Science of Wound Healing: Translation of Bench Science into Advances for Chronic Wound Care

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Introduction

Traditionally, most acute skin wounds heal without clinically significant complications, and the resulting scar tissue functions similarly enough to unwounded skin that the repaired wound does not cause substantial problems. However, some acute skin wounds fail to heal in an expected or predicted manner and become chronic, which invariably leads to a wide range of complications, including infection, poor quality of life, increased risk of lower limb amputation, and, ultimately, death from systemic sepsis. Although much is understood about the basic science of normal skin wound healing, only recently has research begun to unravel the molecular and cellular reasons why some wounds fail to heal. Fortunately, these discoveries are constantly being translated into new therapies that selectively target the bacterial, molecular, and cellular abnormalities that impair healing, correct imbalances, and convert the chronic wound into a healing wound.

Overview of Normal Skin Wound Healing

The process of normal healing within acute skin wounds involves a distinct 4-phase sequence that results in the creation of a scar: hemostasis, inflammation, repair, and remodeling (Plate 8, page 344). During the initial hemostasis phase, fibrinogen is proteolytically converted to fibrin by thrombin, leading to formation of the fibrin clot, which stimulates platelets to degranulate, releasing numerous growth factors and proinflammatory cytokines...

in the wound. These important regulatory molecules chemotactically draw in neutrophils and macrophages, initiating the inflammatory phase. As shown in Plate 9 (page 344), a key function of the inflammatory cells is to engulf invading bacteria and fungi and kill them by generating reactive oxygen species (ROS) inside the endosomes. A second key function of inflammatory cells is to secrete proteases, including the matrix metalloproteinases (MMPs) and elastase, which remove (debride) extracellular matrix (ECM) molecules like collagen that were damaged during the injury.\(^4\) Inflammation continues to increase, reaches a maximum by about 5 to 7 days after injury, and, in the absence of continued inflammatory stimulation, decreases to low levels by about 14 days after injury. Acute inflammation stimulates the wound to enter into the repair phase, which is characterized by proliferation and migration of fibroblasts from the adjacent uninjured dermis into the provisional fibrin wound matrix, where the fibroblasts synthesize large amounts of new collagen and other ECM proteins that replace the fibrin matrix.\(^5\) Vascular endothelial cells in the surrounding vasculature also proliferate and migrate into the fibrin matrix to form new capillaries (neovascularization) that provide essential nutritional support for the rapidly metabolizing fibroblasts. Epithelial cells from the edge of the injury and especially from the stem cell niches in the hair follicles and sweat glands proliferate and migrate across the new scar matrix that is being generated by the fibroblasts. Some fibroblasts in the wound matrix differentiate into myofibroblasts and contract the newly forming scar matrix, reducing the wound area by \(\sim 20\%) in human skin wounds. When the epithelial cells have resurfaced the wound, the first 3 phases of wound healing are completed, but the initial scar matrix is not static. Over the next 6 to 12 months, the initial scar matrix is slowly remodeled by proteases that remove the highly irregular scar tissue, which is replaced by new collagen that is organized into a much more normal, basket-weave structure found in uninjured dermis.\(^4\)

Normal skin wound healing is a highly integrated process that involves platelets, inflammatory cells, fibroblasts, epithelial cells, and vascular endothelial cells. The actions of these wound cells are closely regulated by key proteins including pro- and anti-inflammatory cytokines, growth factors, receptors, proteases, inhibitors, and ECM proteins that dictate the activities of these cells. As normal wound healing proceeds, the regulatory proteins and the responses of the individual cells interact ultimately to result in repair of the injury.

