PROACTIVE AND EARLY AGGRESSIVE WOUND MANAGEMENT:
A Shift in Strategy Developed by a Consensus Panel Examining the Current Science, Prevention, and Management of Acute and Chronic Wounds
Abstract: Normal wound healing is accomplished through a series of well-coordinated, progressive events with overlapping phases. Chronic wounds are described as not progressing to healing or not being responsive to management in a timely manner. A consensus panel of multidisciplinary wound care professionals was assembled to (1) educate wound care practitioners by identifying key principles of the basic science of chronic wound pathophysiology, highlighting the impact of metalloproteinases and biofilms, as well as the role of the extracellular matrix; and (2) equip practitioners with a systematic strategy for the prevention and healing of acute injuries and chronic wounds based upon scientific evidence and the panel members’ expertise. An algorithm is presented that represents a shift in strategy to proactive and early aggressive wound management. With proactive management, adjunct therapies are applied preemptively to acute injuries to reduce wound duration and risk of chronicity. For existing chronic wounds, early aggressive wound management is employed to break the pathophysiology cycle and drive wounds toward healing. Reducing bioburden through debridement and bioburden management and using collagen dressings to balance protease activity prior to the use of advanced modalities may enhance their effectiveness. This early aggressive wound management strategy is recommended for patients at high risk for chronic wound development at a minimum. In their own practices, the panel members apply this systematic strategy for all patients presenting with acute injuries or chronic wounds.

Key words: chronic wounds, wound healing, acute wounds, prevention, wound management, bioburden


BACKGROUND

Prior to a discussion of chronic wounds, a thorough understanding of the normal physiology involved with wound healing is crucial. Normal wound healing is achieved through a series of well-coordinated, progressive events designed to restore the barrier function and mechanical integrity of the skin.1,2 Wound healing involves biochemical and biomechanical interactions between cells and their microenvironment, of which the extracellular matrix (ECM) with its diverse collection of structural, adhesive, and resilient biomolecules is the primary component. Because the interactions between the cells and ECM are reciprocal and dynamic (ie, continually changing in response to cues from their microenvironment), the term dynamic reciprocity was developed to indicate the ongoing, bidirectional interactions between cells and the ECM.2,4 This concept of dynamic reciprocity provides a context from which to understand developmental processes, tumor growth, and wound healing.2,3,5-7

The molecular events associated with wound healing commonly are categorized into 4 phases and are summarized in Figure 1. The first phase (vascular response/hemostasis phase) begins upon disruption of blood vessels, which leads to a series of molecular events designed to stop blood loss. These events include vasoconstriction, formation of a platelet plug, and coagulation, during which cells respond to changes in the ECM and vice versa.1,2,6,8 The second phase (inflammatory) is characterized by the sequential influx of immune cells that have a range of functions, including removal of bacteria, debris, and devitalized tissue.1,2,4,8 The repair, or proliferative, phase involves the formation of granulation tissue, new blood vessels, macrophages, fibroblasts, and loose connective tissues.1,2,4,8 Early contraction and reepithelialization also occur during this third phase of wound healing. During the fourth phase (remodeling/maturation), myofibroblasts interact with collagen bundles and growth factors to contract the wound.1,2,4,8 Metalloproteinases (MMPs) are released by macrophages, endothelial cells, and epidermal cells and, besides removing damaged ECM and bacteria, play a necessary role in remodeling the early matrix.1,2,4,8 Myofibroblasts and fibroblasts replace the early matrix with stronger type I collagen.2,4 This slow remodeling of collagen, including formation of bundles and crosslinks, progresses to scar formation over several months.2
As illustrated in Figure 1, the phases of wound healing overlap.\(^1\) Injuries are the result of trauma, micro- 
trauma, pressure, or iatrogenic causes.\(^2\) Repeated tissue injury, ischemia, and elevated bioburden (Figure 2). Prolonged inflammation ensues, which leads to elevated proteases that destroy essential proteins, such as growth factors, and the ECM that is requisite for healing. This cycle must be broken to achieve healing. The panel identified key principles regarding the basic science of chronic wound pathophysiology using the phases of each phase in the cascade as a framework for discussion. For discussing chronic wound pathophysiology, identifying key principles regarding chronic wound basic science, and discussing prevention and management practices to identify areas of similarity. The second meeting took place on August 15, 2015, in Chicago, Illinois. During this meeting, the basic science key principles were revised and finalized. In addition, prevention and management guidelines, including an algorithm, were developed. The management strategy and algorithm were revised and finalized during subsequent electronic correspondence and teleconference between panel members. The resulting prevention and management guidelines and algorithm were unanimously approved.

