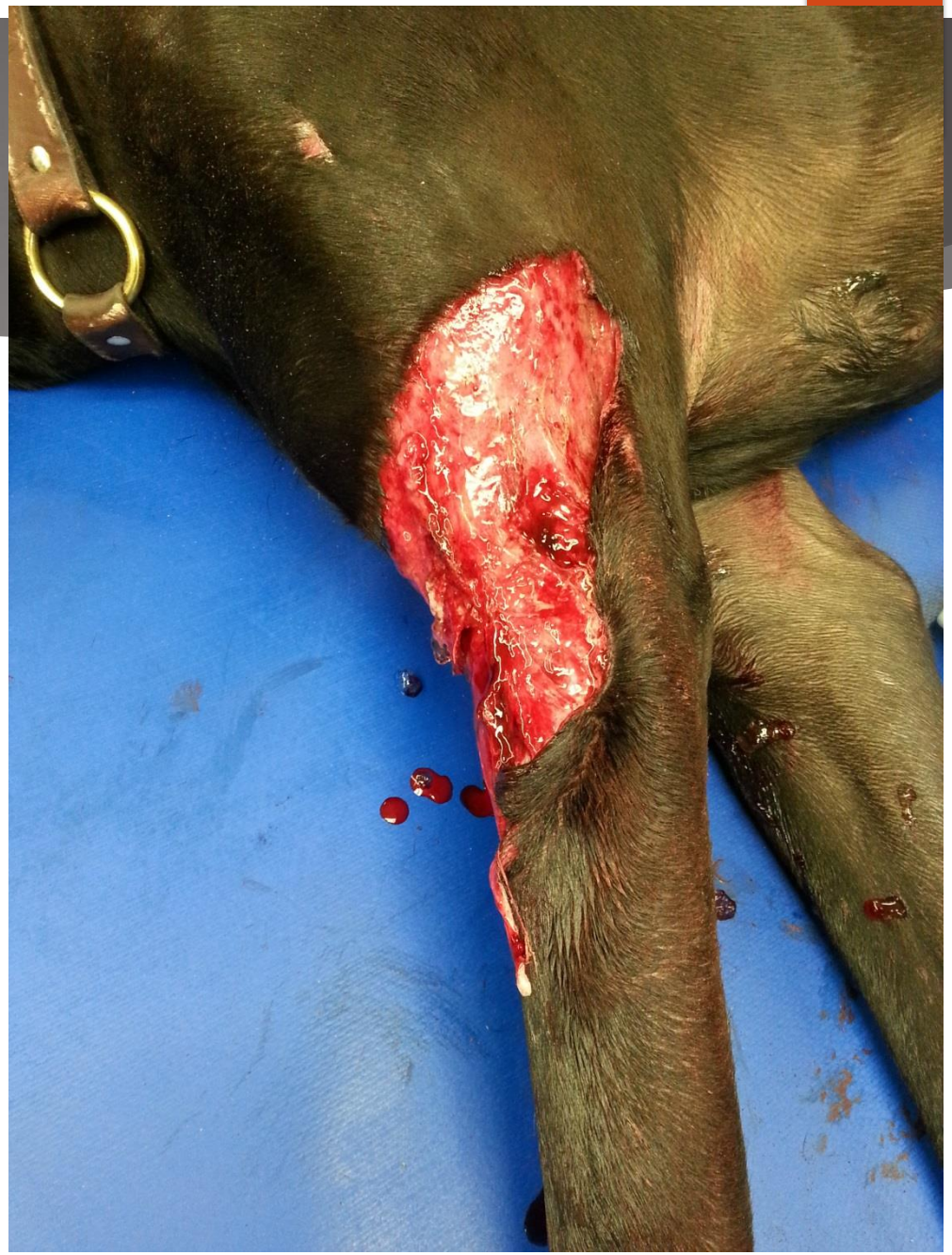
Repair/ Proliferation



# Questions

Name the Stage of Wound Healing

Hemostasis



# Questions

Name the Stage of Wound Healing

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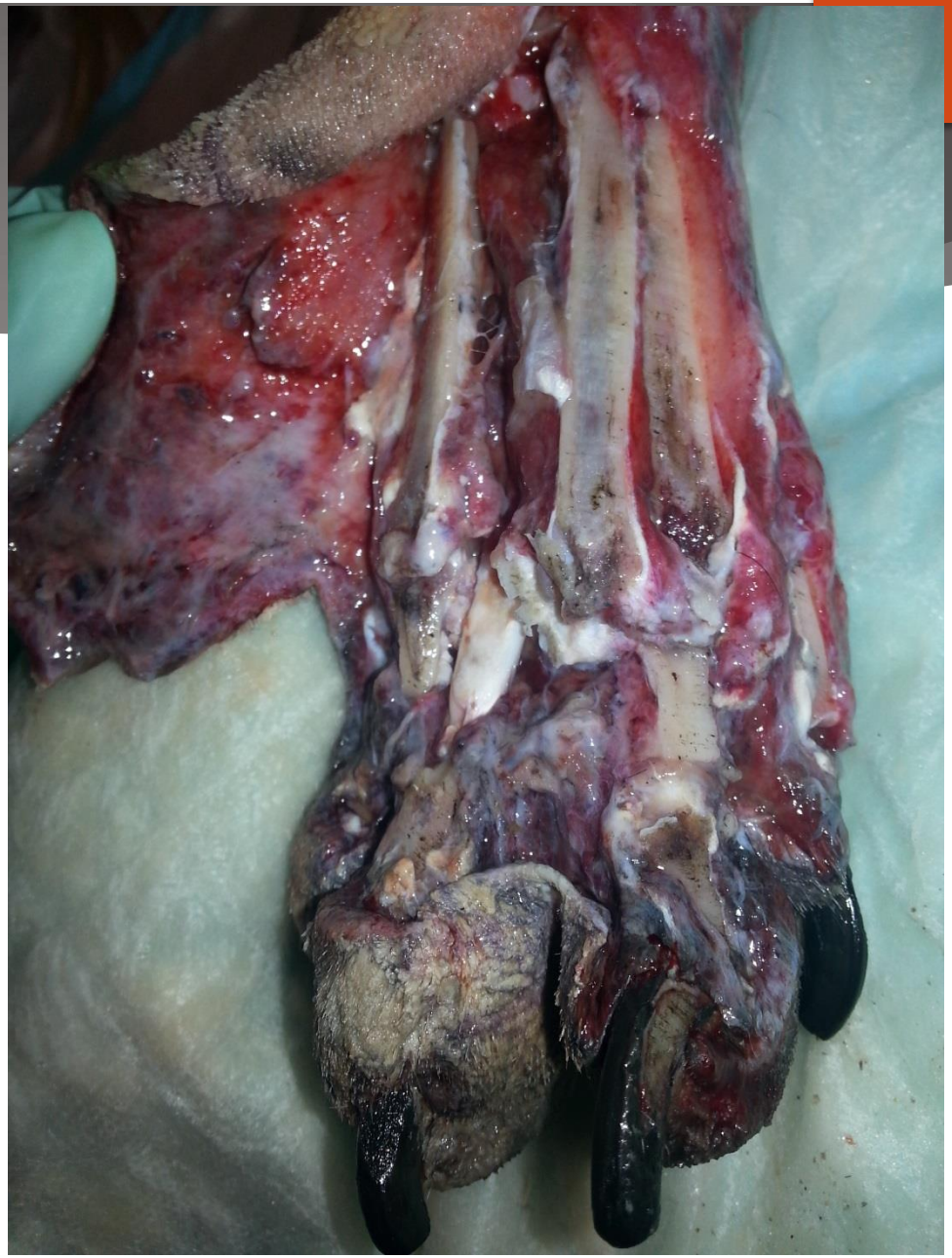

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- Turk, Ryen, Ameet Singh, and J. Scott Weese. "Prospective surgical site infection surveillance in dogs." *Veterinary Surgery* 44.1 (2015): 2-8.

# Wound Solutions

- 0.05% Chlorhexidine solution:

  25 ml of 2% chlorhexidine solution + 1000 ml electrolyte solution

- 0.1% Povidone-Iodine solution:

  10 ml of 10% povidone-iodine solution + 1000 ml electrolyte solution (inactivated by organic material)

- Tris-EDTA solution: *(Pseudomonas aeruginosa, Escherichia coli*, and *Proteus vulgaris)*

  1.2 g of EDTA + 6.05 g of tris + 1000 ml sterile water. Na added until pH is 8, autoclaved for 15 minutes. Can be added to 0.01% chlorhexidine gluconate solution.

**Table 5**
**Stages of wound healing**

| Stage or Phase | Approximate Time | Characteristics | Goal of Bandage |
|---|---|---|---|
| Inflammatory | 0–5 d | Inflammatory cells eliminate contaminants and nonviable tissue.<br>Platelets release growth factors to attract fibroblasts, which produce fibrin and collagen.<br>Fluid extravasation may cause edema. | Maintain a moist wound environment to promote autolytic debridement.<br>Protect the wound from external contaminants.<br>Provide support to tissues. |
| Repair | 5–21 d | Inflammatory cells and mediators diminish.<br>Collagen and neovascularization form granulation tissue, which provides a barrier to infection.<br>Epithelialization may begin once there is granulation tissue.<br>Myofibroblasts in granulation tissue cause wound contraction. | Maintain a moist wound environment to stimulate granulation tissue, epithelialization, and wound contraction.<br>Bandage may need to support tissues, depending on location and severity of tissue damage. |
| Maturation | 21 d to weeks or months | Collagen reorganizes and forms cross-links to strengthen the tissue.<br>Tissue structures are reformed. | Wound is typically no longer open and has contracted/epithelialized.<br>Bandage is no longer needed, unless to support weakened tissues. |