**Overview of Molecular and Cellular Abnormalities in Chronic Wounds**

All chronic wounds begin as acute wounds, but acute wounds become chronic wounds when they fail to progress through the sequential phases of healing as expected.\(^4,6\) A key question to ask is, are there common molecular and cellular patterns in chronic wounds that indicate the stage of the wound healing sequence where most chronic wounds stall? The simple answer is yes. Cellular and molecular data from numerous clinical studies suggest that most chronic wounds get “stuck” in a prolonged inflammatory phase that is due to the presence of both planktonic (free flowing) and biofilm bacteria in the wound (Figure 1).\(^7,8\) The bacteria stimulate production of proinflammatory cytokines like tumor necrosis factor–alpha (TNF-\(\alpha\)) and interleukin 1 (IL-1), which act as chemotactic factors (chemical messengers) to recruit neutrophils, macrophages, and mast cells into the wound. The inflammatory cells that are drawn into the wound secrete proteases (MMPs, neutrophil elastase, and plasmin) and ROS in an attempt to kill bacteria and detach biofilm colonies that are tightly attached to the wound bed. However, because bacterial biofilms are tolerant to ROS as well as antibodies and even antiseptics, the biofilms persist and continue to stimulate inflammation. This results in chronically elevated levels of proteases and ROS that eventually begin to destroy essential proteins that are necessary for healing, including growth factors, their receptors, and ECM proteins. These “off-target” effects of proteases and ROS combine to reduce cell proliferation, migration, and generation of functional scar matrix.\(^1,9-11\) The “biological sum” of this prolonged inflammatory state is a distorted molecular and cellular wound environment that prevents wound healing. In the simplest terms, the molecular and cellular environment between acute
healing wounds and chronic wounds is totally different. As shown in Figure 2, these “imbalances” must be corrected by clinical therapies or the wound will not progress to healing. Strategies designed to reverse these imbalances would be expected to promote healing, and indeed, innovative new treatments are being developed and tested, and some have already been shown to clinically improve healing of chronic wounds. Of utmost importance is attention to evidence-based wound care, adequate wound bed preparation, appropriate management of underlying disease, and correction of other contributing factors (such as too much or too little moisture, excessive friction and shear, and inadequate nutrition) that may impair wound healing.4

Repeated Tissue Injury
Clinical observations indicate that acute wounds that develop into chronic wounds are frequently subjected to repeated episodes of tissue injury leading to ischemia, such as prolonged pressure in spinal cord-injury patients (pressure ulcers), vasculopathies (venous leg ulcers), or blunt trauma that occurs on plantar foot surfaces of people with diabetic neuropathy.6 This causes the epidermis to break down, generating an open wound that quickly becomes colonized with planktonic bacteria.

Bacterial Bioburden and Biofilms
Decades of clinical and laboratory research have conclusively shown that high concentrations of planktonic bacteria found in clinically infected wounds can impair wound healing, primarily by stimulating inflammation and by secreting exotoxins, proteases, and virulence factors that impair inflammatory cell functions and break down host tissue to promote dissemination of the bacteria and to provide nutrients for the rapidly proliferating bacteria. Historically, many nonhealing wounds were not reported to have high levels of planktonic bacteria when assessed by standard clinical microbiology as-

Figure 1. Molecular and cellular pathology of chronic wounds. Acute wounds that become critically colonized by planktonic and biofilm bacteria develop chronic inflammation that is characterized by high levels of proteases and ROS that destroy “off-target” proteins that are essential for healing, resulting in a chronic wound.
Cowan et al. says. However, serial aggressive debridement and systemic and topical treatments designed to reduce bacterial bioburden were frequently found to improve healing. This led to the concept of critical colonization, which was an attempt to recognize that something about the bioburden was impairing healing (Plate 10, page 345). New data suggest that the critical factor determining wound bioburden is usually the presence of bacteria in polymicrobial biofilm communities.

A biofilm is a community of microorganisms surrounded by an extracellular polymeric matrix (EPM), which attaches to a surface. Recent studies demonstrate that biofilms are becoming a significant component of infections in humans. The Centers for Disease Control and Prevention and the National Institutes of Health project that biofilms are associated with 65% of nosocomial (hospital-acquired) infections and up to 80% of all human infections in the United States. In addition, treatment of biofilm-associated infections costs billions of dollars and results in hundreds of thousands of deaths annually in the United States. Both acute and chronic wounds are susceptible to the development of biofilms within the wound bed.

Open wounds provide a perfect environment for opportunistic organisms, such as bacteria, to reside and reproduce. Analyses of the microflora of chronic wounds (such as pressure and diabetic foot ulcers) demonstrate a phenomenon known as chronic wound pathogenic biofilms. Typical mechanisms by which biofilms impede wound healing progress involve heightening the level of inflammation; increasing the amount of ROS and proteases in the wound bed; stimulating overly aggressive immune responses; producing detrimental exogenous toxins within the wound environment; and impairing normal chemokine signalling pathways. Aerobic organisms within biofilms use oxygen and help to create anaerobic niches within the biofilm matrix that support the development of anaerobes within the biofilm. Importantly, the presence of biofilms in a wound may affect the wound healing process without visible clinical signs of infection. However, there

