Wound Healing Physiology: Understanding the Basics So You Can Conquer the Complicated

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Disclosure

➢ NOTHING...
Definition: Wound

➢ Wound  [woond \ˈwʊnd, archaic or dialect ˈwaʊnd]
➢ Noun: an injury, usually involving division of tissue or rupture of the integument or mucous membrane, due to external violence or some mechanical agency rather than disease.
➢ Verb: to inflict a wound upon; injure; hurt.
Definition: Ulcer

- Ulcer [ul·cer \ˈəl-sər]
- Noun: a break in skin or mucous membrane with loss of surface tissue, disintegration and necrosis of epithelial tissue, and often pus
Wound Healing

- **Regeneration** - Partial thickness wounds
  - Returning injured tissue to the original structure and function

- **Repair** - Full thickness wounds
  - Replacement of destroyed tissue with scar tissue
  - Scar tissue
    - Composed primarily of collagen
    - Does not achieve the same function, structure or tensile strength as original tissue
Partial Thickness Wound Healing

➢ Regeneration
   - Wounding involves only epidermis and dermis
   - New tissue is same as original tissue in function and structure

➢ Epithelialization
   - Proliferation and lateral migration Epithelial Cells across surface of wound
Full Thickness Wound Healing

➢ Repair
  • Wounding involves TOTAL loss of epidermis & dermis, extends at least to subcutaneous tissue & may involved deeper tissues
  • New tissue is not the same as original tissue

➢ Phases of Wound Healing
  • Hemostatic, Inflammatory, Proliferative or Reconstructive, Remodeling or Maturation
  • Neutrophil, Macrophage, Fibroblast
Phases of Wound Healing

- Hemostatic (immediate)
- Inflammatory (immediate - 4 days)
- Proliferative or Reconstructive (4 days - 3 weeks)
- Remodeling or Maturation (3 weeks - 2 years)
**ECM** = extracellular matrix.

Hemostasis

- Hemostasis initiates entire wound healing cascade
- Tissue injury and vasculature disruption initiates coagulation, kinin, complement systems
- Exposure of blood to collagen activates coagulation factors & causes platelet aggregation
Hemostasis

- Production of Fibrin Clot
  - **Platelets** release growth factors/cytokines
  - Fibrin clot produces initial wound closure and prevents excess loss of blood & body fluids
- Initial period of brief tissue hypoxia
Plasma Protein Systems

- **Complement system**
  - destroy pathogens

- **Coagulation system**
  - clot formation

- **Kinin system**
  - dilation of blood vessels, pain, smooth muscle contraction, vascular permeability, and leukocyte chemotaxis
Coagulation

➢ Forms a fibrinous meshwork at an injured or inflamed site
  • Prevents the spread of infection
  • Keeps microorganisms and foreign bodies at the site of greatest inflammatory cell activity
  • Forms a clot that stops bleeding
  • Framework for repair and healing

➢ Fibrin
  • Insoluble protein
Inflammation

➢ Tissue injury and activation of Plasma Protein Systems
  • Release of vasoactive substances
  • Bradykinin, Histamine
  • Vascular dilatation and increase vessel permeability
    • Vasocongestion
    • Plasma leakage into surrounding tissues

➢ Neutrophils, Monocytes and Macrophages
  • Control bacterial growth and remove dead tissue
  • Release cytokines
Granulocytes (Polymorphonuclear leukocytes - PMN)
- Neutrophils
- Eosinophils
- Basophils

Agranulocytes
- Lymphocytes
- Monocytes
Neutrophils

➢ Predominate in early inflammatory responses
➢ Ingest bacteria, dead cells, and cellular debris
➢ Cells are short lived and become a component of the purulent exudate
Macrophage

- Derived from monocytes
- Phagocytose bacteria
- Break down necrotic tissue
- Director of healing
  - Produce growth factors/cytokines
  - Convert macromolecules into amino acids & sugars
  - Secrete lactate which stimulates fibroblasts to synthesize collagen
Cytokine [cy-to-kine/ (si´to-kīn”)]

- A generic term for nonantibody proteins released by one cell population on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response.

