WOUND HEALING

SUWITRA
HISTORY OF WOUND HEALING

• 2000B.C. by Sumerians
  – Spiritual method: Incantation.

• Egyptians:
  – Infected & disease wound VS Noninfected wound.

• 1650B.C.Edwin Smith Surgical Papyrus:
  – Describes at least 48 different types of wounds.

• 1550B.C.Ebers Papyrus:
  – ATB properties: Honey.
  – Absorbent properties: Lint
  – Barrier: Grease
HISTORY OF WOUND HEALING

- The Greeks: Acute or chronic wound.
- Galan (120-201 A.D.):
  - Maintaining moist ensure adequate healing.
- Ignaz Philipp Semmelweis: (1818-1865)
  - Decrease incidences of puerperal fever when wash hand with soap & hypochlorite.
- Louis Pasteur (1822-1895):
  - Dispelling Theory of germ.
- Joseph Lister (1865):
  - Using of phenol for soaking instruments & spraying OR, reduce mortality rate from 50 to 15%.
HISTORY OF WOUND HEALING

- Wood Johnson (1876):
  - Antiseptic dressing (cotton gauze impregnated with iodoform).

- The 1960s and 1970s:
  - Developing of polymeric dressing
    - Permeability to gases (occlusive vs semiocclusive).
    - Varying degrees of absorbency.
    - Different physical form.

- Currently: For optimal wound healing.
  - Inflammatory cytokines.
  - Growth factors.
  - Bioengineered tissue.
Phases of Wound Healing

- Hemostasis and Inflammation
- Proliferation
  - Matrix Synthesis
- Maturation and Remodeling
  - Epithelialization
  - Role of GF in Normal wound healing
  - Contraction
Hemostasis and Inflammation

- Hemostasis releases chemotactic factors from the wound site initiating inflammation.
- Wounded tissue directly exposes the ECM to platelets -> plt aggregation, degranulation, activation of coagulation cascade.
- Plt α granules – PDGF, TGF-β, PAF, fibronectin, serotonin.
Inflammation

Fibrin clot-assists influx of PMNs/monocytes

– PMNs-1st to arrive, peak 24-48h,

- Vasc permeability, local PG rease, chemoattractants (complement factors, IL-1, TNF-α, TGF-β, PF4)
- Phagocytosis of bacteria & tissue debris
- Secrete TNF-α which angiogenesis & collagen synthesis
- Release proteases (collagenases) which degrade matrix and ground substance in early wound healing
- May delay epithelial closure by neutrophil factors
Inflammation

- Macrophages – peak 48-96h
  - Phagocytosis, O2 radical & nitric oxide.
  - Activation & recruitment of other cells (cytokines, GF, cell-cell, IAM)
  - Regulate cell proliferation, matrix synth, angiogenesis (via TGF-β, VEGF, IGF, EGF)
Inflammation

- T lymphocyte – peak 1 week
  - Bridging from inflammatory to proliferative phase.
  - The role is not fully defined.
    - Moduration of the wound environment.
    - Depletion: decrease strength & collagen.
  - Downregulating effect on fibroblast collagen synthesis (IL-1, TNF-α, interferon grammar)
Proliferation

- Days 4-12
- PDGF recruits fibroblasts which proliferate
  - Assist in matrix/collagen synthesis and remodeling
- Lactate: collagen synthesis
- Endothelial cells proliferate
  - Migrate from nearby intact venules
  - Angiogenesis of capillaries
  - Regulated by cytokines/GFs (VEGF, TNF-α, TGF-β)
Matrix Synthesis

- Collagen- wound repair types I & III
- Type I – prominent in skin ECM
- Type III – skin, esp during repair
Collagen Synthesis

- Glycine q3 aa
- 2nd position: Pro or Lys
- mRNA -> 1000 aa protocollagen
- In E.R.
  - Hydroxylation of Pro/Lys
    - Prolyl hydroxylase requires: O2, Fe, ascorbic acid, α-ketoglutarate
  - Glycosylation (Glc, Galactose) of hydroxylysine
  - Steric changes cause an α-helix to form
- 3 entwining α-helices -> rt-handed superhelix = procollagen
Collagen Synthesis

- Covalent cross-linking of Lys and after cleavage of terminal registration peptides
- Postranslational modifications require
  - Adequate oxygenation
  - Good nutritional status (aa, carbs)
  - Cofactors (vitamins, trace minerals)
  - Healthy local environment (good vascularity, no infection)
Proteoglycans

- Glycosaminoglycans form the “ground substance” of granulation tissue
- Glycosaminoglycans + proteins = proteoglycans
  - Dissacharide units
    - Length varies (10 units = heparin, 2000 u = hyaluronic acid)
- In wounds, fibroblasts synthesize dermatan and chondroitin sulfate
  - Increase during the first 3 wks
  - Lattice is used to assemble collagen fibrils/fibers
  - Amount of proteoglycan sulfation determines collagen configuration
  - Incorporated into collagen scar tissue
  - Amount in scar tissue decreased with maturation and remodeling
Maturation and Remodeling

- Wound strength depends upon the quality and quantity of deposited collagen
- Early matrix – fibronectin and collagen type III
- Fibroplastic phase – reorganization of collagen
  - Collagenolysis by collagenase – a matrix metalloproteinase (MMPs)
- Second matrix – glycosaminoglycans and proteoglycans
- Final matrix – collagen type I
  - Deposited over several weeks, but tensile strength increases over months
Maturation and Remodeling

- **Fibril formation & cross-linking** ->
  - Decrease collagen solubility
  - Increase strength
  - Increase resistance to enzymatic degradation of matrix

- **Remodeling 6- 12 wks**
  - Cytokines & GF control Synth & lysis
  - Resulting scar are avascular, mature, acellular ECM
  - Mechanical strength never reaches preinjury levels
Epithelialization