**Figure 2.** Imbalanced molecular and cellular environments of healing and chronic wounds. The molecular and cellular environment of acute healing wounds is dramatically different than that of chronic wounds and must be “rebalanced” to approximate the environment of healing wounds before healing can progress. Adapted with permission from Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. *Wound Repair Regen.* 1996;4(4):411.
may be indications of bacterial imbalance (eg, change in wound color or odor together with the presence of devitalized tissue and ischemia).15

Studies suggest that certain bacterial groups, which by themselves are considered essentially harmless (such as Corynebacterium spp), tend to form symbiotic communities with other bacteria and fungi in chronic wounds. These polymicrobial groups in biofilms are termed functional equivalent pathogroups because they have been shown to have functionally detrimental effects on wound healing similar to other well known pathogens, such as Staphylococcus aureus.12 In addition, biofilm colonies may extend 2 mm beneath the wound bed and into surrounding healthy tissue, making them difficult to eradicate by many traditional bedside debridement methods. Treatment options to consider include debridement and the use of a broad-spectrum topical antimicrobial agent directly after debridement to control the planktonic bacterial load and to reduce the progression into biofilms. Importantly, recent data indicate that mature biofilm communities can re-establish in wounds within 3 days following debridement.5 If control of microbial progression from planktonic to mature biofilms is not achieved, a change from an early stage biofilm to a polymicrobial “complex” mature wound biofilm may develop and ultimately lead to a compromised state.15

Biofilm experts suggest that traditional culturing methods, which involve inoculating a culture medium with a cotton swab sample obtained from the patient, are insufficient to identify true components of the polymicrobial mature biofilm colonies.12,15 The exact microbial composition of biofilms is largely undetectable by traditional cotton swab culture techniques due to the protective polymeric coating that biofilms produce. This self-protective coating encapsulates the colony and is also impervious to most systemic and topical antimicrobials/antibiotics. Other limitations of the traditional clinical swab sampling approach include the following:

• Cotton swab cultures typically query only the most common aerobic organisms
• Culture results are often unavailable for 2 to 3 days
• The culture is naturally biased toward identifying only those cultivable bacterial species that are easily cultured under standard laboratory conditions on standard growth media.12

Recent literature suggests that the polymerase chain reaction (PCR) assay is a cost-effective, rapid, and more sensitive method to detect microbial pathogens (particularly biofilm microbes) in clinical specimens. The diagnostic value of PCR may be clinically superior to traditional swab cultures as well as other modern options, such as pyrosequencing techniques. Pyrosequencing essentially generates millions of short ~100 nucleotide sequences, and software scans the entire bacterial and fungal DNA databases for matches of DNA sequences. Thus, pyrosequencing can identify all bacterial and fungal species present in a biopsy, but it is more expensive and requires about a week to generate the data. The PCR identification of bacteria and fungi in wound biopsies is a more focused and limited approach that uses primer sequences that “probe” for unique DNA sequences of ribosomal RNAs. This real-time PCR testing specifically probes for ~30 bacteria and fungi species in a wound sample. However, it is less expensive and rapid (costs ~$100 and is completed in less than 24 hours).15

Elevated Proinflammatory Cytokines

Closely linked to the bacterial bioburden in a wound is the proinflammatory cytokine profile. In general, fluids from acute healing wounds tend to have an early peak of major proinflammatory cytokines, TNF-α and IL-1β, and their natural inhibitors, P55 and IL-1 receptor antagonist, within the first few days after injury, which corresponds to the rapid increase in inflammatory cells in the acute wound.16 The levels of proinflammatory cytokines begin to decrease after 6 to 7 days as the inflammatory stimuli in acute wounds decrease. However, in a study of chronic leg ulcers, the levels of inflammatory cytokines, IL-1β, IL-6, and TNF-α were significantly higher than in acute healing wounds, and as the chronic ulcers began to heal, the levels decreased.8 These findings indicate that chronic wounds have persistently elevated levels of proinflammatory cytokines, but as chronic wounds heal, the molecular environment changes to a less proinflammatory wound environment.
**Elevated Proteases**