**Chronic Wound Basic Science: Key Principles**

Wounds fail to heal when they enter a pathophysiology cascade stimulated by repeated tissue injury, ischemia, and elevated bioburden (Figure 2). Prolonged inflammation ensues, which leads to elevated proteases that destroy essential proteins, such as growth factors, and the ECM that is requisite for healing. This cycle must be broken to achieve healing. The panel identified key principles regarding the basic science of chronic wound pathophysiology using the phases of this cascade as a framework for discussion.

**Repeated tissue injury.**

1. Injuries are the result of trauma, microtrauma, pressure, or iatrogenic causes.\(^2\)
2. Repeated microtrauma may lead to the development of chronic wounds due to the prolonged elevated inflammation caused by recurrent tissue injury.\(^1,2\)
3. Ischemia may lead to chronic wounds, as adequate blood flow provides the nutrition and oxygen necessary for sustaining healthy tissue.\(^2,23\)

**Role of bioburden and biofilm.**

1. Chronic wounds have a high bioburden by a host of microorganisms, some of which are free-living (planktonic bacteria) and others that may colonize within an insoluble ECM barrier to form biofilm.\(^8,12,17,19,24-33\)
2. Biofilm can develop within 2 to 4 days of initial colonization and is very difficult to remove by surface irrigation or cleansing.\(^12,15\) In addition, biofilm is not highly susceptible to intravenous or oral antibiotics or topical antimicrobials.\(^15,25,29-31,34,35\) Therefore, prevention and excisional debridement are critical for biofilm management.\(^15,17,26,30,31,34,35\)
3. The presence of microorganisms stimulates production of proteases by the body’s inflammatory cells.\(^8,15,16,20,28\)
4. Bacterial proteases contribute to overall protease levels in the colonized wound and also disrupt the host’s protease/protease inhibitor systems.\(^1,8,15,16,20,24,28\)
5. Effective management of bioburden may reduce excessive protease production in the chronic wound.\(^16,19,36\)
Prolonged elevated inflammation.
1. Proteases are produced by inflammatory cells stimulated by bioburden.1,15,16,28
2. Excessive protease activity in the wound leads to degradation of key proteins (ie, ECM proteins, growth factors, receptors), thereby impairing healing.1,10,13,15,16,18,24,28,37-40
3. Fibronectin is sensitive to many proteases, including neutrophil elastase, and is degraded in chronic wounds.16,47,48 Because fibronectin promotes adhesion, migration, chemotaxis, and phagocytosis by diverse cell types, it plays a role in multiple phases of wound repair, including thrombosis, inflammation, angiogenesis, and epithelialization.48 Therefore, degradation of fibronectin by proteases has an inhibitory effect on healing.48