- Day 1 – proliferation and migration of epith cells adjacent to wound
- Marginal basal cells lose their dermal attachment, enlarge, flatten, and migrate across the matrix (leapfrog) to cover the defect
- Fixed marginal basal cells undergo rapid mitosis
- Once covered, epith cells become more columnar, increase mitotic activity and reestablish the layered epithelium
- Eventual keratinization
- In 48 hours
Role of Growth Factors

- GF and cytokines stimulate migration, proliferation, and function of cells during wound healing
- Act in many ways: autocrine, paracrine, endocrine
- Effected by timing, concentration and receptor binding
- Having divergent actions on different cells
- Cell->phosphorylation / dephosphorylation (phosphatase/kinase)-> activate/deactivate prot. in cytosol/nucleus
- Stop by Receptor-ligand complex
Wound Contraction

- All wounds contract
- Myofibroblasts contain $\alpha$-smooth muscle actin in thick bundles called stress fibers
  - May be responsible for contraction
  - Increases from day 7-21, fades after 4 wks
- Movement & reorganization of skeleton -> contraction
Connective Tissue Disorders

- **Ehlers-Danlos** – 10 disorders, defect in collagen formation
  - Thin, friable skin, prominent veins, easy bruising, poor wound healing, abnormal scar formation, recurrent hernias, hyperextensible joints, decreased coagulation, intestinal diverticulae, rectal prolapse, aneurysms, AV-fistulas, varicosities
  - Children: Recurrent hernias & coagulopathy (esp. plt abnormality & low factor level)
  - Difficult to suture vessels; recurrent hernias, thin transversalis fascia so mesh may lower recurrence rate

- **Marfan Syndrome** – defect in fibrillin (assoc with elastic fibers)
  - Tall stature, arachnodactyly, lax ligaments, hyper extensible skin, myopia, scoliosis, pectus excavatum, ascending aortic aneurysm, prone to hernias
  - Genetic defect in extracellular prot.& fibril
  - Aortic aneurysm repair is difficult 2’ to soft tissue, normal wound healing

- **Osteogenesis Imperfecta** – collagen Type I mutation, 4 subtypes
  - Osteopenia/brittle bones, low muscle mass, hernias, lax ligaments, dermal thinning, increased bruising, normal scarring, blue sclera
  - Mutation of type I collargen
<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild bone fragility, blue sclera</td>
<td>Dominant</td>
</tr>
<tr>
<td>II</td>
<td>“Prenatal lethal”; crumpled long bones, thin ribs, dark blue sclera</td>
<td>Dominant</td>
</tr>
<tr>
<td>III</td>
<td>Progressively deforming; multiple fractures; early loss of ambulation</td>
<td>Dominant/recessive</td>
</tr>
<tr>
<td>IV</td>
<td>Mild to moderate bone fragility; normal or gray sclera; mild short stature</td>
<td>Dominant</td>
</tr>
</tbody>
</table>
Connective Tissue Disorders

- Epidermolysis Bullosa – defect in tissue adhesion
  - 3 subtypes: simplex (epidermis), junctional (basement membrane), dystrophic (dermis)
  - Tissue separation and blistering
  - Oral erosions and esophageal obstruction cause poor nutrition
  - Esophageal dilations, G-tube, nonadhesive dressings

- Acrodematitis Enteropathica – inability to absorb zinc via cell surface binding and cellular translocation, autosomal recessive
  - Zinc is a cofactor for DNA polymerase, RT (inhibit proliferation)
  - Impaired granulation tissue formation, erythematous pustular dermatitis
  - Oral supplementation (100-400mg) is curative for impaired wound healing
GI Tissue Healing

• Surgical reanastamosis with sutures or staples
• Failure of healing – dehiscence, leak, fistula
• Excessive healing – stricture, stenosis
• Submucosa provides highest tensile strength &suture-holding capacity
• Serosa provides a watertight seal via a fibrin seal
GI Tissue Healing

- Serosa/mucosa heals without scarring
- Decrease in strength during wk1 due to collagenolysis, collagenase colon > sm. int
- Anastamosis should be tension-free, good blood supply, adequate nutritional status, no sepsis
Bone Wound Healing

1. injury -> hematoma
2. liquefaction, degradation of nonviable products, revascularization of nearby normal bone = inflammation, erythema, edema
3. 3-4d post injury soft tissue fibrocartilaginous callus bridges fractured bone segments = internal splint
4. hard callus – mineralization of the soft callus and conversion to bone, 2-3 mos
5. remodeling/reabsorption of hard callus, marrow cavity is recanalized
Cartilage Wound Healing

- Cartilage is an avascular ECM of proteoglycans, collagen fibers, and water
- Nutrients diffuse from a hypervascular perichondrium
- Injury to cartilage have poor healing
  - Superficial – disruption of ECM, injur chondrocytes – no inflammation, ↑ synth of proteoglycans&collagen, poor regeneration
  - Deep – involve underlying bone&tissue. Hemorrhage initiates inflammation and cellular repair. Fibroblasts migrate across granulation tissue to fill defects which are eventually undergo chondrification and hyaline cartilage is formed
Tendon Wound Healing

- Tendons/ligaments – parallel bundles of collagen interspersed by spindle cells
- Healing:
  - 1. hematoma
  - 2. organization,
  - 3. laying down ECM (collagen types I & III)
  - 4. scar formation
- Hypovascular tendons heal with less motion and more scarring
- Mechanical integrity may never reach pre-injury levels
Nerve Wound Healing

- **Nerve injury** –
  - neurapraxia (focal demylenation)
  - axonotmesis (disrupted axonal continuity with maintenance of Schwann cell basal lamina)
  - neurotmesis (transection)

- **Healing** –
  1. survival of axonal cell bodies
     - Wallerian degeneration – phagocytosis of degenerating axons/sheath from the distal stump
  2. regeneration of axons from the proximal stump, remyelination
  3. migration/connection of regenerating ends to targets
Fetal Wound Healing

- No scar formation until 3rd trimester
- Environment: sterile, temperature stable, fluid
- Inflammation: reduced 2° immaturity of immune system = no scarring
- Growth Factors: absence of TGF-β
- Matrix: excessive and extended hyaluronic acid production by fibroblasts (stimulated by fetal urine components)
Wound Healing

Schwartz’s Principles of Surgery 9th edition
Anuchit Lerstsirithong MD.