- Growth Factor

- Action and Function
  - Cell migration (chemotaxis)
  - Cell proliferation (mitosis)
  - Angiogenesis
  - Extracellular matrix production & degradation
Interleukins

Produced primarily by macrophages and lymphocytes in response to a pathogen or stimulation by other products of inflammation

- IL-1 is a proinflammatory cytokine
- IL-10 is an anti-inflammatory cytokine
Tumor Necrosis Factor

- TNF, TNF-α, cachexin, or cachectin
- Produced chiefly by activated macrophages
  - CD4+ lymphocytes, NK cells, neurons
- Cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction
- Primary role of TNF is in the regulation of immune cells
  - As an endogenous pyrogen, is able to induce fever, apoptotic cell death, sepsis (through IL1 & IL6), cachexia, inflammation, inhibit tumorigenesis and viral replication.
Cytokines & Inflammation
Cytokines & Inflammation

Image Source: www.jakpathways.com
Bioburden

Image Source: www.biologyexams4u.com
## Bioburden Battle

<table>
<thead>
<tr>
<th>Neutrophils Release</th>
<th>Organisms Produce</th>
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<tbody>
<tr>
<td>➢ Cytolytic enzymes</td>
<td>➢ Proteases and exotoxins</td>
</tr>
<tr>
<td>➢ Oxygen radicals</td>
<td>➢ Increased metabolic load</td>
</tr>
<tr>
<td>➢ Inflammatory mediators</td>
<td>➢ Cellular waste products</td>
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Matrix Metalloproteinases

- MMPs are zinc-dependent endopeptidases capable of degrading all kinds of extracellular matrix proteins.
- Play a major role on cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis, and host defense.
- More than 25 types:
  - Collagensases, Gelatinases, Stromelysins, Matrilysins
  - Membrane type

Endotoxins and Exotoxins

- Exotoxins are secreted by cells
  - botulinum toxin from clostridium
- Endotoxins are found in the outer membrane of gram-negative bacteria and are released only with cell lysis
  - Lipopolysaccharide (LPS) is prototype

Image Source: phagetherapylightandshade.blogspot.com
Biofilm

- Aggregate of colony forming microorganisms in which cells adhere to each other on a surface complex
- Synthesize and secrete a protective matrix of extracellular polymeric substance (EPS)
  - extracellular DNA, proteins, and polysaccharides
- Biofilms greatly enhance the tolerance of microorganisms embedded in the matrix to the immune system, antimicrobials and environmental (nutrients, hypoxia)
  - Blocking: diffusion barrier
  - Mutual Protection: protective enzymes or antibiotic binding proteins
  - Hibernation: bacterial quiescence

Biofilm

- Bacteria protected from topical agents
- Low oxygen in biofilm niches
- Impaired migration and proliferation of keratinocytes
- Bacteria protected from systemic antibiotics
- Host defenses unable to clear infection

Image Source: www.hypertextbookshop.com
Prolonged Inflammation

- Inflammation lasting 2 weeks or longer
- Often due to an unsuccessful acute inflammatory response
  - Poor tissue perfusion slows inflammatory response
  - Pro-inflammatory cytokines prolong inflammation
  - Oxygen-free radicals damage
  - Tissue ischemia impacts negatively, decreased bactericidal activity, diminished cellular migration

- Other causes of chronic inflammation:
  - High lipid and wax content of a microorganism
  - Bacterial ability to survive inside the macrophage
  - Toxins, Chemicals, particulate matter, or physical irritants
Clinical Manifestations

➢ Local

- Results from vascular changes and corresponding leakage of circulating components into the tissue
- Edema, Erythema, Warm, Exudate, Pain
Clinical Manifestations