Another major concept to emerge from wound fluid analyses is that levels of proteases, especially MMPs and neutrophil elastase, are much higher in chronic wounds than in acute wound fluids.\(^6,16,17\) During the early phase of acute wound healing, the average level of protease activity in mastectomy fluids was found to be low, suggesting that protease activity is tightly controlled during the early phase of wound healing.\(^9\) However, in chronic wounds, the average level of protease activity was found to be approximately 116-fold higher than in acute mastectomy wound fluids. Furthermore, as chronic venous ulcers began to heal, the levels of protease activity decreased.\(^9\) Similar results were reported for fluids or biopsies of chronic pressure ulcers, where levels of MMP-2, MMP-9, and MMP-1 were 10 to 25 times higher than levels in acute surgical wound fluids.\(^18,19\) Levels of the tissue inhibitors of metalloproteinases (TIMPs), which are the natural inhibitors of MMPs, were found to be decreased in wound fluids from chronic venous ulcers compared to acute mastectomy wound fluids.\(^20\)

In nonhealing chronic pressure ulcers, MMP-8, the neutrophil-derived collagenase, was elevated, indicating that there may be a persistent influx of neutrophils releasing MMP-8 and elastase, which could contribute to the destruction of ECM proteins and growth factors that are essential for healing.\(^21\) Chronic venous ulcers were found to have 10-fold to 40-fold higher levels of neutrophil elastase activity and to have degraded \(\alpha_1\)-antitrypsin. Elevated MMP-2 and MMP-9 levels in chronic venous ulcers also were observed to coincide with degradation of fibronectin in the wound bed.\(^22,23\) Fibronectin is an important multidomain adhesion protein that is present in the ECM and granulation tissue and is important in promoting epithelial cell migration. Proteases in chronic wound fluids were shown to rapidly degrade exogenously added growth factors, such as transforming growth factor-alpha (TGF-\(\alpha\)), epidermal growth factor (EGF), or platelet-derived growth factor (PDGF), using *in-vitro* laboratory tests. In contrast, exogenously added growth factors were stable when added to acute surgical wound fluids.\(^1,9,11\)

**Reduced Mitogenic Activity of Chronic Wound Fluids**

Another key concept that emerged from laboratory analysis demonstrates that the mitogenic activity of chronic wound fluids is dramatically less than levels in acute wound fluids. For example, fluids from chronic leg ulcers did not stimulate DNA synthesis of cells in culture, while acute wound fluids strongly stimulate proliferation of cells in culture. Furthermore, when acute and chronic wound fluids were combined, the mitotic activity of acute wound fluids was inhibited.\(^7,24,25\) These results show that the proteases in chronic wound fluid degrade growth factors that are normally present in acute wound fluids, and without the essential actions of these growth factors, wound healing will not progress.

**Factors Affecting Cell Senescence**

In chronic wounds, the capacity of the wound cells to respond to cytokines and growth factors is altered. Research suggests that fibroblasts (cells that manufacture collagen and perform other essential functions in wound healing) have a diminished response to growth factors in chronic wounds. For example, fibroblast cultures established from chronic venous leg ulcers proliferated slowly and formed less dense confluent cultures when compared to normal fibroblast cultures established from uninjured dermis.\(^26\) In another study of chronic venous leg ulcers that were present for more than 3 years, fibroblasts proliferated poorly in response to PDGF added to the culture medium and rapidly approached senescence compared to fibroblasts cultured from venous ulcers that had been present for less than 3 years.\(^27\)

The molecular environments of acute and chronic wounds are dramatically different (Figure 2). Healing wounds have low bacterial bioburden and no biofilms, low levels of inflammatory cytokines, low levels of proteases, high levels of growth factors, and cells that divide rapidly in response to growth factors. The molecular and cellular environment of chronic wounds is exactly the opposite. Chronic wounds have high levels of bacterial biofilms, elevated levels of inflammatory cytokines, high levels of proteases, low levels of growth factors, and cells that are approaching senescence.\(^27–29\) With this in mind, new treatment strategies should be designed to re-establish in
chronic wounds the balance of bacterial bioburden, cytokines, growth factors, proteases, their natural inhibitors, and competent cells found in healing wounds. Chronic wounds fail to heal because of molecular and cellular abnormalities in the wound environment. For example, studies have shown altered signaling pathways and levels of gene expression (eg, elevated c-myc and beta-catenin, altered intracellular localization of EGF receptor) that reflect the stalled migration of keratinocytes at the edge of chronic wounds. Several innovative approaches to identifying and managing chronic wounds are being developed and are based on identifying and correcting these types of molecular and cellular abnormalities.