Imbalanced proteases and protease inhibitors.
1. The major proteases involved in wound healing are the MMPs and the serine proteases, such as neutrophil elastase.15,16,19,37,43,45,49-51
2. Proteases are secreted by cells involved in wound repair, such as fibroblasts and endothelial cells, and also by immune cells, as previously described.1,15,16,37,39,42,49,52,53
3. In chronic wounds, excessive levels of protease activity disrupt the balance between tissue breakdown and repair.16,18,19,30,42,43,52-57
4. In nonhealing or chronic wounds, there is an imbalance between increased levels of various MMPs and decreased levels of tissue inhibitors of MMPs (TIMPs).1,2,11,15,16,22,28,38,40-42,45,50,52,54,57-62
5. In chronic wounds, elevated levels of proteases (ie, MMPs and neutrophil elastase) degrade ECM, growth factors (ie, platelet-derived growth factor [PDGF]), and cellular receptors (ie, transforming growth factor beta [TGF-β] receptors).1,2,11,15,16,22,28,39,43,45,51,63,64
6. Excessive degradation of ECM, growth factors, and receptors reduces cell attachment, migration, proliferation, and differentiation, which disrupts the microenvironment in the wound bed and interrupts the dynamic reciprocity communication, resulting in impaired healing.2

Figure 2. Chronic wound pathophysiology.
ECM: extracellular matrix; TIMP: tissue inhibitor of metalloproteinase; α1-P1: alpha 1-proteinase inhibitor; MMP: matrix metalloproteinase

Promote aggressive wound management: A shift in strategy
An increased understanding of the normal wound healing process, the pathophysiology of chronic wounds, and the advances in molecular biology and technology have resulted in the development of a wide range of advanced modalities that have the potential to positively influence the molecular events associated with wound healing (Figure 1). Advanced wound management therapies are often defined as interventions used when standard wound care has failed.47 Although not an exhaustive list, modalities employed in such situations include topical biological products (ie, PDGF, platelet-rich plasma), advanced dressings (ie, antimicrobial, collagen, alginate, cavity, honey), tissue-engineered skin substitutes, allograft or xenograft matrix, negative pressure wound therapy, hyperbaric oxygen therapy, stem cell therapy, and intermittent pneumatic compression therapy. Promising clinical outcomes of chronic wounds managed with such advanced modalities have been reported in studies with varying levels of clinical evidence.34,53,68-89

However, when normal wound healing is regarded as adequate rather than optimal, wound care professionals can employ many of the aforementioned interventions typically reserved for chronic wound management early in the acute wound phase as adjunct therapy to enhance healing. Viewing normal wound healing as a continuum, just as healing may be stalled and possibly lead to the development of a chronic wound, it also may be expedited. The consensus panel developed an algorithm (Figure 3) to illustrate this shift in strategy to proactive and early aggressive wound management; the
pathway depicted in blue represents the phases of normal wound healing.

With proactive wound management (Figure 3; illustrated in green), adjunct therapies are applied to the acute injury early in the wound healing process — preemptively intervening prior to the development of chronicity instead of responding afterward. By enhancing healing, wound duration and risk of chronicity may be reduced. This proactive approach has emerging support, as Utz et al. demonstrated in their investigation of MMP expression in traumatic acute wounds, where they reported significantly higher serum levels of MMPs in patients with impaired healing versus those with normally healing wounds. Furthermore, serum levels of these MMP biomarkers were shown to be significant predictors of wound healing, as the elevated levels among patients with impaired healing likely are contributing to an exaggerated inflammatory response and the subsequent impairment. With this preliminary evidence of elevated MMP levels in acute wounds correlating with wound failure and chronicity, wound care practitioners have the knowledge that excessive proteases and their resulting activities contribute to failed healing in both acute injuries and chronic wounds, underscoring the importance of a proactive strategy, particularly in terms of protease management.

In the other scenario, as previously discussed, if healing does not progress and prolonged inflammation ensues, the wound may enter the pathophysiology cycle (Figure 3; illustrated in red). Early aggressive wound management (Figure 3; illustrated in green), involving the use of adjunct therapies, may be employed to break the pathophysiology cycle in a chronic wound and drive it toward healing. A chronic wound may exit the pathophysiology cycle at any point and have delayed healing (Figure 3; illustrated in light blue), but this is unlikely without some type of intervention.