# Honey Dressing Considerations

**Table III.** Some practical considerations using honey in clinical practice

| |
|---|
| The various beneficial effects of honey on wound tissues will be reduced or lost if small amounts of honey become diluted by large amounts of exudate |
| The frequency of dressing changes required depends on how rapidly the honey is being diluted by exudate |
| More honey is required on deeper infections, to obtain an effective level of antibacterial activity diffusing deep into the wound tissues |
| Typically, 20ml of honey (25 to 30g) is used on a 10cm x 10cm absorbent dressing pad |
| Most commonly, dressing are changed daily, but up to 3 times daily may be needed at first for heavily exuding wounds |
| The antibacterial and anti-inflammatory action of honey soon reduces the amount of exudation from the wound – twice-weekly dressing changes may be suitable later |
| A heavy flow of exudate tends to wash the honey to the outer surface of the dressing, thus allowing the dressing to stick to the wound: more frequent dressing changes prevent this |
| If a non-adherent dressing is used under the honey dressing, it has to have sufficient porosity to allow the components of the honey to diffuse through to the wound bed (paraffin-impregnated dressings prevent diffusion from the honey) |
| Honey at body temperature is fluid and tends to run off wounds (fig. 2). Absorbent dressing pads preimpregnated with honey are the most convenient way of applying honey to surface wounds (fig. 3) |
| Filling abscesses, cavities and depressions in the wound bed with honey before applying the honey dressing pad ensures honey is always in contact with the wound bed (fig. 4) |
| Occlusive or absorbent secondary dressings are needed to prevent honey oozing out from the wound dressing. Occlusive dressings have the advantage of preventing honey from soaking away from the wound (the high osmolarity of honey prevents maceration of the skin) |
| Where there is no problem with containing exudate, fluid honey can be held in place on a wound by an adhesive polyurethane film dressing |
| For varicose ulcers, multi-layer pressure bandaging can be used over honey-impregnated dressing pads |

**Table 4. Strategies to Promote Wound Healing in Newborns/Infants**

| Care Strategy | Wound Healing Event Trageted | Scientific Rationale |
|---|---|---|
| Maintain normal serum calcium levels | Collagen maturation; wound contraction | Actin-myosin contractility is calcium dependent[39] |
| Maintain normal perfusion | Metabolic activities within the wound microenvironment | Maximizes oxygen delivery to the wound bed |
| Maintain adequate oxygenation | Collagen synthesis; fibroblast proliferation; keratinocyte mitosis | Collagen synthesis and secretion depends on oxygen-dependent enzyme reactions[19]; increases tissue resistance to infection[2] |
| Maintain iron stores and/or provide ferrous iron | Collagen synthesis and remodeling | Ferrous iron is a co-factor for collagen hydroxylation reactions[19] |
| Cover injuries with an occlusive hydrocolloid dressing | Keratinocyte migration; sequestering of growth factors | The hydrocolloid dressing provides a temporary cover under which wound exudate can collect; this allows the wound bed to be bathed with growth-factor rich fluid that facilitates keratinocyte migration; the application of an occlusive hydrocolloid may decrease the risk of wound infection[40–43] |
| Keep the infant in a neutral thermal environment | Inflammatory cell activity; Leukocyte activity | Hypothermia decreases leukocyte mitotic activity[44]; the ideal wound temperature is 37°C[44] |
| Maintain renal function | Production of granulation tissue; Fibroblast and keratinocyte proliferation | Animal data shows that acute renal failure leads to inadequate granulation tissue production[45–47]; chronic renal failure is associated with decreases in plasma fibronectin concentration[37] |
| Prevent sepsis/infections | Inflammatory response; collagen synthesis; epithelialization | Infection prolongs the inflammatory process, which delays wound healing; prolonged exposure to inflammatory cytokines also produces tissue damage[2] |
| Avoid the use of corticosteroids | Every aspect of wound healing | Corticosteroids have a substantial impact on every stage of wound healing; they reduce macrophage migration, suppress the inflammatory response decrease keratinocyte and fibroblast proliferation, impair capillary budding, decrease ECM production, decrease protein synthesis, delay epithelialization, and block the release of vasoactive factors[2,6,48,49] |