Laparoscopic Surgery:
Leading the Way to the Future of Colon Surgery

ColorSurgery.com
Classification of Wounds

- Acute wounds
  - Predictable manner and time frame
  - The end result is a well-healed wound

- Chronic wounds
Classification of Wounds

- Primary intention
- Secondary intention
- Tertiary intention
Classification of Wounds

- **Primary Intention**
  - Epithelialization
  - Connective Tissue Repair

- **Secondary Intention**
  - Contraction
  - Epithelialization

- **Tertiary Intention**
  - Contraction
  - Connective Tissue Repair
Classification of Wounds

• Normal Healing
  ➢ A constant and continual increase that reaches a plateau at some point postinjury

• Delayed Healing
  ➢ Decreased wound-breaking strength in comparison to wounds that heal at a normal rate

• Impaired Healing - Chronic
  ➢ A failure to achieve mechanical strength equivalent to normally healed wounds
Classification of Wounds

- Normal healing
- Delayed healing
- Impaired healing - chronic

Wound mechanical strength vs. time
Factors Affecting Wound Healing

• **Systemic**
  - Age
  - Nutrition
  - Trauma
  - Metabolic diseases
  - Immunosuppression
  - Connective tissue disorders
  - Smoking
Factors Affecting Wound Healing

• **Local**
  - Mechanical injury
  - Infection
  - Edema
  - Ischemia/necrotic tissue
  - Topical agents
  - Ionizing radiation
  - Low oxygen tension
  - Foreign bodies
Factors Affecting Wound Healing

**Advanced Age**

- Aging produces intrinsic physiologic changes that result in delayed or impaired wound healing

- Studies of hospitalized surgical patients show a direct correlation between older age and poor wound healing outcomes such as dehiscence and incisional hernia
Factors Affecting Wound Healing

**Advanced Age**

- These statistics fail to take into account underlying illnesses or diseases as a possible source of impaired wound healing in the elderly

- However, more recent clinical experience suggests that major operative interventions can be accomplished safely in the elderly
Factors Affecting Wound Healing

**Advanced Age**

- In healthy human volunteers there was a significant delay of 1.9 days in the epithelialization of superficial skin defects in those older than 70 years of age

- No difference in DNA or hydroxyproline wound accumulation
Factors Affecting Wound Healing

**Advanced Age**

- The young volunteers had a significantly higher amount of total -amino nitrogen in their wounds.

- Non-collagenous protein accumulation at wounded sites is decreased with aging.
Hypoxia, Anemia, and Hypoperfusion

- Low oxygen tension has a profoundly deleterious effect on all aspects of wound healing

- Optimal collagen synthesis requires oxygen as a cofactor, particularly for the hydroxylation steps
Hypoxia, Anemia, and Hypoperfusion

- Increasing FiO$_2$ during and immediately after surgery → ↑collagen deposition + ↓rates of wound infection after elective surgery

- Major factors affecting local oxygen delivery include hypoperfusion either for systemic reasons or due to local causes
Hypoxia, Anemia, and Hypoperfusion

- The level of vasoconstriction is exquisitely responsive to fluid status, temperature, and hyperactive sympathetic tone as is often induced by postoperative pain.

- Mild to moderate normovolemic anemia does not appear to adversely affect wound oxygen tension and collagen synthesis, unless the hematocrit falls below 15%.
Factors Affecting Wound Healing

Steroids and Chemotherapeutic Drugs

- Large doses or chronic usage of glucocorticoids reduce collagen synthesis and wound strength

- The major effect of steroids is to inhibit the inflammatory phase of wound healing and the release of lysosomal enzymes
Factors Affecting Wound Healing

**Steroids and Chemotherapeutic Drugs**

- Steroids used after the first 3 to 4 days postinjury do not affect wound healing as severely as when they are used in the immediate postoperative period.

- Steroids also inhibit epithelialization and contraction and contribute to increased rates of wound infection, regardless of the time of administration.
Factors Affecting Wound Healing

Steroids and Chemotherapeutic Drugs

- Steroid-delayed healing of cutaneous wounds can be stimulated to epithelialize by topical application of vitamin A.

- Collagen synthesis of steroid-treated wounds also can be stimulated by vitamin A.
Factors Affecting Wound Healing

**Steroids and Chemotherapeutic Drugs**

- All chemotherapeutic antimetabolite drugs adversely affect wound healing by inhibiting early cell proliferation and wound DNA and protein synthesis.

- Delay in the use of such drugs for about 2 weeks postinjury appears to lessen the wound healing impairment.
Factors Affecting Wound Healing

**Metabolic Disorders**

- DM is the best known of the metabolic disorders contributing to increased rates of wound infection and failure
Factors Affecting Wound Healing

Metabolic Disorders

- Uncontrolled diabetes results in
  - ↓ Inflammation
  - ↓ Angiogenesis
  - ↓ Collagen synthesis
  - ↓ Granulocyte function
  - ↓ Capillary ingrowth
  - ↓ Fibroblast proliferation
**Factors Affecting Wound Healing**

*Metabolic Disorders*

- Insulin restores collagen synthesis and granulation tissue formation to normal levels if given during the early phases of healing.

- Type I diabetes mellitus was noted to decrease wound collagen accumulation in the wound, independent of the degree of glycemic control.
**Metabolic Disorders**

- Type II diabetic patients showed no effect on collagen accretion when compared to healthy, age-matched controls.

- The diabetic wound appears to be lacking in sufficient growth factor levels, which signal normal healing.
Factors Affecting Wound Healing

Metabolic Disorders

- Careful preoperative correction of blood sugar levels improves the outcome of wounds in diabetic patients

- Increasing the inspired oxygen tension, judicious use of antibiotics, and correction of other coexisting metabolic abnormalities all can result in improved wound healing
Factors Affecting Wound Healing

**Metabolic Disorders**

- Uremic animals demonstrate decreased wound collagen synthesis and breaking strength

- The clinical use of dialysis to correct the metabolic abnormalities should impact greatly on the wound outcome of such patients
Factors Affecting Wound Healing

**Nutrition**

- Poor nutritional intake or lack of individual nutrients significantly alters many aspects of wound healing.

