Biology of Wound Healing

What Goes Wrong When Wounds Don't Heal?

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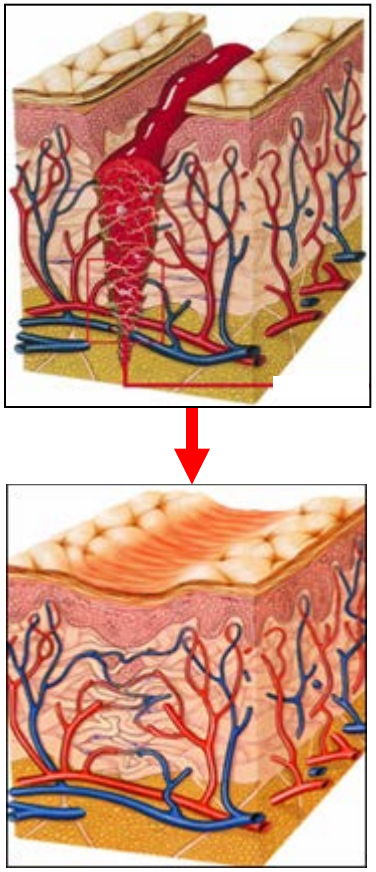
BRIEF BIOSKETCH

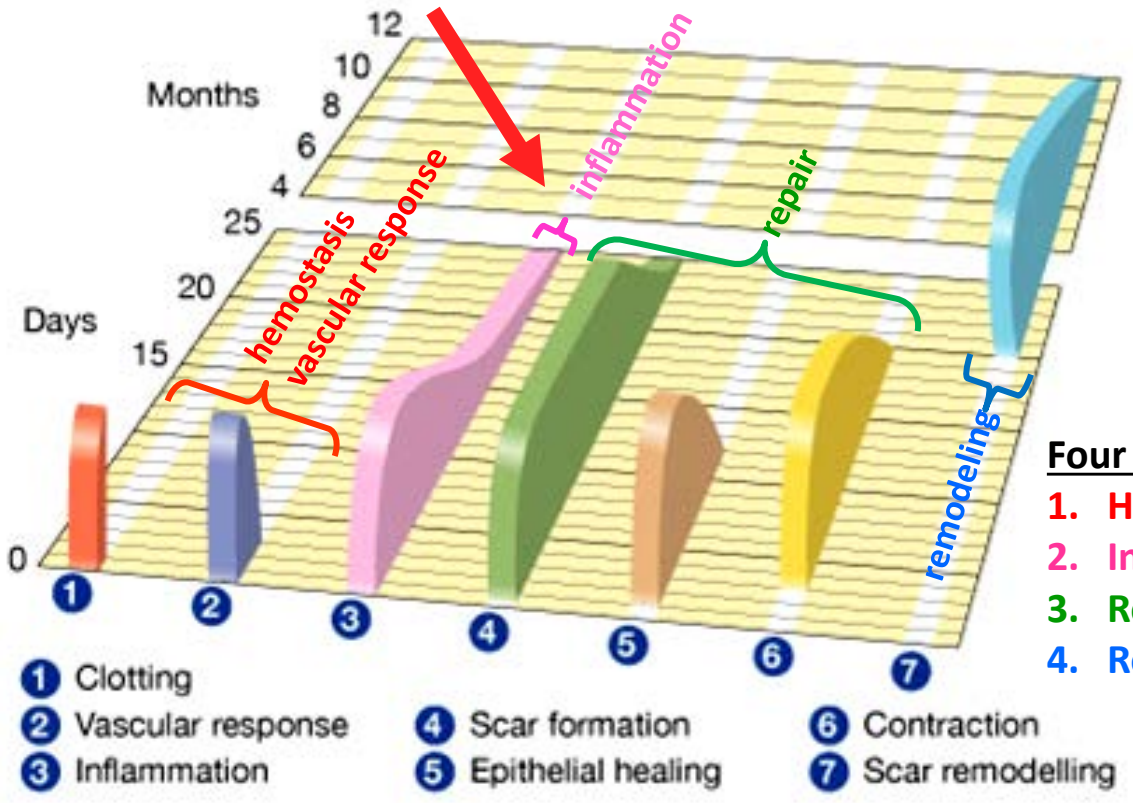
- **BS, PhD in Biochemistry from Oklahoma State University**
- **Postdoctoral fellow in Cell Biology at Yale University**
- **Published over 350 scientific articles cited over 15,000 times**
- **PI or Co-Investigator on $30 million of grants from NIH, DoD, medical device and drug companies**
- **Inventor on 26 awarded patents**
- **Cofounder - two successful biotech companies (QuickMed, Excaliard)**
- **President of Wound Healing Society 1999-2001**
- **Member of National Pressure Ulcer Advisory Panel (2007-2010)**