**Innovative Approaches for Correcting Molecular Abnormalities of Chronic Wounds**

**Debridement.** Clearly, proper wound debridement is a key element of wound bed preparation. This was demonstrated by Steed et al who performed a clinical study that showed that healing of chronic diabetic foot ulcers (treated at 10 different centers) was closely correlated with the frequency of debridement. The benefit of wound debridement was seen in both patients who received standard care and patients who were treated with topical PDGF. It is possible that frequent sharp debridement of diabetic ulcers may reduce the level of inflammation in the wound by mechanically removing biofilms as well as by converting the chronic wound into a pseudo-acute wound molecular environment. Therefore, appropriate wound debridement should be considered a vital component in the care of patients with chronic diabetic foot ulcers.

**TIME to heal wounds.** A second category of approaches to correcting the molecular imbalance in chronic wounds is targeted at the elevated levels of inflammatory cytokines. The simplest approach to correcting this condition is to prepare the wound bed using debridement and moisture control. This concept has been more thoroughly described in an article that unites wound bed preparation under a **TIME** acronym that stands for **T**issue debridement, **I**nfection/inflammation, **M**oisture balance, and **E**dge effect (Plate 11, page 345). Correctly applying the concepts of wound bed preparation
to the care of a patient’s wound requires a tool that helps assess when each of the 4 components has been optimized. As shown in Table 1, assessment of the TIME components involves good clinical judgment and objective measurements of wound parameters, as described by Dowsett and Ayello.

Proteases. Another important clinical approach to correcting molecular imbalances in chronic wounds is to lower the levels of MMPs and other proteases. Several therapeutic approaches are currently used. Innovative wound dressings that contain denatured collagen (gelatin) and oxidized regenerated cellulose (Promogran, Systagenix Wound Management, Quincy, Massachusetts) are available. The gelatin in the dressing acts as a substrate sink for proteases, especially MMPs, and has been shown to reduce levels of protease activities in fluids from chronic human wounds measured in vitro. One study of chronic diabetic plantar surface ulcers found that 31% of 51 patients treated with Promogran added to conventional dressings had complete wound closure compared with 28% of 39 patients treated with conventional dressings (P = .12). Analysis of healing rates in subcategories of patients suggested that the effect of Promogran was more dramatic in healing in ulcers of less than 6 months’ duration.

Another clinical approach that has been used to correct elevated levels of proteases, especially MMPs, is applying topical protease inhibitors. One study investigated topical treatment of diabetic foot ulcers with doxycycline. Doxycycline is a member of the tetracycline family of antibiotics and is an effective inhibitor of metalloproteinases, including MMPs and the TNF-α converting enzyme (TACE). A randomized controlled trial of 1% topical doxycycline treatment of patients with chronic diabetic foot ulcers found that all 4 ulcers treated daily with doxycycline in a carboxymethyl cellulose vehicle healed in less than the 20-week treatment period, while only 1 of 3 ulcers treated with vehicle healed in 20 weeks. Importantly, no adverse events attributable to the doxycycline treatment occurred.

Other methods of wound care can be used to lower levels of proteases in wound beds. For example, negative pressure wound therapy (NPWT) removes wound fluid containing high levels of proteases from the wound bed while drawing fresh plasma that contains protease inhibitors (α2 macroglobulin, α1-antitrypsin) into the wound bed. In addition, dressings that absorb large amounts of wound exudate, especially dressings that contain highly charged polymers (eg, negatively charged polyacrylic acid or carboxymethylated cellulose or positively charged polyquats), can ionically bind the charged protease proteins and sequester the proteases in the matrix of the dressing, thus sparing the proteins in the wound bed that are essential for healing.

Optimal use of advanced therapies to reduce the elevated levels of proteases would ideally depend on actually measuring the levels of proteases in a patient’s wound. Thus, clinicians may find a rapid, point-of-care (POC) detector that measures levels of MMP activities in a wound fluid sample useful. Two prototype MMP detectors are currently under final development. Both MMP detectors would enable clinicians to assess the level of MMP protease activity in wound fluid samples collected at the bedside in approximately 10 minutes. One device utilizes lateral flow strip (LFS) technology like that used in early pregnancy test kits that are performed at home on urine samples. This LFS detector for MMPs produces a line on the test strip when MMP activities in a wound fluid sample are low and no line on the test strip when the MMP activities are high, which is opposite from how LFS detectors typically indicate if a biomarker is present in a sample. A second prototype MMP detector generates a fluorescent signal that is proportional to the level of MMP activities in wound fluid that is collected on a swab and added to the MMP substrate solution. Gibson et al used the fluorescence POC detector prototype to measure MMP levels in samples of acute and chronic wound fluids collected by swabs at the bedside. After 10 minutes of reaction, MMP levels were almost 6 times higher in chronic wounds (n = 6) than the average level measured in acute wounds (n = 3). Assessing the level of MMPs in wounds should help clinicians determine if the level of proteases is so high that healing would not likely occur and could help clinicians determine if the wound should be debrided and treated with dressings that reduce protease activities and/or reduce bacterial bioburden.
Growth factors. The application of recombinant growth factors to the wound is another approach to correcting the abnormal molecular environment of chronic wounds. Several clinical studies have reported improved healing of various types of chronic wounds with recombinant human growth factors and cytokines, including PDGF, keratinocyte growth factor-2 (KGF-2), transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). It is important to recognize that growth factors can only function well in chronic wounds when the environment is similar to that found in acute wounds. In other words, growth factors cannot convert a chronic wound to an acute wound and do not function in a necrotic, inflamed, protease-laden wound. Thus, the principles of wound bed preparation must be used in conjunction with topical growth factor treatments.