Each wound care practitioner must decide when to apply his/her preferred advanced modality(ies) to an acute injury. Some justifiably may reason that adjunct therapy should be applied to all acute injuries to enhance healing, while others may choose to reserve use for chronic wounds. At a minimum, the consensus panel recommends this early aggressive wound management strategy for patients already considered at high risk for the development of chronic wounds. In this regard, advanced modalities may be prophylactically applied to acute injuries as a means of active wound management to enhance healing and reduce the likelihood of chronic wound development in patients with established risk factors for chronicity. In their own practices, the panel members utilize this management strategy for all patients presenting with acute injuries or chronic wounds and have summarized a series of guidelines related to their wound management philosophies.

**Prevention and Management Guidelines**

Early aggressive wound management involves the use of advanced intervention (as appropriate to the time between injury and treatment) at the beginning of wound care treatment to optimize wound bed preparation. Initial use of appropriate adjunct therapies, such as calcium alginate, collagen, antimicrobial, and compressive dressings, increases the probability of achieving sufficient wound area reduction by the second to fourth week, which, in turn, improves the likelihood that the wound will advance to full closure. For example, a 20% to 40% reduction in wound area of venous leg ulcers within 2 to 4 weeks is a good predictor of healing. Diabetic foot ulcers that exhibit a reduction of at least 50% by week 4 is predictive of healing.

**Debridement and bioburden management**

1. Debridement of dead, devitalized tissue, as appropriate to the injury/wound, may help reduce excessive protease activity by removing necrotic tissue and reducing the bacterial load that may be contributing to inflammation. Debridement also has been shown to stimulate healing, promoting the release of tissue cytokines and growth factors.

2. The least cytotoxic bioburden management strategy that addresses wound bioburden during the healing process should be used. Appropriate bioburden management options include topical broad-spectrum-based antimicrobials (iodine, silver therapy, methylene blue with gentian violet, polyhexamethylene biguanide [PHMB], hypochlorous acid [HOCl], and honey).

3. Collagen dressings and topical doxycycline are recommended for protease management.
4. Certain advanced modalities, such as topical growth factors and bioengineered skin substitutes, may not be effective if high protease levels are not addressed first.\(^{17,64,119}\) Adjunct therapies that modulate MMP activity (e.g., collagen dressings) may be used prior to these options to reduce excess proteases in the wound bed and also to potentially protect endogenous and exogenous growth factors.\(^{13,40,64,116,117,120}\)

**Management of fluids through dressing selection.** The wound environment may be influenced through dressing selection to achieve the desired level of moisture in the wound bed.\(^{17,46,96}\) Appropriate fluid management promotes a healthy microenvironment and optimizes the wound bed for acceptance of later advanced modalities. A nonoptimal wound bed environment in either direction — either hyperhydrated or desiccated — has been linked to a host of negative consequences, including maceration of surrounding skin, biofilm development, eschar formation, and inhibition of cellular activity, all of which may impede wound healing.\(^{17,20,26,46,96}\) The accumulation of wound fluid must be managed, as prolonged contact leads to the breakdown of ECM proteins and growth factors, as well as the inhibition of cell proliferation.\(^{20,96}\) The appropriate wound dressing is capable of removing wound exudate while retaining a moist environment to accelerate healing.\(^{20,96,121}\) Wound dressings also assist in reducing protease levels in the wound bed because proteases are held within the dressing until they are absorbed.\(^{15}\) Chronic wound management should focus on conditioning the wound bed and its microenvironment (i.e., rebalancing growth factors, cytokines, proteases, and their natural inhibitors to levels observed in acute wounds).\(^{13,20}\)

1. Dressings with antimicrobial properties should be used only when needed. If used, antimicrobial dressings should be selected based upon the environment in which the injury/wound was created and the resultant level of potential infection.

