The Effect of pH on the Extracellular Matrix and Biofilms

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Significance: Chronic wounds become caught in a state of inflammation causing an increase in levels of degrading proteases, which destroy components of the extracellular matrix (ECM) that are essential for the wound healing process. This review aims to highlight and provide readers with an overview of what is currently known about the role of pH and its effect on the ECM and biofilms within healing and nonhealing wounds.

Recent Advances: The pH profiles of healthy skin, acute wounds, and chronic wounds differ significantly. Chronic wounds have an alkaline pH whereas healthy skin has a slightly acidic pH. Although there is evidence on the effect of pH on protease production and bacterial proliferation in wounds, there is little evidence to show its effect on ECM synthesis and degradation.

Critical Issues: The implications for the complex nature of chronic wounds are that no single treatment is relevant for all wounds, but rather a combination of methodologies must be adopted. It is known that pH of a wound reduces throughout the stages of healing, suggesting that wound pH measurements could be beneficial to identify nonhealing wounds earlier and decide on the most appropriate course of treatment.

Future Direction: Wound healing is a very complex process with multiple factors known to play a role. All aspects of the nonhealing wound (defective ECM, pH, microbial invasion, and excess proteases) need to be taken into account when investigating or clinically treating a chronic wound.

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SCOPE AND SIGNIFICANCE

CHRONIC WOUNDS become caught in a state of inflammation causing an increase in levels of degrading proteases, which destroy components of the extracellular matrix (ECM) that are essential for the wound healing process. pH has a significant role to play in both directly and indirectly affecting cellular processes in the wound which in turn affects the wound healing process. Further, the pH will also affect the antimicrobial efficacy of antiseptics used in at-risk or infected wounds. In addition, biofilms are known to also affect wound healing. The ability to eradicate

these from the wound is significantly affected by changes in pH. Consequently, this review aims to highlight and provide readers with an overview of what is currently known about the role of pH and its possible effect on the ECM and biofilms within healing and nonhealing wounds. Current findings and areas where scientific research knowledge of chronic wounds is missing will be highlighted and discussed in this article.

TRANSLATIONAL RELEVANCE

The pH of chronic wounds is predominantly alkaline and they exhibit

slow rates of healing.¹⁻³ Nonhealing wounds are caused by a breakdown in ECM synthesis and/or abundance of defective ECM. The wound becomes caught in a state of inflammation, leading to increased levels of degrading proteases, which destroy components of the ECM that are essential for the wound healing process. A better understanding of the effect of pH and how changing pH modulates biological and biochemical processes in wound healing is required such that future treatment can be better directed preventing the occurrence of a chronic wound.

CLINICAL RELEVANCE

There are currently various treatments clinically available and used for treating a chronic wound. The complex nature of a chronic wound, including a defective ECM, presence of microorganisms, and change in pH, means that not one single treatment is relevant for all wounds. An improved knowledge of the complex interactions within wound healing and what leads to a chronic wound could improve therapeutic treatments with more specific dressings to target the problem as well as the possibility in finding new methods of diagnosing a nonhealing wound and preventative strategies.

BACKGROUND

Chronic wounds are a major health problem worldwide, specifically in older patients, with an estimated 200,000 patients suffering in the United Kingdom alone.⁴ Due to an aging population and the growing incidence of diabetes and obesity worldwide, the burden is fast increasing.⁵ This means that chronic wound healing will soon become a significant problem not only for the welfare of patients but also the cost of treatment to governments and healthcare organizations. The most common types of chronic wounds are venous leg ulcers, diabetic foot ulcers, and pressure ulcers. Wounds typically heal in a timely and efficient manner, following distinct and overlapping phases of hemostasis, inflammation, proliferation, and remodeling.⁶ Several components of the ECM are involved in regulating these processes of healing. A chronic wound occurs when it fails to progress through these phases, becoming caught in the inflammatory phase and as a result re-epithelialization cannot occur, which affects the anatomic and functional integrity of the skin. Chronic wounds are found to reside at an alkaline pH.^{3,7} These wounds exhibit slower rates of healing than acute wounds with a neutral pH.¹ The effects of pH on

some aspects of wound healing are known. These include the effects on matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of matrix metalloproteinases [TIMPs]),⁸ immunological responses,³ and cellular activity.⁹

DISCUSSION

Clinical problem addressed

Due to the complex nature of chronic wounds, such as a defective ECM, presence of microorganisms, and change in pH, no one single treatment is relevant for all wounds. Consequently, a combination of methodologies for the management of chronic wounds should be adopted. An improved knowledge of the complex interactions within wound healing and what leads to a chronic wound will help in enhancing the efficacy of new therapeutic treatments.