- Experimental rodents fed either a 0 or 4% protein diet have impaired collagen deposition with a secondary decrease in skin and fascial wound-breaking strength and increased wound infection rates.
Factors Affecting Wound Healing

**Nutrition**

- Induction of energy-deficient states by providing only 50% of the normal caloric requirement leads to decreased granulation tissue formation and matrix protein deposition in rats.

- Acute fasting in rats markedly impairs collagen synthesis while decreasing procollagen mRNA.
Factors Affecting Wound Healing

**Nutrition**

- Malnutrition correlates clinically with enhanced rates of wound complications and increased wound failure after diverse surgical procedures

- Impaired healing response as well as reduced cell-mediated immunity during protein-calorie malnutrition
Factors Affecting Wound Healing

Effect of malnutrition on collagen deposition in experimental human wounds. OHP = hydroxyproline.

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Factors Affecting Wound Healing

Nutrition

- Arginine deficiency results in decreased wound-breaking strength and wound collagen accumulation in chow-fed rats

- Rats that are given 1% arginine HCl supplementation, and are therefore not arginine-deficient, have enhanced wound-breaking strength and collagen synthesis when compared to chow-fed controls
Factors Affecting Wound Healing

**Nutrition**

- Young, healthy, human volunteers were found to have significantly increased wound collagen deposition after oral supplementation with arginine daily for 14 days.

- Healthy older humans, daily supplements arginine for 14 days resulted in significantly enhanced collagen and total protein deposition at the wound.
Nutrition

- Arginine supplementation had no effect on the rate of epithelialization of a superficial skin defect.

- Suggests that the main effect of arginine on wound healing is to enhance wound collagen deposition.
Factors Affecting Wound Healing

**Nutrition**

- Vitamin C deficiency, leads to a defect in wound healing, particularly via a failure in collagen synthesis and cross-linking.

- Vitamin C deficiency has also been associated with an increased incidence of wound infection, and if wound infection does occur, it tends to be more severe.
Factors Affecting Wound Healing

**Nutrition**

- The recommended dietary allowance is 60 mg daily.

- In severely injured or extensively burned patients this requirement may increase to as high as 2 g daily.
Nutrition

- Vitamin A increases the inflammatory response in wound healing, probably by increasing the lability of lysosomal membranes.

- Vitamin A directly increases collagen production and epidermal growth factor receptors when it is added in vitro to cultured fibroblasts.
Factors Affecting Wound Healing

**Nutrition**
- In the severely injured patient, supplemental doses of vitamin A have been recommended.
- Doses ranging from 25,000 to 100,000 IU per day have been advocated.
Nutrition

- Zinc is the most well-known element in wound healing and has been used empirically in dermatologic conditions for centuries.

- With zinc deficiency there is decreased fibroblast proliferation, decreased collagen synthesis, impaired overall wound strength, and delayed epithelialization.
Factors Affecting Wound Healing

**Nutrition**

- To date, no study has shown improved wound healing with zinc supplementation in patients who are not zinc deficient.
Infections

- Infections can weaken an abdominal closure or hernia repair and result in wound dehiscence or recurrence of the hernia

- Cosmetically, infections can lead to disfiguring, unsightly, or delayed closures
Factors Affecting Wound Healing

Infections

- Antibiotic prophylaxis is most effective when adequate concentrations of antibiotic are present in the tissues at the time of incision, and assurance of adequate preoperative antibiotic dosing and timing has become a significant hospital performance measure.
Factors Affecting Wound Healing

**Infections**

- Addition of antibiotics after operative contamination has occurred is clearly ineffective in preventing postoperative wound infections
Infections

- Repeat dosing of antibiotics when

  ✓ Durations exceeding the biochemical half-life \((t_{1/2})\) of the antibiotic

  ✓ Large-volume blood loss and fluid replacement
Factors Affecting Wound Healing

Infections

➢ Additional doses of antibiotic may be administered for 24 hours

 ✓ Prosthetic implants are used

 ✓ Unexpected contamination is encountered
# Factors Affecting Wound Healing

## Table 9-7 Antimicrobial Prophylaxis for Surgery

<table>
<thead>
<tr>
<th>Nature of Operation</th>
<th>Common Pathogens</th>
<th>Recommended Antimicrobials</th>
<th>Adult Dosage before Surgery&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td><em>Staphylococcus aureus, S. epidermidis</em></td>
<td>Cefazolin or</td>
<td>1–2 g IV&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefuroxime or</td>
<td>1.5 g IV&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g IV</td>
</tr>
<tr>
<td>GI, esophageal, gastroduodenal</td>
<td>Enteric gram-negative bacilli, gram-positive cocci</td>
<td>High risk&lt;sup&gt;d&lt;/sup&gt; only: cefazolin</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>Enteric gram-negative bacilli, enterococci, clostridia</td>
<td>High risk&lt;sup&gt;e&lt;/sup&gt; only: cefazolin</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Enteric gram-negative bacilli, anaerobes, enterococci</td>
<td>Oral: neomycin + erythromycin base&lt;sup&gt;f&lt;/sup&gt; or metronidazole&lt;sup&gt;f&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Appendectomy, nonperforated&lt;sup&gt;h&lt;/sup&gt;</td>
<td>—</td>
<td>Parenteral: cefoxitin&lt;sup&gt;g&lt;/sup&gt; or</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefazolin +</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metronidazole&lt;sup&gt;g&lt;/sup&gt; or</td>
<td>0.5 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ampicillin/sulbactam</td>
<td>3 g IV</td>
</tr>
</tbody>
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## Factors Affecting Wound Healing