2. Dressings impregnated with methylene blue and gentian violet are antibacterial options that may be safely used with tissue-engineered skin substitutes or collagen dressings.\(^{13,11}\) Methylene blue with gentian violet also may be used with enzymatic debridement agents.\(^{99,122}\)

3. As drainage is reduced, conversion to a polyurethane sponge or other reduced-fluid capacity dressing may be used to maintain a moist wound environment, which has been shown to accelerate wound healing while reducing pain, tenderness, fibrosis, and infection incidence.\(^{20,121}\)

**Special consideration of collagen dressings.** Collagen dressings used in wound care are comprised of a variety of carriers and combining agents, including gels, pastes, polymers, oxidized regenerated cellulose (ORC), and ethylenediaminetetraacetic acid.\(^{22,123}\) Dressing additives, such as alginates and cellulose derivatives, enhance absorbency, flexibility, comfort, and retain moisture.\(^{42,56}\) Antimicrobial agents, including silver ions (Ag\(^+\)) and PHMB, may be included to control pathogens within the wound.\(^{42,46,56}\) Collagen is derived from various sources (bovine, equine, fish, ovine, and porcine) and varies in type, composition, and structure, with some dressings containing native collagen with a triple-helix formation and others utilizing denatured or reconstituted collagen (gelatin).\(^{11,34,42,56,123,124}\) The use of collagen dressings is advantageous because collagen has multiple roles in wound healing due to its chemotactic properties, including attracting fibroblasts and keratinocytes to the wound, which encourages debridement, angiogenesis, and reepithelialization.\(^{42,56,123,125}\) Research has shown that collagen-based dressings attract and stimulate a variety of cells (fibroblasts, macrophages, epithelial cells) and promote the deposition and organization of newly formed collagen.\(^{42,56,123,126}\)

**Biomaterials derived from an intact ECM.** Provide options that take advantage of the evolving understanding of the complex nature of a native ECM and the retention of its structure and function.\(^{11,11}\) Collagen ECM dressings are a specific subset of collagen dressings, and to date there is only 1 such dressing available commercially. In vitro biophysical analysis has demonstrated that this biomaterial, derived from decellularized ovine forestomach matrix, retains a native collagen architecture (types I and III), along with intact and functional secondary ECM components necessary for structural, adhesive, and resilience properties. It is relatively strong and elastic, making it ideal for wound healing and tissue regeneration applications.\(^{129,130}\) Along with the preserved collagen microarchitecture of native ECM, the biomaterial contains many components of the ECM, including fibronectin, glycosaminoglycans, and elastin.\(^{130}\) Basement membrane components, such as laminin and collagen IV, also are retained.\(^{129,130}\) These sec-

1. Collagen dressings buffer excess MMP activity in the wound.\(^{10,28,42,43,49,53,63,116,117,123-124}\) Given the overexpression and high concentration of proteases (such as MMPs and neutrophil elastase that disrupt the balance between tissue breakdown and repair in chronic wounds), the ability to modulate MMP activity in the wound is beneficial. Collagen dressings may help reduce the destructive effects of elevated levels of proteases and reactive oxygen species, reducing excessive protease activity to a level at which healing may proceed.\(^{36,43,45,49,63,116,117}\)

2. Application of collagen dressings should be sufficient to buffer MMP activity for the duration of the treatment interval.\(^{49,63}\)

3. Use of collagen dressings early in chronic wound management may have a protective effect on the physiological processes of healing by facilitating epithelialization.\(^{63}\)

4. Due to varying levels of protease activity in the wound bed, different quantities of collagen dressing are required to balance elevated protease levels.\(^{47,76}\)

5. Different collagen dressings exhibit substrate specificity and inhibit different proteases with varying efficiencies.\(^{45,134}\)

6. Collagen ECM dressings exhibit broad-spectrum MMP reduction.\(^{45,63}\) A recent assay analysis comparing a collagen ECM dressing with an ORC/collagen dressing demonstrated that the former had inhibitory potency for collagenases (MMP-1 and MMP-8), stromelysin (MMP-3, MMP-10, and MMP-11), gelatinases (MMP-2 and MMP-9), and neutrophil elastase.\(^{45}\) The ORC/collagen dressing exhibited similar inhibitory potency of the gelatinases, but had no significant inhibitory impact on the other MMPs tested.\(^{45}\) Through
the inhibition of a wide range of MMP classes, collagen ECM dressings may offer a significant clinical advantage by more effectively addressing protease imbalance compared with ORC/collagen dressings.45

7. Collagen ECM dressings can provide a provisional matrix that will not degrade when protease levels are buffered satisfactorily. The intact ECM provides a natural scaffold or substrate for wound cell ingrowth,63,130,131 an advantage not offered by dressings comprised of denatured or reconstituted collagen.