| | | |
|---|---|---|
| Maximize protein in parenteral and/or enteral nutrition | Collagen synthesis; wound contraction and remodeling | Additional protein is needed to meet the demands of wound healing[49,50] |
| Provide vitamins A, and C and B-complex vitamins (thiamine, niacin, riboflavin, folate, $B_{12}$) | Epithelialization; collagen synthesis; cell metabolism | Vitamin A promotes epithelial integrity; the B-complex vitamins are important for anabolic reactions such as wound healing; vitamin C is a co-factor for collagen synthesis and is important for normal immune function[49,50] |
| Provide zinc and copper | Collagen synthesis | Zinc is a co-factor for collagen synthesis,[19] epithelialization, and fibroblast proliferation[6] Copper is a co-factor for collagen cross-linking reactions[6] |
| Maintain euvolemia | Tissue oxygenation | Normal perfusion is needed to maintain the wound microenvironment and the developing ECM[51] |
| Provide adequate pain management | Wound perfusion; all aspects of wound healing | Connective tissue perfusion is sensitive to autonomic nervous activity[18]; pain results in catecholamine release that can lead to vasoconstriction and impaired wound perfusion,[2] pain also stimulates corticosteroid release that can interfere with wound healing |

Strodtbeck et al, 2001

## *Growth Factors in the Wound Healing Process and Cells That Produce Them*

| CYTOKINE | ABBREVIATION | SOURCE | FUNCTIONS |
|---|---|---|---|
| Platelet-derived growth factor | PDGF | Platelets, macrophages, endothelial cells, keratinocytes | Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts and endothelial cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction; remodeling |
| Transforming growth factor-β (including isoforms β1, β2, and β3) | TGF-β | Platelets, T-lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts | Chemotactic for PMNs, macrophages, lymphocytes, and fibroblasts; stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; induces TGF-β production |
| Epidermal growth factor | EGF | Platelets, macrophages | Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration |
| Transforming growth factor-α | TGF-α | Macrophages, T-lymphocytes, keratinocytes | Similar to EGF |
| Fibroblast growth factor-1 and -2 family | FGF | Macrophages, mast cells, T-lymphocytes, endothelial cells, fibroblasts | Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition |
| Keratinocyte growth factor (also called FGF-7) | KGF | Fibroblasts | Stimulates keratinocyte migration, proliferation, and differentiation |
| Insulin-like growth factor | IGF-1 | Macrophages, fibroblasts | Stimulates synthesis of sulfated proteoglycans, collagen, keratinocyte migration, and fibroblast proliferation; endocrine effects similar to those of growth hormone |
| Vascular endothelial cell growth factor | VEGF | Keratinocytes | Increases vasopermeability; mitogenic for endothelial cells |

Modified from Schwartz SI, editor: Principles of surgery, ed 7, New York, 1999, McGraw-Hill.
From Ethridge R, Leong M, Phillips L: Wound healing. In Townsend C, Beauchamp R, Evers B, Mattox K, editors: Sabiston textbook of surgery, ed 18, St Louis, 2007, Saunders/Elsevier.
*HA*, Hyaluronic acid; *MMPs*, matrix metalloproteinases; *PMNs*, polymorphonuclear leukocytes; *TIMP*, tissue inhibitor of matrix metalloproteinase.

**TIME – Principles of wound bed preparation**

| Clinical observations | Proposed pathophysiology | WBP clinical actions | Effect of WBP actions | Clinical outcome |
|---|---|---|---|---|
| Tissue non-viable or deficient | Defective matrix and cell debris impair healing | Debridement:<br>» Autolytic, sharp surgical, enzymatic, mechanical or biological | Restoration of wound base and functional extracellular matrix proteins | Viable wound base |
| Infection or Inflammation | *High bacterial counts or prolonged inflammation* | Remove infected foci<br>*Topical/systemic:*<br>» Antimicrobials<br>» Anti-inflammatories<br>» Protease inhibition | *Low bacterial counts or controlled inflammation:* | Bacterial balance and reduced inflammation |
| Moisture imbalance | Desiccation slows epithelial cell migration | Apply moisture-balancing dressings | Restored epithelial cell migration, desiccation avoided | Moisture balance |
| | Excessive fluid causes maceration of wound margin | Compression, negative pressure or other methods of removing fluid | Oedema, excessive fluid controlled, maceration avoided | |
| Edge of wound — non-advancing or undermining | Non-migrating keratinocytes<br>Non-responsive wound cells and abnormalities in extra-cellular matrix or abnormal protease activity | Re-assess cause or consider corrective therapies:<br>» Debridement<br>» Skin grafts<br>» Biological agents<br>» Adjunctive therapies | Migrating keratinocytes and responsive wound cells.<br>Restoration of appropriate protease profile | Advancing edge of wound |

**Fig. 1.** TIME concept.