DISCLOSURES

- **Dr. Schultz has research grant funding during the last year from Smith & Nephew, Acelity, Medline, Biomonde, and CorMedix**
- **Dr. Schultz has given educational lectures in the last year sponsored by Smith & Nephew, Medline, and Organogenesis**
- **Dr. Schultz is a scientific consultant for Acelity, Smith & Nephew, Medline, Medskin Solutions, QuickMed Technologies, AbbVie**
- **Dr. Schultz is an inventor of BIOGUARD® dressings, PROFIND® protease detector, Herpezyme® anti-herpes drug, and EXC-ASO anti-scarring drug**
- **Dr. Schultz has significant financial interests in QuickMed Technologies and Biomonde**
- **Smith & Nephew provided partial funding for travel to this meeting**

Sequence of Molecular & Cellular Events in Skin Wound Healing

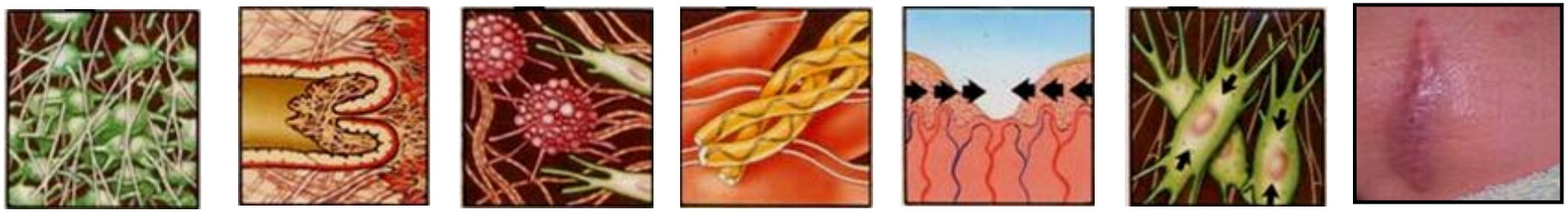




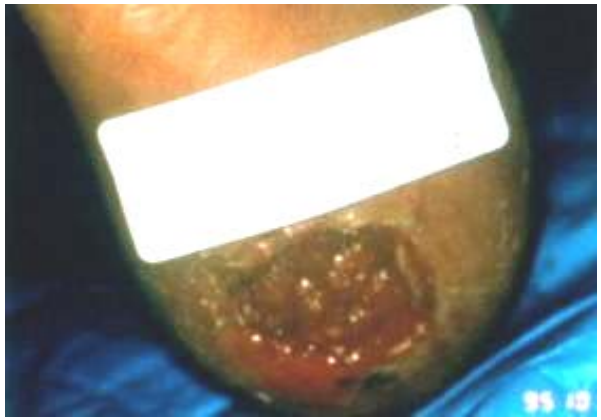
Four Phases of Healing

1. **Hemostasis**
2. **Inflammation**
3. **Repair**
4. **Remodeling**

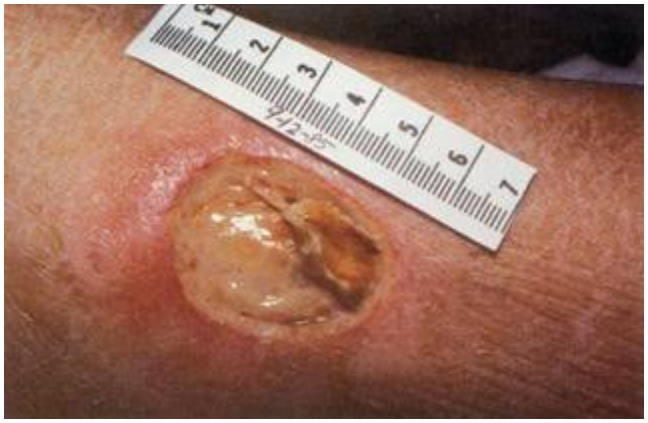
1	2	3	4	5	6	7
Clotting	Vascular Response	Inflammation	Scar Formation	Epithelial Healing	Contraction	Scar Remodeling