8. Collagen ECM dressings also have been shown to contain secondary molecules associated with the ECM, including laminin, fibronectin, and glycosaminoglycans, all of which may have a protective effect on degradation of the matrix being produced by wound fibroblasts.53,129,130

Differing between the collagen compositions offered by the various collagen dressings currently marketed is important. Due to substrate specificity, each type of collagen dressing has different mechanisms of action on the wound bed and attracts different proteases.20,42,50,135 Dressings utilizing native collagen that has not been denatured or reconstituted, especially those with an intact ECM, have the ability to affect multiple steps in the pathophysiology of chronic wounds and may be more effective in rebalancing the wound microenvironment and promoting healing.2,30,63,82 Utilization of a dressing in which the native structure of collagen is retained has been shown to offer several advantages versus their denatured counterparts, including promoting more efficient angiogenesis and greater fibroblast chemotaxis, as well as maximizing the functional behavior of fibroblasts and macrophages, as they are anchored to a three-dimensional architectural structure.11,50,123,136-138

Collagen ECM dressings have the ability to function as a dual-phase dressing throughout the wound management process, which is essential to the success of the early aggressive wound management advocated by the consensus panel. By applying collagen ECM dressings in 2 phases – early in the wound management process for proactive protease management and, again, later in the healing cycle, as is more common – the characteristics of collagen as both a protease reduction agent and a cellular tissue scaffold can be optimized because the collagen ECM retains the properties and functions of native tissue. The first phase of collagen use early in chronic wound management addresses elevated protease levels. In this scenario, a collagen ECM dressing provides consumable intact collagen, with proteases breaking down the collagen in the dressing, thereby reducing the protease activity in the wound bed and preserving the resident collagen in the wound tissues.52,63 Choosing a dressing with broad-spectrum MMP management abilities, such as those with native collagen and an intact ECM, may optimize protease balance in the wound bed. Furthermore, because elastase has a substantial affinity for the triple-helix structure of native collagen, dressings containing native collagen alter the proteolytic environment for elastase, as well as MMPs.50,123 Due to elastase converting precursor pro-MMPs to active MMPs, the MMP levels may be substantially reduced by lowering elastase levels in the wound.50,123 Once optimal protease balance has been achieved, the role of collagen ECM dressings shifts to the second phase, serving as a cellular scaffold that may be incorporated into the wound bed and utilized to achieve cellular migration, proliferation, and organization.63,130,131

The quantity of collagen delivered to the wound must be sufficient to buffer protease activity during the treatment interval; however, protease levels are difficult to assess in the wound bed.16 Therefore, as a general guideline, if all of the collagen has been resorbed at the next dressing change, then an insufficient amount was used and more dressing should be applied for the next treatment interval or the frequency of dressing changes should increase.6 Each application provides the wound a fresh start for achieving protease balance as well as support for production of granulation tissue. Conversely, if too much collagen remains or is dried out, then more moisture should be applied for the next treatment interval. Consistent formation of granulation tissue indicates the quantity and interval of dressing changes are adequate.

Using collagen ECM as a dual-phase dressing for wound bed preparation also is advantageous if later advanced modalities (such as skin grafts or tissue-engineered skin substitutes) are planned or required for full wound closure.19 Biological therapies that aid in wound closure, including recombinant growth factors and grafts, may not be as effective in the presence of excessive proteases or may be destroyed.57,64,119 A collagen ECM dressing assists in balancing protease levels in the wound, while its cellular scaffold feature further enhances the wound bed for the acceptance and optimization of skin grafts or tissue-engi-

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