➢ Systemic

- Fever
  - Exogenous (pathogens)
  - Endogenous pyrogens (cytokines, IL-1)
  - Act directly on the hypothalamus
- Leukocytosis
  - Increased numbers of circulating leukocytes, esp. neutrophils
  - “left shift” ratio of immature to mature neutrophils (bands)
- Increased plasma protein synthesis
  - Acute-phase reactants
  - IL-1, C-reactive protein, fibrinogen, etc
Proliferative Phase (Reconstructive)

- Fibroblast
- Granulation tissue
  - Neoangiogenesis
  - Collagen synthesis
- Contraction
- Epithelialization
Granulation Tissue

- Neoangiogenesis
  - Capillary proliferation in response to oxygen gradient between hypoxic wound and vascularized periphery
  - Angiogenic factors secreted by macrophage are chemoattractants for endothelial cells

- Collagen Synthesis – Fibroblast
  - Extracellular matrix (ECM) is composed of an interlocking mesh of fibrinous proteins and glycosaminoglycans (GAGs)
Fibroblasts

- Responsible for collagen synthesis and ECM production
- Originate from perivascular cells
- Migration & proliferation occur in response to cytokines
- Must be stimulated to synthesize collagen
  - lactate & ascorbate
  - activate enzymes
- Collagen synthesis peaks at day 6-7
  - Prolonged in wounds healing by secondary intention
Extracellular matrix (ECM)

- Fibrinous Proteins
  - Collagen, Elastin, Fibronectin, Laminin
  - Proteins and Glycoproteins
- Glycosaminoglycans (GAGs)
  - Proteoglycans
  - Heparan sulfate, Chondroitin sulfate, Keratan sulfate
- Non-proteoglycan polysaccharide
  - Hyaluronic acid
Collagen

- Main component of connective tissue
- Most abundant protein in mammals
  - 25% to 35% of the whole-body protein content
- Procollagen precursor - lycine and proline
- Hydroxylation of lysine and proline amino acids is dependent on ascorbic acid (Vitamin C) as a cofactor
Collagen

➢ 90% of the collagen in the body is type I
➢ 28 types of collagen have been identified
➢ Five most common types are:
  • Collagen I: skin, tendon, vascular ligature, organs, bone (main component of the organic part of bone)
  • Collagen II: cartilage (main component of cartilage)
  • Collagen III: reticulate (main component of reticular fibers), commonly found alongside type I
  • Collagen IV: forms bases of cell basement membrane
  • Collagen V: cell surfaces, hair and placenta
Contraction

- Contraction
  - occurs concurrently with granulation
  - reduces scar tissue needed for repair

- Myofibroblasts
  - actin rich cells synthesize & pull collagen fibers to cell body by pseudopodia
  - Location mobility limits contraction forces
Epithelialization

- Migration of epithelial cells from wound edges to resurface defect
- Concurrent with collagen synthesis
- Moist granulation bed
- Limit to epidermal migration of 3cm
- Rolled edges create non-proliferative edge
Chronic Wound Compromise

Stagnation between Inflammatory-Proliferative Phase

- Activity of matrix proteases perpetuated
  - Increased proinflammatory cytokines
  - Increased tissue inhibitors of metalloproteinases (TIMP)
- Fibronectin partially degraded
- Lowered growth factor levels in wound fluid
- Increased bacteria
- Delayed keratinocyte migration
Remodeling or Maturation

- Simultaneous process of collagen lysis & synthesis
- Mediated by macrophages
- Disorganized collagen replaced mature Type I fibers
- Aligned along mechanical stress points
- Tensile strength
  - 30% by 3 weeks
  - 60% by 6 weeks
  - 80% by 9 months
Dysfunction

- Impaired epithelialization
  - Anti-inflammatory steroids, hypoxemia, and nutritional deficiencies
- Impaired collagen matrix assembly
  - Keloid scar
  - Hypertrophic scar
- Impaired contraction
  - Tissue contracture
Wound Chronicity