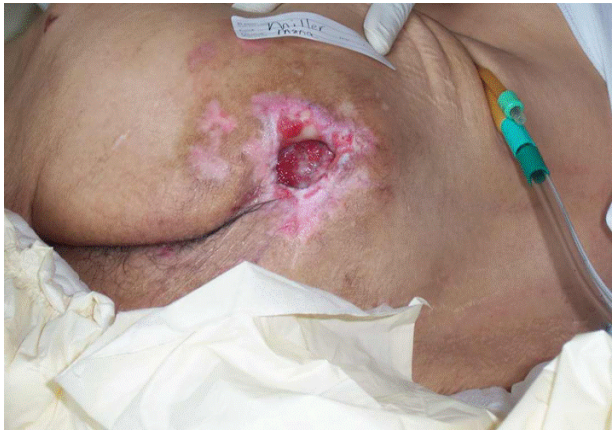
Is There a Common Molecular Pathology Of Chronic Wounds??



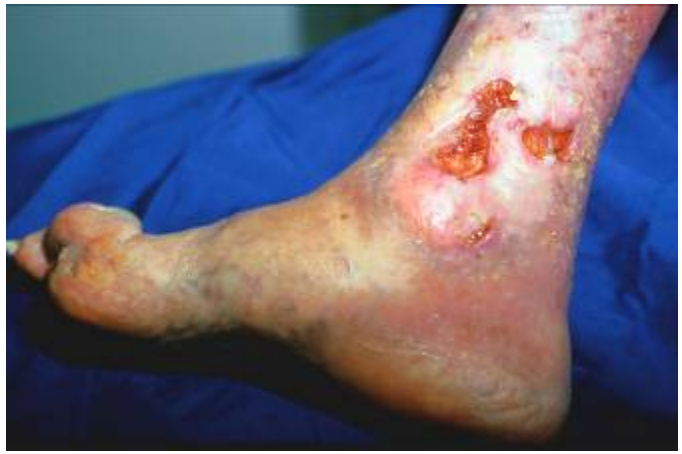