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<tbody>
<tr>
<td>Genitourinary†</td>
<td>—</td>
<td>High risk only: ciprofloxacin</td>
<td>500 mg PO or 400 mg IV</td>
</tr>
<tr>
<td>Gynecologic and obstetric</td>
<td>Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci</td>
<td>Cefoxitin&lt;sup&gt;g&lt;/sup&gt; or cefazolin&lt;sup&gt;g&lt;/sup&gt; or Ampicillin/sulbactam&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td>Vaginal, abdominal, or laparoscopic hysterectomy</td>
<td>Same as for hysterectomy</td>
<td>Cefazolin&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3 g IV</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>Same as for hysterectomy</td>
<td>First trimester, high risk&lt;sup&gt;†&lt;/sup&gt;: aqueous penicillin G or Doxycycline</td>
<td>1–2 g IV after cord clamping</td>
</tr>
<tr>
<td>Abortion</td>
<td>Same as for hysterectomy</td>
<td>Second trimester: cefazolin&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2 million units IV</td>
</tr>
<tr>
<td>Head and neck surgery</td>
<td>Anaerobes, enteric gram-negative bacilli, S. aureus</td>
<td>Clindamycin + Gentamicin or Cefazolin</td>
<td>300 mg PO&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incisions through oral or pharyngeal mucosa</td>
<td></td>
<td></td>
<td>1–2 g IV</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates the time of administration before surgery.

<sup>g</sup>Recommended for susceptible pathogens.

<sup>k</sup>Administered with probenecid (500 mg PO 2 hours before surgery).
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</thead>
</table>
| Neurosurgery        | *S. aureus, S. epidermidis*                                                      | Cefazolin<sup>or</sup>  
                          |                                                                                      | Vancomycin<sup>b</sup>  
                          |                                                                                      | 1–2 g IV  
                          |                                                                                      | 1 g IV  |
| Ophthalmic          | *S. epidermidis, S. aureus, streptococci, enteric gram-negative bacilli, Pseudomonas spp.* | Gentamicin, tobramycin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin<sup>or</sup>  
                          |                                                                                      | Neomycin, gramicidin, polymyxin B or cefazolin  
                          |                                                                                      | Multiple drops topically over 2 to 24 h  |
| Orthopedic          | *S. aureus, S. epidermidis*                                                      | Cefazolin<sup>or</sup>  
                          |                                                                                      | Cefuroxime<sup>or</sup>  
                          |                                                                                      | Vancomycin<sup>b, l</sup>  
                          |                                                                                      | 1 g IV  
                          |                                                                                      | 1–2 g IV  
                          |                                                                                      | 1.5 g IV  |

<sup>a</sup> Dosage may vary based on clinical judgment.

<sup>b</sup> Use vancomycin with caution due to resistance.

<sup>l</sup> Cefuroxime may be used as an alternative in some cases.
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<tr>
<td>Thoracic (noncardiac)</td>
<td><em>S. aureus, S. epidermidis, streptococci, enteric gram-negative bacilli</em></td>
<td>Cefazolin or</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefuroxime or</td>
<td>1.5 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g IV</td>
</tr>
<tr>
<td>Vascular</td>
<td><em>S. aureus, S. epidermidis, enteric gram-negative bacilli</em></td>
<td>Cefazolin or</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td>Arterial surgery involving a prosthesis, the abdominal</td>
<td></td>
<td>Vancomycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g IV</td>
</tr>
<tr>
<td>aorta, or a groin incision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremity amputation for ischemia</td>
<td><em>S. aureus, S. epidermidis, enteric gram-negative bacilli, clostridia</em></td>
<td>Cefazolin or</td>
<td>1–2 g IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 g IV</td>
</tr>
</tbody>
</table>
Factors Affecting Wound Healing

**Infections**

- Patients with prosthetic heart valves or any implanted vascular or orthopedic prostheses should receive antibiotic prophylaxis before any procedure in which significant bacteremia is anticipated.
Factors Affecting Wound Healing

Infections

- Dental procedures
  - Broad-spectrum penicillins or amoxicillin

- Urologic instrumentation
  - Second-generation cephalosporin

- GI surgery
  - Anaerobic coverage combined with a cephalosporin
Factors Affecting Wound Healing

**Infections**

- If the wound is contaminated with $> 10^5$ microorganisms, the risk of wound infection is markedly increased

- Threshold may be much lower in the presence of foreign materials
Infections

- The source of pathogens for the infection is usually the endogenous flora of the patient's skin, mucous membranes, or from hollow organs.

- The incidence of wound infection bears a direct relationship to the degree of contamination that occurs during the operation from the disease process itself.
Factors Affecting Wound Healing

**Infections**
- Clean → Class I
- Clean contaminated → Class II
- Contaminated → Class III
- Dirty → Class IV
Factors Affecting Wound Healing

**Infections**

- Most surgical wound infections become apparent within 7 to 10 days postoperatively.

- With the hospital stay becoming shorter and shorter, many infections are detected in the outpatient setting.
**Factors Affecting Wound Healing**

**Infections**

- **Definition of wound infection**
  - Wounds that drain purulent material, with bacteria identified on culture (Narrowest definition)
  - All wounds draining pus, whether or not the bacteriologic studies are positive
  - Wounds that are opened by the surgeon
  - Wounds that the surgeon considers infected
**Factors Affecting Wound Healing**

**Infections**
- Wound infections can be classified as
  - Superficial or suprafascial (75%)
  - Deep, involving fascia, muscle, or the abdominal cavity (25%)
**Factors Affecting Wound Healing**

*Infections*

- Superficial wound infections
  - Involving skin and subcutaneous tissue
  - Postoperative wound looks edematous and erythematous and tender
  - Development of postoperative fever (usually low-grade)
Factors Affecting Wound Healing

**Infections**

- **Superficial wound infections**
  - Development of a mild and unexplained leukocytosis
  
  - Presence of undue incisional pain should direct attention to the wound
Factors Affecting Wound Healing

Infections

- If a wound infection is suspected, several stitches or staples around the most suspicious area should be removed with insertion of a cotton-tipped applicator into the subcutaneous area to open a small segment of the incision.