It has been found that wound pH reduces as the wound progresses through the stages of healing, suggesting that wound pH could be a useful tool to predict the likelihood of successful wound healing. However, clinical predictions of wound pH can be difficult to make. Current technology only allows for wound surface or wound fluid pH to be measured due to unsuitable probes that can cause further tissue disruption and cell death. Most studies make use of flat glass membrane probes² or litmus paper to simply measure the pH of wounds. However, the conventional glass pH probe only provides localized measurements and does not provide complex measurements for the whole wound area.^{10,11} Wound pH is currently not a factor that is routinely measured clinically. Increasing evidence suggests that chronic wounds are in a state of alkalinity such that, if further studies proved that pH does play an important role in nonhealing wounds, simple pH measurements in a hospital setting could make it possible to identify and diagnose nonhealing wounds earlier. Many wound dressings are currently available, but can these dressings aid in changing wound pH and further improve healing times? Dressings do not alter the pH of normal healthy skin,¹² but some studies have found that dressings applied to a chronic wound can alter its pH.

In a study by Schneider *et al.* it was found that following the application of a nonpermeable dressing wound secretions became more acidic compared with the application of a permeable dressing on a chronic wound.² Some clinical studies looked into the benefit of acidity in wound healing where patients were treated with a solution at a pH of 7.3 or 6.0.^{2,13} Patients treated with the solution

at pH 6.0 showed a much quicker healing time than if treated with the solution at pH 7.4.¹³

Targeting the pH of the wound by the simple application of a specialized dressing could provide a simple healthcare approach to improving wound healing.

Relevant basic science context

The ECM

The synthesis of ECM from skin fibroblasts plays a vital role in supporting normal wound healing. Fibroblasts are summoned to migrate to the wound area and are present in a healing wound from late inflammatory phase until re-epithelialization is complete.¹⁴ Fibroblasts migrate into the wound site secreting ECM proteins, including collagen, glycoproteins, proteoglycans (PGs), glycosaminoglycans (GAGs), and hyaluronic acid. The ECM supports and directs a specific organized response throughout the four phases of healing influenced by specific cellular interactions and growth factors.¹⁵ This allows for successful angiogenesis, granulation tissue formation, re-epithelialization, and remodeling of the skin. However, in a chronic nonhealing wound, the fibroblasts become unresponsive and the ECM molecules become disorganized, leading to a disruption in the phases of wound healing. To date, no studies have shown whether pH has an effect on the synthesis of skin ECM.

The ECM is a highly complex noncellular component of all tissues within the body. It is the largest component of the skin and is fundamental in the process of wound healing. Not only does it provide the cells with an essential scaffold for support, it is also key in initiating and directing biochemical and biomechanical processes crucial for tissue differentiation and homeostasis. In the context of wound healing the ECM consists of four main groups of proteins: structural proteins, adhesive glycoproteins, GAGs, and matricellular proteins (Table 1).

Collagen. Collagen is the most abundant ECM protein; the skin consists of mainly collagen type I, along with small amounts of collagen III, IV, and V.¹⁶ Collagen provides the skin with tensile strength and stability.¹⁷ During early phases of wound healing, collagen III is secreted that is eventually replaced by collagen I in normal wound healing.¹⁶ Collagen type IV is found along the basement membrane where it interacts with other ECM proteins where the epidermal keratinocyte cells attach.¹⁷ In a chronic wound, the synthesis of collagen becomes disorganized, resulting in excess granulation tissue. When the wound eventually

Table 1. The major classes and extracellular matrix components involved in wound healing