Diabetic foot ulcer



Arterial ulcer

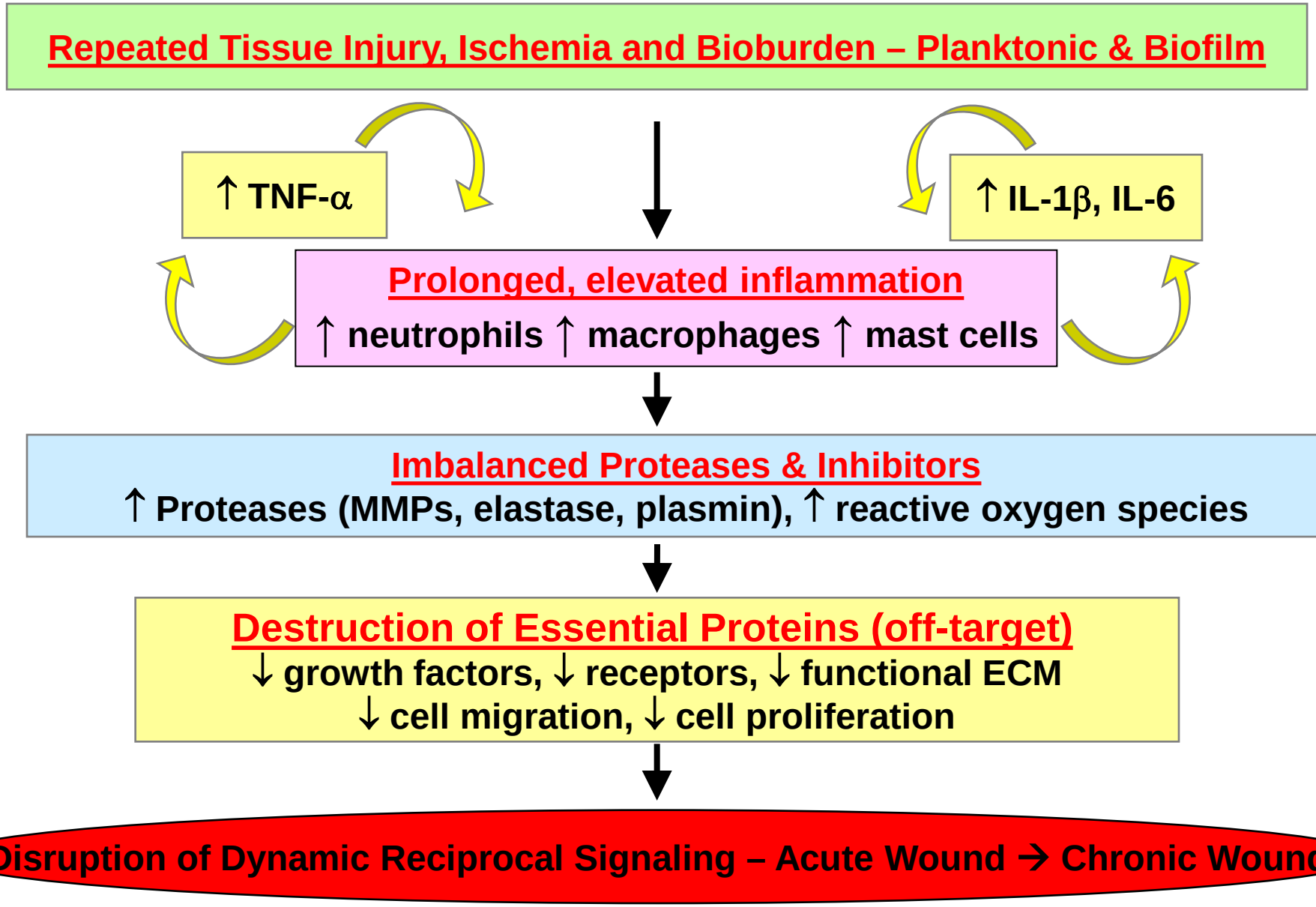


Pressure ulcer



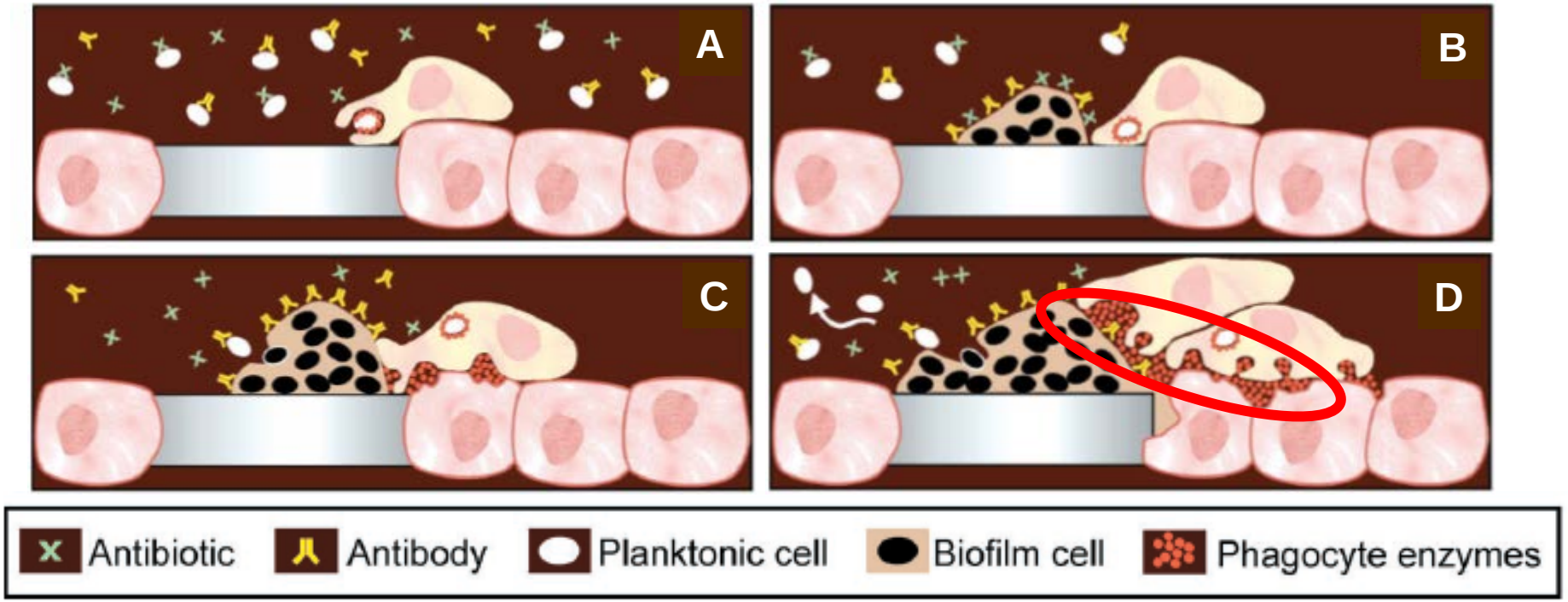
Venous ulcer