- Presence of pus mandates further opening of the subcutaneous and skin layers to the full extent of the infected pocket.
Factors Affecting Wound Healing

**Infections**

- Samples should be taken for aerobic and anaerobic cultures

- Systemic antibiotics treatment in
  - Immunosuppressed patients
  - Evidence of tissue penetration or systemic toxicity
  - Patients who had prosthetic devices inserted
Factors Affecting Wound Healing

**Infections**

- Deep wound infections
  - Fever and leukocytosis
  - The incision may drain pus spontaneously
  - The intra-abdominal extension may be recognized after the drainage of what was thought to be a superficial wound infection
Factors Affecting Wound Healing

Infections

- Deep wound infections
  - Necrotizing fasciitis is the most dangerous of the deep infections
  - The skin demonstrates hemorrhagic bullae and subsequent frank necrosis
  - The fascial necrosis is usually wider than the skin involvement or than the surgeon estimates on clinical grounds
Infections

- Deep wound infections
  - The patient is toxic, has high fever, tachycardia, and marked hypovolemia
  - Mixed infection, and samples should be obtained for Gram's stain smears and cultures to aid in diagnosis and treatment
  - High-dose penicillin treatment needs to be started (20 to 40 million U/d IV)
Factors Affecting Wound Healing

Infections

- Deep wound infections
  - The aim of surgical treatment is thorough removal of all necrosed skin and fascia
  - Careful inspection every 12 to 24 hours will reveal any new necrotic areas, and these need further debridement and excision
**Infections**

- The mere presence of bacteria in an open wound does not constitute an infection
  - *Contamination* is the presence of bacteria without multiplication
  - *Colonization* is multiplication without host response
  - *Infection* is the presence of host response in reaction to deposition and multiplication of bacteria
Factors Affecting Wound Healing

**Infections**

- The host response that helps in diagnosing wound infection

  - Cellulitis
  - Abnormal discharge
  - Delayed healing
  - Change in pain
  - Abnormal granulation tissue
  - Abnormal color and odor
**Infections**

- Chronic granulomatous disease (CGD) comprises a genetically heterogeneous group of diseases in which the reduced nicotinamide adenine dinucleotide phosphate - dependent oxide enzyme is deficient.

- Impairs the intracellular killing of microorganisms, leaving the patient liable to infection by bacteria and fungi.
Infections

- When CGD patients require surgery, a preoperative pulmonary function test should be considered

- Wound complications, mainly infection, are common
**Factors Affecting Wound Healing**

*Infections*

- Sutures should be removed as late as possible because the wounds heal slowly

- Abscess drains should be left in place for a prolonged period until the infection is completely resolved
Chronic Wounds

- *Chronic wounds* are defined as wounds that have failed to proceed through the orderly process that produces satisfactory anatomic and functional integrity or that have proceeded through the repair process without producing an adequate anatomic and functional result.

- The majority of wounds that have not healed in 3 months are considered chronic.
Chronic Wounds

- **Skin ulcers**, which usually occur in traumatized or vascularly compromised soft tissue, are also considered chronic in nature, and proportionately are the major component of chronic wounds.

- Repeated trauma, poor perfusion or oxygenation, and/or excessive inflammation contribute to the causation and the perpetuation of the chronicity of wounds.
Chronic Wounds

- Any wound that does not heal for a prolonged period of time is prone to malignant transformation.

- Malignant wounds are differentiated clinically from nonmalignant wounds by the presence of overturned wound edges.

- In patients with suspected malignant transformations, biopsy of the wound edges must be performed.
Chronic Wounds

- Ischemic arterial ulcers
- Venous stasis ulcers
- Diabetic ulcers
- Decubitus/pressure ulcers
Ischemic Arterial Ulcers

- Symptoms of peripheral vascular disease
  - Intermittent claudication
  - Rest pain
  - Night pain
  - Color changes
  - Distal portions of the extremities
  - Diminished or absent pulses
Ischemic Arterial Ulcers

- Symptoms of peripheral vascular disease
  - Decreased ankle-brachial index
  - Poor formation of granulation tissue
  - Dryness of skin
  - Hair loss
  - Scaling
  - Pallor
**Ischemic Arterial Ulcers**

- The wound itself usually is shallow with smooth margins, and a pale base and surrounding skin.

- The management of these wounds is revascularization and wound care.
Chronic Wounds

Ischemic Arterial Ulcers
**Ischemic Arterial Ulcers**

- Non-healing of these wounds is the norm unless successful revascularization is performed.

- Adequate blood supply, most such wounds progress to heal satisfactorily.
Chronic Wounds

Venous Stasis Ulcers

- Alteration and distention of the dermal capillaries with leakage of fibrinogen into the tissues

- Polymerization of fibrinogen into fibrin cuffs leads to perivascular cuffing that can impede oxygen exchange
Venous Stasis Ulcers

- Neutrophils adhere to the capillary endothelium and cause plugging with diminished dermal blood flow

- Venous hypertension and capillary damage lead to extravasation of hemoglobin
**Venous Stasis Ulcers**

- This breakdown are irritating and cause pruritus and skin damage

- Brownish pigmentation of skin combined with the loss of subcutaneous fat produces characteristic changes called *lipodermatosclerosis*
Venous Stasis Ulcers

- Chronic venous ulcers usually are due to the incompetence of the deep venous system and are commonly painless.

- The most common being above the medial malleolus, over Cockett's perforator.
**Venous Stasis Ulcers**

- Typical location combined with a history of venous incompetence and other skin changes is diagnostic

- The wound usually is shallow, with irregular margins and pigmented surrounding skin
Chronic Wounds

Venous Stasis Ulcers

[Image of a leg with venous stasis ulcers]
Venous Stasis Ulcers

- Treatment of venous ulcers is compression therapy

- Wound care in these patients focuses on maintaining a moist wound environment, which can be achieved with hydrocolloids
**Venous Stasis Ulcers**

- Most venous ulcers can be healed with perseverance and by addressing the venous hypertension

- Recurrences are frequent because of patients' lack of compliance
**Chronic Wounds**

*Diabetic Wounds*
- 60 to 70% are due to neuropathy
- 15 to 20% are due to ischemia
- 15 to 20% are due to a combination of both
Diabetic Wounds

- The neuropathy is both sensory and motor, and is secondary to persistently elevated glucose levels.