- Deviation from the expected sequence of repair in terms of time, appearance and response to aggressive and appropriate treatment
- Prolonged inflammation is believed to be the most significant factor in delayed wound healing
- May lack the cardinal signs of inflammation
- Chronic wounds can be compromised also by internal and/or external barriers to healing
- May be unable to progress through the phases of healing without intervention
Age Related Changes

**Neonates**
- Transiently depressed inflammatory and immune function
- Neutrophils are not capable of efficient chemotaxis
- Neonates express complement deficiency

**Elders**
- Impaired inflammation due to chronic illness
  - Diabetes, cardiovascular disease, etc.
- Chronic medication intake decreases inflammatory response
- Healing response is diminished due to loss of the regenerative ability of the skin
- Infections more common
Intrinsic Barriers

- Compromised nutritional status
- Inadequate hydration
- Uncontrolled glucose levels
- Multi-system failure
- Obesity
- Immunosuppression
- Malignancy
- Medications that interfere in cellular functioning and wound healing physiology
Extrinsic Barriers

- Medication
- Infection
- Debris & Necrotic Tissue
- Aging process
- Smoking/tobacco use
- Iatrogenic factors affecting wound management; inappropriate treatment
- Failure to maintain a clean, moist wound environment conducive to healing
Principles of Wound Healing

➢ Classification of Wound
  • Etiology
  • Appearance

➢ Appropriate Management Algorithms
  • Control or eliminate compromising factors

➢ Provide Optimal Wound Environment
  • Basic wound care

➢ Support the Patient
WOUND CLASSIFICATION guides Treatment and Management
Wound Classification Guides Treatment & Management

➢ Etiology
  ➢ Provides an algorithm or strategy for the global management of the patient, with the ultimate goal of achieving wound healing

➢ Appearance
  ➢ Generally guides the wound care management regarding the use of topicals and dressings
Wound Classification
Based on Wound Etiology

➢ Pressure
➢ Venous
➢ Diabetic
➢ Surgical
➢ Arterial
➢ Atypical
Common Wound Etiologies

- 90% of All Wounds
  - Pressure
  - Venous
  - Arterial
  - Diabetic
  - Surgical
- Atypical Wound less than 10% of all wounds
Wound Classification Guides Treatment & Management

➢ Etiology

➢ Provides an algorithm or strategy for the global management of the patient, with the ultimate goal of achieving wound healing
Pressure Ulcer
Pressure Ulcer

A pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated.

Pressure Ulcer

- Soft tissue is compressed.
- Circulation becomes impaired, depriving the tissue of oxygen and nutrients which results in tissue death.
- Injury begins in deep tissues…
Pressure Ulcer

Treatment

- Pressure Relief – Redistribution
- Minimize Sheer and Friction
- Nutritional Support
- Management of Incontinence
Arterial Ulcer
Arterial Ulcers

➢ Due to thickening, hardening and loss of elasticity of the walls of arteries resulting in decreased blood flow and tissue perfusion
Arteriosclerosis

Arteriolosclerosis
- thickening of the walls, affecting mainly the arterioles, seen especially in chronic hypertension
Arteriosclerosis

- Atherosclerosis
  - the most common type, plaques of fatty deposits form in the inner layer (tunica intima) of the arteries
Arterial Ulcers

- All forms of arteriosclerosis may be present in the same patient, but in different blood vessels
- Arterial ulcers are frequently located on the lower leg, the foot or the toes
Arterial Ulcers Treatment

- Vascular Diagnostics
- Risk Factor Modification
- Exercise Therapy
  - Pharmacotherapeutics
- Endovascular Intervention
- Surgical Revascularization
- Adjunctive Management
  - Hyperbaric Oxygen Therapy
  - Arterial Assist devices
Venous Ulcer
Venous Ulcer

- The valves in the veins of the leg do not function properly and venous blood does not completely leave the veins, resulting in venous hypertension.
  - Congenital, History of DVT
Venous Ulcer