Hypothesis Of Chronic Wound Pathophysiology



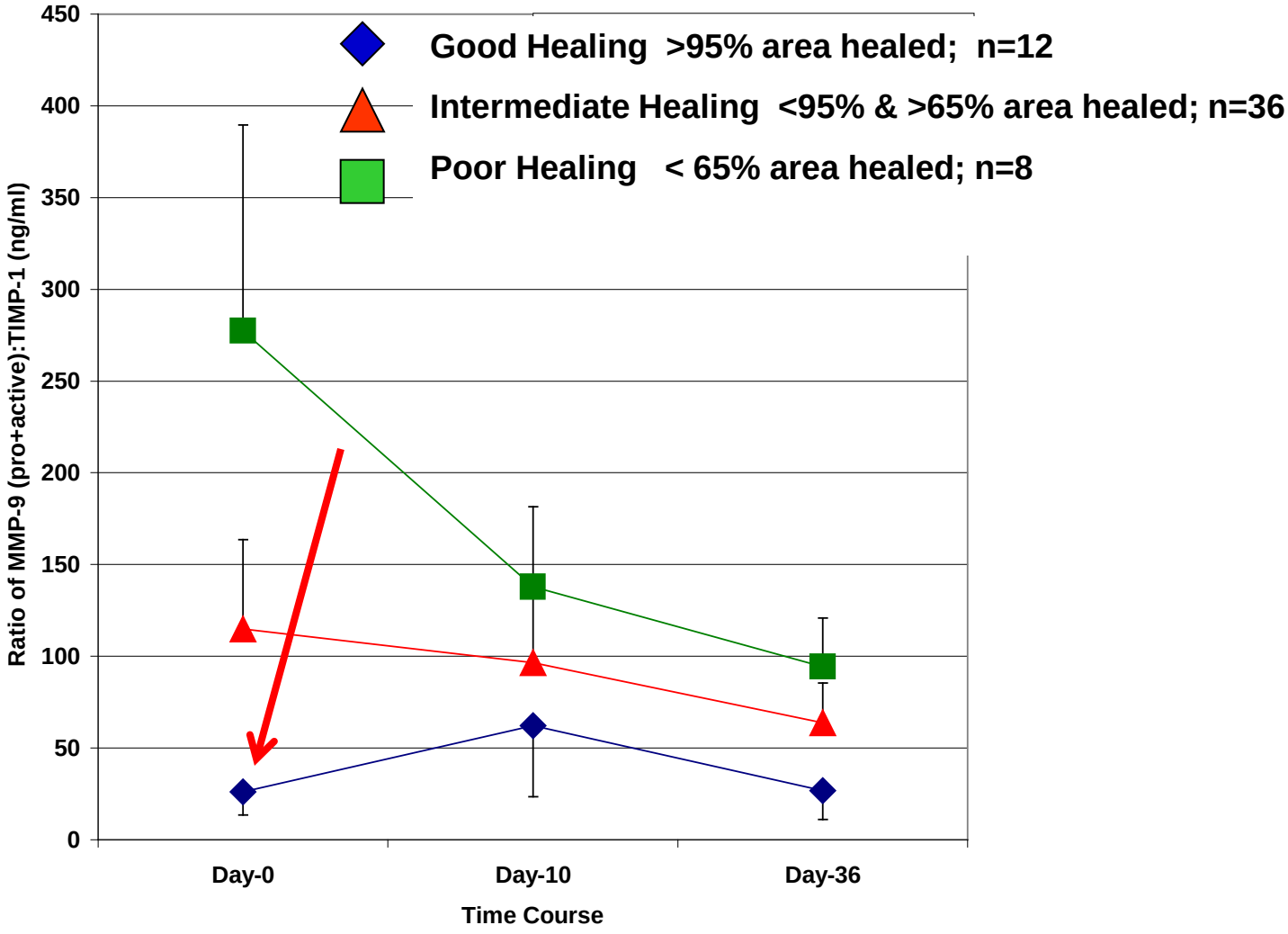
B.A. Mast and G.S. Schultz. Wound Rep Reg 4:411-420, 1996.

