Wound healing and treating wounds

Differential diagnosis and evaluation of chronic wounds

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Learning objectives
After completing this learning activity, participants should be able to describe the physiologic steps of wound healing; generate a thorough differential for acute and chronic wounds; and commence the appropriate work-up for accurate and expedient diagnosis.

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Wounds are an excellent example of how the field of dermatology represents a cross-section of many medical disciplines. For instance, wounds may be caused by trauma, vascular insufficiency, and underlying medical conditions, such as diabetes, hypertension, and rheumatologic and inflammatory disease. This continuing medical education article provides an overview of wound healing and the pathophysiology of chronic wounds and reviews the broad differential diagnosis of chronic wounds. It also describes the initial steps necessary in evaluating a chronic wound and determining its underlying etiology. (J Am Acad Dermatol 2016;74:589-605.)

Key words: chronic wounds; chronic wound differential diagnosis; chronic wound evaluation; chronic wound work-up; wound healing; wound pathophysiology.

INTRODUCTION

Wound management often falls within dermatologists' scope of practice. We create acute surgical wounds and frequently see poorly healing ulcers in our clinics. In this article, we briefly discuss the physiology of wound healing, the causes of poor wound healing, the broad differential diagnoses for chronic wounds, and the appropriate steps for clinical evaluation of chronic wounds.

WOUND HEALING

Acute wounds undergo a well understood series of steps as they heal. In chronic wounds, these steps

Abbreviations used:

ABI:	ankle brachial index
CVI:	chronic venous insufficiency
DFU:	diabetic foot ulcer
MMP:	matrix metalloproteinase
MPA:	microscopic polyangiitis
PAN:	polyarteritis nodosa
PDGF:	platelet-derived growth factor
PG:	pyoderma gangrenosum
PU:	pressure ulcer
SCC:	squamous cell carcinoma
TGF-β:	transforming growth factor—beta
VLU:	venous leg ulcer

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are disrupted. Researchers continue to work to understand the pathophysiology of nonhealing wounds, and several of the most important factors will be discussed below.

NORMAL WOUND HEALING

Key points

- **The 4 phases of normal wound healing include hemostasis, inflammation, proliferation/repair, and remodeling**
- **Macrophages are the most important inflammatory cell in wound healing—they phagocytose pathogenic organisms, degrade debris, and stimulate granulation tissue formation**
- **Fibroblasts are essential for proliferation and lay down important structural elements, including collagen, elastin, and extracellular matrix proteins**
- **During the remodeling process, which can take weeks to years, type III collagen is converted to type I collagen**
- **Mature scar strength is about 80% of that of unwounded skin**

Wound healing occurs in 4 overlapping phases: hemostasis, inflammation, proliferation, and remodeling.

Hemostasis occurs via a fibrin and platelet plug, which triggers the coagulation cascade. Damage to endothelial cells exposes collagen that stimulates platelets to undergo activation, adhesion, and aggregation. Platelets produce chemotactic factors, including platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β). These growth factors attract macrophages, neutrophils, fibroblasts, endothelial cells, and smooth muscle cells,[1] which are essential for the inflammatory and proliferative phases. Fibrin, derived from platelet-derived fibrinogen, acts as a matrix for incoming macrophages and fibroblasts.[2]

The inflammatory phase begins as neutrophils adhere to endothelium within minutes of trauma.[3] Neutrophils use elastase and collagenase to facilitate migration into the extracellular space, where they phagocytose bacteria, degrade matrix proteins, and attract additional neutrophils and macrophages.[3] Macrophages are arguably the most important inflammatory cell in the acute healing process, dominating within 3 to 5 days.[4] They phagocytose pathogenic organisms, degrade wound debris, and stimulate granulation tissue formation and angiogenesis. Macrophage growth factors include PDGF, TGF-β, fibroblast growth factor, interleukin-1, interleukin-6, and tumor necrosis factor—α.[5] TGF-β is particularly important, stimulating macrophages and influencing fibroblast function, chemotaxis, and collagen deposition.[4]

The proliferation phase encompasses fibroplasia, granulation, epithelialization, and angiogenesis and begins within 24 hours of wound infliction. An early fibrin matrix allows keratinocytes, in part stimulated by TGF-β, to migrate from the wound edge and hair follicles and slide over keratinocytes already in the wound bed in a "leap-frogging" action.[1,5,6] Concurrently, vascular endothelial growth factor, upregulated by low oxygen tension, promotes angiogenesis.[5,7] Nearby capillary endothelial cells are recruited[1] and stimulated to proliferate by vascular endothelial growth factor, which also induces smooth muscle cell migration.[8]

Fibroblasts, which migrate in between 48 and 72 hours postinjury, are important for dermal matrix proliferation, regulated by PDGF, fibroblast growth factor, and others.[9] Fibroblasts produce structural proteins, including collagen, elastin, extracellular matrix proteins, and matrix metalloproteinases (MMPs). MMPs degrade the initial fibrin plug and facilitate fibroblast movement.[9] Collagen is apparent 48 to 72 hours after the wound appears and is maximally secreted between postinjury days 5 to 7. Type III collagen (fetal collagen) is initially more dominant, stimulated by TGF-β.[1] Glycosaminoglycans and proteoglycans, components of the extracellular matrix, provide strength, support, and density.[1]

The remodeling process takes weeks to years. Wound contraction begins by day 5 because of the phenotypic change of fibroblasts into actin-laden myofibroblasts.[10] MMPs and tissue inhibitors of metalloproteinases reorganize type III collagen fibers into a stronger network of type I collagen.[1]

Collagen reaches ~20% of its tensile strength after 3 weeks and 80% strength at 12 months. The maximum scar strength is 80% of that of unwounded skin.

CHRONIC VERSUS ACUTE WOUNDS

Key points

- **Wound healing time depends on multiple factors, including wound size, depth, location, patient age, and local and systemic disease**
- **Acute wounds progress through the phases of healing in a normal and timely manner**
- **Chronic wounds fail to progress through a normal orderly and timely sequence of repair or without restoring normal anatomy and function**