- The loss of sensory function allows unrecognized injury to occur from ill-fitting shoes, foreign bodies, or other trauma.
Diabetic Wounds

- The motor neuropathy or Charcot foot leads to collapse or dislocation of the interphalangeal or metatarsophalangeal joints.

- There is also severe micro- and macrovascular circulatory impairment.
Chronic Wounds

Diabetic Wounds

Deformity of both feet from collapse of the midfoot arch due to Charcot neuropathic arthropathy - in this case in a patient with alcoholic peripheral neuropathy.
Diabetic Wounds

- Treatment of diabetic wounds involves local and systemic measures
  - Adequate blood sugar levels
  - Eradication of the infectious source
  - Employ antibiotics that achieve adequate levels both in soft tissue and bone
Diabetic Wounds

- Treatment of diabetic wounds involves local and systemic measures
  - Wide debridement of all necrotic or infected tissue
  - Off-loading of the ulcerated area
  - Topical application of PDGF and granulocyte-macrophage colony-stimulating factor
  - Engineered skin allograft substitutes
Decubitus or Pressure Ulcers

- A localized area of tissue necrosis that develops when a soft tissue is compressed between a bony prominence and an external surface

- Excessive pressure causes capillary collapse and impedes the delivery of nutrients to body tissues
Chronic Wounds

Decubitus or Pressure Ulcers
Decubitus or Pressure Ulcers

- The four stages of pressure ulcer formation are as follows
  - Stage I, nonblanchable erythema of intact skin
  - Stage II, partial-thickness skin loss involving epidermis or dermis, or both
Decubitus or Pressure Ulcers

- The four stages of pressure ulcer formation are as follows
  - Stage III, full-thickness skin loss, but not through the fascia
  - Stage IV, full-thickness skin loss with extensive involvement of muscle and bone
Chronic Wounds

Decubitus or Pressure Ulcers

[Diagram showing stages of decubitus ulcers]
Decubitus or Pressure Ulcers

- The treatment of pressure ulcers
  - Debridement of all necrotic tissue
  - Maintenance of a favorable moist wound environment
  - Relief of pressure
  - Addressing host issues such as nutritional, metabolic, and circulatory status
**Hypertrophic scars**

- Usually develop within 4 weeks of trauma
- Collagen bundles are wavy pattern
- Stay within the original wound, elevated less than 4 mm
Hypertrophic scars

- Occur across areas of tension/flexing
- Often regress

Tx: excision + corticosteroids
**Excess Healing**

**Keloids**

- 15x more common in pts with darker skin pigmentation
- Develop 3 months-years after trauma
- Collagen fibers are larger, random & not bundled
- Expand beyond wound edges, can become large
**Excess Healing**

*Keloids*

- Rarely regress
- Excision alone (45-100% recurrence)
- Excision + corticosteroid injections
- Topical silicone + external compression,
Excess Healing

**Keloids**

- Radiation (10 to 100% recurrence when used alone)
- Topical retinoids
- IFN-γ
- Chemotherapy (5-FU, bleomycin)
Excess Healing

**Hypertrophic scars**  **Keloids**
Excess Healing

**Peritoneal Scarring**

- Fibrous bands of tissue between normally separated organs

- Usually result from prior surgery, or intra-abdominal infection

- Most common cause (65-75%) of small bowel obstruction
**Excess Healing**

*Peritoneal Scarring*

- Operations in the lower abdomen have a higher chance of producing small bowel obstruction

- Adhesions also are a leading cause of secondary infertility in women and can cause substantial abdominal and pelvic pain
Excess Healing

Peritoneal injury

- Macrophages mesothelium
- Coagulation
- Platelets

TF → Fibrin

Thrombin + Fibrinogen → Fibrin

Peritoneal fluid
Bleeding
Inflammation

PAI-1, PAI-2
Fibrin residues

→ tPA, uPA

→ Fibrinolysis
→ Fibrinolysis degradation

Fibroblasts and capillaries
Restitution

→ Fibrous adhesion

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Fibrin formation and degradation in peritoneal tissue repair and adhesion formation. PAI-1, -2 = types 1 and 2 plasminogen activator inhibitor; TF = tissue factor; tPA = tissue plasminogen activator; uPA = urokinase plasminogen activator.
Excess Healing

Peritoneal Scarring

- Prevention
  - Careful tissue handling
  - Avoiding desiccation and ischemia
  - Spare use of cautery, laser, and retractors
  - Laparoscopic surgical techniques
Treatment of Wounds

- Local Care
- Antibiotics
- Dressings
- Skin Replacements
- Growth Factor Therapy
Management of acute wounds

1. Examination
   a) Depth?
      - Underlying structures injured
   b) Configuration?
   c) Nonviable tissue?

2. Preparation
   a) Anesthetic
      - Lidocaine w or w/o epinephrine
   b) Exploration
      - Underlying structures injured
   c) Cleansing
      - Pulsed irrigation, saline only
   d) Hemostasis
   e) Débride nonviable tissue
   f) Betadine on surrounding skin
   g) Antibiotics (rare)
   h) Tetanus

3. Approximation
   a) Deep layers
      - Fascial layers only
      - Absorbable suture
   b) Superficial layers
      - Meticulous alignment
      - Nonabsorbable sutures in skin
      - Staples
      - Monofilament
      - Dermal glues

4. Follow-up
   a) Cellulitis/drainage?
   b) Suture removal
      - 4–5 days for face
      - 7–10 days other skin
Treatment of Wounds

**Antibiotics**

- Use only when there is an obvious wound infection

- Signs of infection: erythema, cellulitis, swelling, purulence

- Base on organisms suspected to be found within the infected wound and the patient's overall immune status
Treatment of Wounds