A logical extension of the principles of wound bed preparation is to combine therapies that address more than one aspect of TIME. Indeed, combining topical growth factor treatment (Regranex®, Healthpoint, Ltd., Fort Worth, Texas) with protease inhibiting dressings (Fibracol Plus® collagen-alginate, Systagenix Wound Management, Quincy, Massachusetts, or Oasis® small intestinal submucosa, Healthpoint, Ltd.) rapidly healed 34 of 36 chronic wounds that had failed to heal by other wound care techniques, including when these therapies were used alone. However, combining therapies should be used with caution because some combinations of topical treatments can inactivate or impair active components of one or more of the treatments. For example, combining microbicidal dressings that contain PHMB, ionic silver, or iodine with Santyl® debriding ointment reduces the enzymatic activity of the collagenase enzyme in the Santyl.

Conclusion

Wound healing occurs through 4 phases. These phases are sequentially regulated by the actions of cytokines, growth factors, ECM proteins, and proteases. If an acute wound fails to move through a phase of healing, molecular imbalances will occur, leading to a chronic wound. Chronic wounds

Take Home Messages for Practice

- Moist wound healing is evidence-based. Avoid using products or therapies in chronic full-thickness wounds that dry out the wound bed at any time. Remember, balance is important. Keeping the wound bed moist but not too moist (as evidenced by periwound maceration or dressings that need to be changed more than 2 or 3 times per day) is sometimes a challenge.
- Always attempt to include the patient’s preferences, values, and any unique patient limitations (cognitive, physical, and psychosocial/emotional) in your treatment plan. For example, a patient or his or her caregiver is not likely to be compliant with a daily treatment plan that requires him or her to manually “milk” and discard bloody drainage from tubing left in a surgical wound if he or she faints at the sight of blood.
- Start with the simple and most cost-effective products and therapies for chronic wound care that address TIME principles. Always recheck wound progress within 2 weeks of starting or changing wound treatments. If wound healing is the goal (not palliative wounds) and no improvement is seen within 2 to 4 weeks of initiating a wound treatment, 1) verify that all TIME principles are being addressed, 2) verify patient/caregiver understanding/compliance with treatment orders, 3) assess and address comorbid conditions that may impair wound healing (unrelieved friction/shear/pressure; inadequate nutrition), and 4) consider tissue biopsy to rule out other pathology (eg, malignancy, pyoderma gangrenosum). If all of these factors have been satisfactorily addressed, consider changing wound treatment modalities, possibly including the initiation of advanced therapies.
are characterized by bacterial biofilms, elevated inflammatory cytokines and proteases, low levels of mitogenic activity, and senescent cells that are unable to respond to growth factors. Healing of chronic wounds occurs as the molecular environment of the wound shifts to the environment of an acute wound. New therapies are designed to correct the molecular abnormalities of chronic wounds and correspond to the principles of wound bed preparation.

Self-Assessment Questions

1. Which of the following is NOT a reason why PCR as a diagnostic tool may be more desirable than standard swab cultures for measuring bacterial strains present in a biofilm?
   A. Results are obtained quicker than standard culture techniques
   B. It identifies more strains with greater accuracy
   C. The test can be done at the bedside like a rapid strep test
   D. It may be more cost effective

2. What does the M stand for in the TIME acronym approach to wound management?
   A. Manage nutrition
   B. Manage moisture
   C. Manage edema
   D. Manage infection

Answers: 1-C, 2-B

References

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