- The valves in the veins of the leg do not function properly and venous blood does not completely leave the veins, resulting in venous hypertension.
  - Congenital, History of DVT
- Fluid leaks from the vessels and forms edema in the tissue.
- The swelling and tissue pressure that results causes ulceration, usually located on the ankle or calf.
Venous Ulcer Treatment

➢ Compression Therapy
  • Graduated Compression Wraps
  • Short Flex Dressings
➢ Segmental External Compression Devices
➢ Venous Ablation (EVLT)
➢ Subfascial Endoscopic Perforating Vein Surgery (SEPS)
Diabetic Ulcer
Neuropathic
Diabetic Neuropathy

- Results from damage to peripheral nerves causing decreased sensation which allows for undetected and inappropriate pressure, or trauma to the plantar surface of the foot.
Diabetic Ulcer Treatment

- Offloading
- Glycemic Control
- Bioburden Reduction
- Arterial Vascular Assessment
Surgical Wound
Surgical Wound

➢ Primary Intention
  • closed through (staples, sutures)
  • 3-5% wound dehiscence

➢ Secondary Intention
  • wounds left open due to contamination or infection
  • connective tissue must fill in the defect
Surgical Wound Treatment

- Postoperative and Peri-operative Care
- Management of Chronic and Acute Diseases
- Nutritional Support
- Management of Fluid and Electrolytes
- Moist Wound Healing Protocols/Devices
- Reduction of Wound Bioburden
Wound Classification Guides Treatment & Management

➢ Etiology
  ➢ Provides an algorithm or strategy for the global management of the patient, with the ultimate goal of achieving wound healing

➢ Appearance
  ➢ Generally guides the wound care management regarding the use of topicals and dressings
  ➢ Débridement decisions
Wound Classification
Based on Wound Appearance

➢ Necrotic

➢ Infected

➢ Draining

➢ Granular
Necrotic
Necrosis

➢ a form of cell injury that results in the premature death of cells in living tissue by autolysis

Necrotic Wounds

- Dead, avascular tissue.
- May appear black, gray, yellow, or tan in color.
- Staging and depth determinations often cannot be accomplished until the wound is débrided to a viable tissue base.
Necrotic Wound Treatment

➢ Debridement
  • Soften and remove the necrotic tissue

➢ Control Infection
  • Decrease bioburden (colonization)
  • Appropriate utilization of antimicrobials
    • Topical
    • Local
    • Systemic
Infected
Infected Wounds

➢ All wounds are contaminated… But not all wounds are necessarily infected.
Infected Wound Treatment

- Debridement
- Decrease bioburden/biofilm
  - Wound Cleansing
- Control Infection
  - Parenteral antibiotics
  - Topical antimicrobial

AHRQ: “Institute appropriate systemic antibiotic therapy for patients with bacteremia, sepsis, advancing cellulitis, or osteomyelitis. Systemic antibiotics are not required for [wounds] with only clinical signs of local infection.”
Draining
Draining Wounds

➢ Excessive Drainage or Exudate
  ➢ Transudate
  ➢ Exudate
  ➢ Lymphatic
Draining Wound Treatment

- Control and Absorb
  - prevent the drainage as much as possible
- Protect the Periwound
  - prevent maceration
- Consider the Possibility of Bacterial Colonization
Granular
Granular Wounds

- Red Wounds with a “beefy” Appearance
  - Angiogenesis
  - Granulation Tissue
- Suggests Proliferative Phase of Healing
  - Growth of small blood vessels and connective tissue in a full thickness wound
Granular Wounds

➢ Treatment

➢ Provide a balanced moist wound environment
➢ Prevent hemagglutination
➢ Control and prevent bioburden/biofilm
Wound Management Based on Wound Etiology

- Pressure
- Venous
- Diabetic
- Surgical
- Arterial

- Pressure Redistribution
- Compression
- Offload
- Moisture Balance
- Revascularization
Wound Management
Based on Wound Appearance

➢ Necrotic

➢ Infected

➢ Draining

➢ Granular

Debridement

Control Bioburden

Absorption

Moisture Balance
Thank You!