How Does The Immunological Response to Biofilms Cause Tissue Damage and Impair Healing?



In Panel A, planktonic bacteria can be cleared by antibodies, phagocytosis, and are susceptible to antibiotics. Adherent bacterial cells (Panel B) form biofilms preferentially on inert surfaces or devitalized tissue, and these sessile communities are tolerant to antibodies, phagocytosis and antibiotics. Neutrophils (Panel C) are attracted to the biofilms, but cannot engulf biofilm. Neutrophils still release proteases and reactive oxygen species. Phagocytic enzymes (Panel D) damage tissue around the biofilm, and planktonic bacteria are released from the biofilm, causing dissemination and acute infection in neighboring tissue. Costerton, Stewart, Greenberg, Science 284, 1999

Low Protease Activity in Chronic Wound Fluids of Pressure Ulcers Predicts the Rate and Extent of Healing

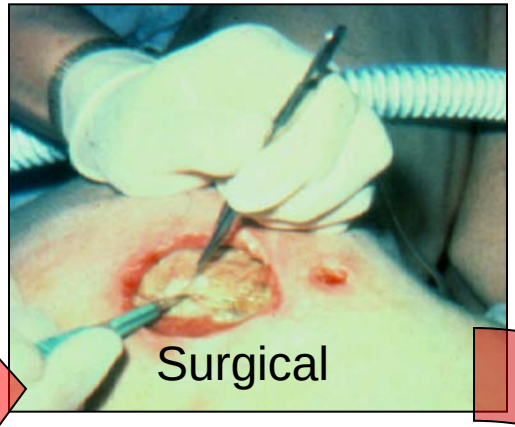


Ladwig, Robson, Liu, Kuhn, Muir, Schultz. Ratios of activated matrix metalloproteinase-9 to tissue inhibitor of matrix metalloproteinase-1 in wound fluids are inversely correlated with healing of pressure ulcers. **Wound Repair Reg** 10:26-37, 2002

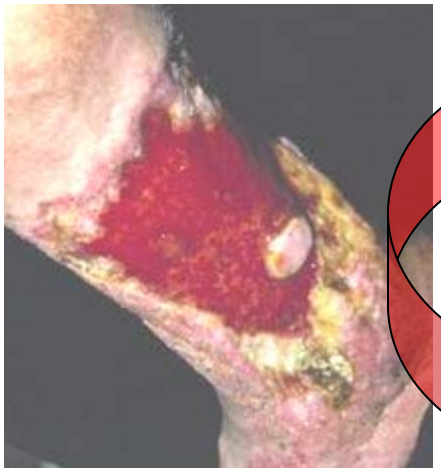
Wound Bed Preparation and ‘T I M E’