Antibiotics

- **Single organism** → a single antibiotic

- **Multiple organisms** → a broad-spectrum antibiotic or several agents in combination

- IV form, oral form or topically as irrigations/dressings
## Treatment of Wounds

### Table 9-8 Desired Characteristics of Wound Dressings

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote wound healing (maintain moist environment)</td>
</tr>
<tr>
<td>Conformability</td>
</tr>
<tr>
<td>Pain control</td>
</tr>
<tr>
<td>Odor control</td>
</tr>
<tr>
<td>Nonallergenic and nonirritating</td>
</tr>
<tr>
<td>Permeability to gas</td>
</tr>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>Nontraumatic removal</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
</tr>
<tr>
<td>Convenience</td>
</tr>
</tbody>
</table>
Treatment of Wounds

Dressings

- Mimics epithelial barrier, protection of site
- Compression provides hemostasis, decreases edema
- Occlusion controls hydration and allows for oxygenation/gaseous diffusion
- Occlusion stimulates collagen synthesis and epithelial cell migration
Dressings

- A primary dressing is placed directly on the wound and may provide absorption of fluids and prevent desiccation, infection, and adhesion of a secondary dressing.

- A secondary dressing is one that is placed on the primary dressing for further protection, absorption, compression, and occlusion.
Treatment of Wounds

**Dressings**

- **Absorbent**: absorbs wound fluid which could lead to maceration and bacterial overgrowth.

- **Non-adherent**: impregnated with paraffin, petroleum jelly or water-soluble jelly. Requires a secondary dressing to seal edges and prevent desiccation/infection.
**Dressings**

- **(Semi)occlusive**: Film dressing good for minimally exudative wounds. Waterproof, impervious to microbes, permeable to water vapor and O2

- **Hydrophilic**: Aid in absorption

- **Hydrophobic**: Waterproof, prevents absorption
Dressings

- **Hydrocolloid**: Absorption of exudates leaves a gelatinous mass after dressing removal (atraumatic, can be washed off)

- **Hydrogels**: Useful for burns because they allow for a high rate of evaporation without decreasing wound hydration
Dressings

- **Alginites**: Derived from brown algae. Polysaccharide polymers have a high absorbency. Good for skin loss, open surgical wounds with medium exudation, and full-thickness chronic wounds.

- **Absorbable**: Within wounds as hemostatic agent. Collagen, gelatin, cellulose.
**Treatment of Wounds**

*Dressings*

- **Medicated**: Benzoyl peroxide, zinc oxide, neomycin, bacitracin-zinc. Increase epithelialization.

- **Mechanical**: Vacuum-assisted closure system applies negative pressure to the surface and margins of the wound via a foam dressing. Exudate absorption, odor control. Effective for chronic ulcers, trauma, flaps/grafts, dehiscent incisions.
Skin Replacements

- Conventional Skin Grafts
  - Split/partial thickness graft = Epidermis + partial dermis (require less vascular supply)
  - Full thickness = Entire epidermis and dermis
    Greater mechanical strength, increased resistance to wound contraction, improved cosmesis
Skin Replacements

- Conventional Skin Grafts
  - Autograft – Transplant from another site
  - Allograft – Transplant from a living non-identical donor or cadaver, may rejection and contain pathogens
Skin Replacements

- Conventional Skin Grafts
  - Xenograft – From another species, may rejection and contain pathogens

- Preparation of wound bed – Debridement of necrotic/fibrinous tissue, control of edema, minimizing exudate, revascularization of wound bed, ↓ bacterial load
Skin Replacements

- Skin Substitutes
  - Good for extensive wounds with limited availability of autografts
  - Now may be used as a wound dressing
  - Tissue engineered with living cells
Treatment of Wounds

**Skin Replacements**

- **Skin Substitutes**
  - Does not require tissue harvesting, readily
  - Available, may be sutured or applied topically
  - Promote healing
Skin Replacements

- Skin Substitutes
  - Does not require tissue harvesting, readily
  - Available, may be sutured or applied topically
  - Promote healing
Table 9-9 Desired Features of Tissue-Engineered Skin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid re-establishment of functional skin (epidermis/dermis)</td>
<td></td>
</tr>
<tr>
<td>Receptive to body's own cells (e.g., rapid &quot;take&quot; and integration)</td>
<td></td>
</tr>
<tr>
<td>Graftable by a single, simple procedure</td>
<td></td>
</tr>
<tr>
<td>Graftable on chronic or acute wounds</td>
<td></td>
</tr>
<tr>
<td>Engraftment without use of extraordinary clinical intervention (i.e., immunosuppression)</td>
<td></td>
</tr>
</tbody>
</table>
# Treatment of Wounds

## Table 9-10 Advantages and Disadvantages of Various Bioengineered Skin Substitutes

<table>
<thead>
<tr>
<th>Skin Substitute</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultured allogeneic keratinocyte graft</td>
<td>No biopsy needed, &quot;Off the shelf&quot; availability, Provides wound coverage</td>
<td>Unstable, Does not prevent wound contracture, Inadequate cosmesis</td>
</tr>
<tr>
<td></td>
<td>Promotes healing</td>
<td>Possibility of disease transmission, Fragile</td>
</tr>
<tr>
<td>Bioengineered dermal replacement</td>
<td>Prevents contracture, Good prep for graft application</td>
<td>Limited ability to drive re-epithelialization, Largely serves as temporary dressing</td>
</tr>
<tr>
<td>Cultured bilayer skin equivalent</td>
<td>More closely mimics normal anatomy, Does not need secondary procedure, Easily handled</td>
<td>Cost, Short shelf life, True engraftment questionable</td>
</tr>
<tr>
<td></td>
<td>Can be sutured, meshed, etc.</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Wounds

Growth Factor Therapy

- At present, only platelet-derived growth factor BB (PDGF-BB) is currently approved by the Food and Drug Administration for treatment of diabetic foot ulcers

- Recombinant human PDGF-BB in a gel suspension to these wounds increases the incidence of total healing and decreases healing time
Thank you for your attention