Tissue, Inflammation/Infection, Moisture, Edge

Tissue debridement

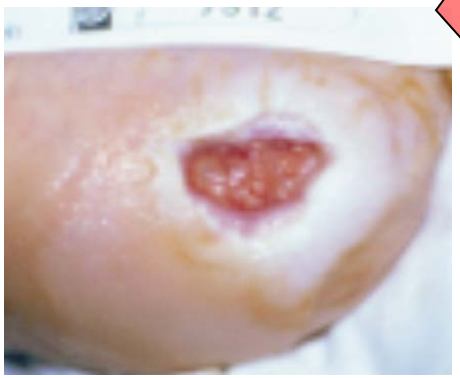


Epithelial Edge

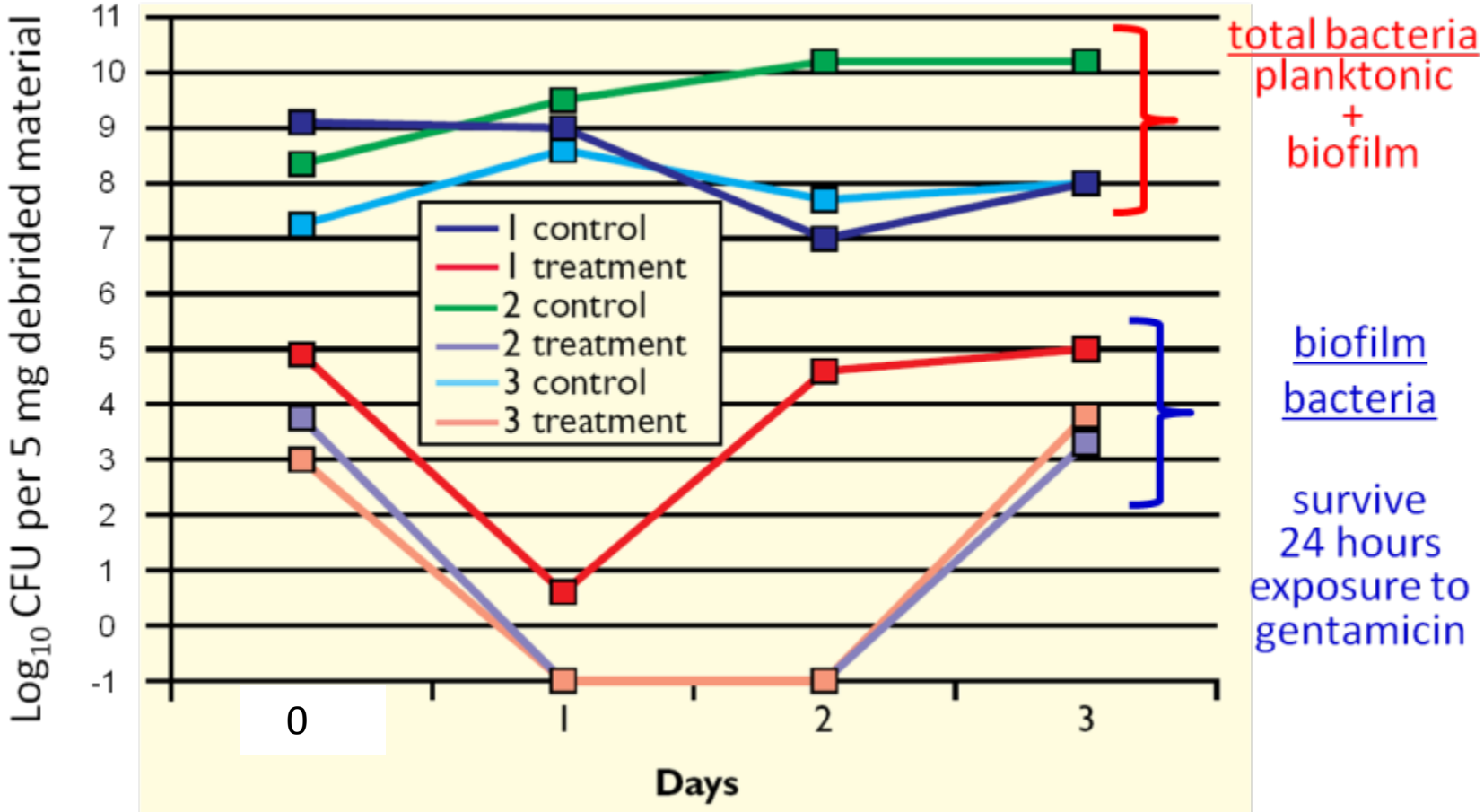


Infection/Inflammation

Moisture balance



Biofilm Maturity Studies Indicate Sharp Debridement Opens a Time-Dependent Therapeutic Window



Biopsies from three patients with large (>10 cm^2) venous ulcers were take at entry into the study and levels (CFUs) of total viable bacteria and biofilm bacterial were measured (day 0). Wounds were dressed with "non-bacterial barrier" dressings and new biopsies were collected on days 1, 2, and 3 at dressing changes. Total levels of bacteria at days 1, 2, and 3 after initial debridement remained consistently high, but by 3 days post-debridement, all three wounds had re-established substantial levels of biofilm bacteria (10^3 – 10^5 CFU/5 gm).

R.D. Wolcott, K.P. Rumbaugh, G. James, G. Schultz, P. Phillips, Q. Yang, C Watters, P.S. Stewart, S.E. Dowd, J Wound Care 19: 320-328, 2010.

SUMMARY

- Healing of acute healing wounds proceeds through four major sequential phases (hemostasis, inflammation, repair, and remodeling)
- Chronic wounds frequently have bacterial biofilms that cause elevated levels of pro-inflammatory cytokines, leading to chronic inflammation
- Elevated proteases from inflammatory cells destroy essential growth factors, receptors, and ECM proteins, impairing healing; POC detector for MMPs selects chronic wounds that respond to collagen/ORC dressing
- Debride biofilm and prevent reformation with "bacterial barrier dressings"
- Integrate "Biofilm Based Wound Care" with principles of Wound Bed Preparation