Major protein classes	Extracellular matrix proteins		
Structural proteins	Collagens I, III, IV, and V Elastin		
Glycoproteins	Fibronectin Vitronectin Laminin		
Glycosaminoglycans and proteoglycans	GAGs	Small PGs	Large PGs
	Dermatan sulfate	Decorin	Versican
	Chondroitin sulfate	Biglycan	Perlecan
	Heparin sulfate	Fibromodulin	Aggrecan
	Keratan sulfate	Lumican	
	Hyaluronic acid		
Matricellular proteins	SPARC (also known as osteonectin) Thrombospondin-1 Tenascin-C Osteopontin		

heals the resulting scar tissue never achieves the same tensile strength.¹⁵ Studies found that chronic fibroblasts are not able to synthesize collagen to the same extent as normal healthy fibroblasts¹⁸; other investigators, however, found no differences unless cells were stimulated with transforming growth factor- β (TGF- β).¹⁹ In contrast to this, histological studies found that chronic wound tissues are abundant in collagen.²⁰

Elastin. Elastin is an important ECM protein as it functions in the skin to provide elasticity and give such tissues their recoil ability following stretching.¹⁷ Fibroblasts secrete monomers of tropoelastin into the extracellular space where they are then transformed into elastic fibers.²¹ The presence of elastin has not been found in chronic wound granulation tissue to date and data on elastin in chronic wound healing are lacking.¹⁵ Details of elastin degradation are limited within chronic wounds, but in burn wounds it is known that elastase is responsible for the degradation of fibronectin.²²

Fibronectin. Fibronectin is an adhesive glycoprotein synthesized by local cells. It is a multifunctional protein that can act as a biological glue allowing it to interact with other ECM components to direct cell attachment and organization.²³ Fibronectin is essential for cellular migration and wound closure. Upon injury to the skin, fibronectin is incorporated into the fibrin clot forming a provisional matrix that acts as a scaffold to guide migrating cells into the wounded area.²⁴ A histological time course study of a healing wound showed an increase in the presence of fibronectin

over time.²⁰ Strong fibronectin staining was present in the base of ulcer wounds that correlates with the requirement of fibronectin for epidermal cells to migrate across the wound bed.²⁰ These studies have shown that fibronectin is critical in the process of normal wound healing. However, in chronic wounds, fibronectin is degraded by proteases. Fibronectin degradation products have been found in chronic wound fluid along with the degrading protease elastase.²⁵

GAGs and PGs. GAGs are long polysaccharide molecules that are present in the skin ECM. They have specific properties (viscosity and lubrication) contributing to cell adhesion and water attraction such that local cells maintain hydrated. Hyaluronan (HA) is the predominant GAG in the skin and is also found in increased amounts in damaged or growing tissues.¹⁷ During wound healing, GAGs bind to chemoattractants such as TGF- β to provide cues to direct the migration of inflammatory cells toward the wounded area. In chronic granulation tissue, GAG levels are increased correlating with high levels of HA found in fetal wound healing that supports scarless wound healing.²⁶

All GAGs, with the exception of HA, are covalently linked to a protein core forming a PG. In the skin, the predominant PGs are versican and decorin. PGs may have a role to play during wound healing as they are important in regulating cell proliferation, matrix adhesion, and assembly.²⁷ PGs in chronic wounds have not been studied in depth; a histological study found some differences between normal and chronic skin.²⁷ The location of PGs in chronic wounds could have an important role as their function in binding to growth factors could further influence wound healing.

Matricellular proteins. Matricellular proteins (SPARC, thrombospondin-1, tenascin-C, and osteopontin) do not act as structural proteins but control and regulate interactions between the cells and the ECM.¹⁵ Therefore, any defects in these proteins could result in a nonhealing wound. Levels of tenascin-c are elevated in chronic wounds specifically at the wound edge.²⁸ Tenascin-c disrupts the binding of fibronectin such that cell migration becomes limited and disorganized.

Proteases. Proteases, specifically MMPs, play a key role in the degradation and remodeling of the ECM during wound healing. MMPs and their inhibitors (TIMPs) are carefully regulated such that there is a balance between the synthesis and degradation of the ECM during wound healing.⁸

Table 2. *Changes in extracellular matrix molecules within a chronic wound*

<i>Extracellular matrix protein</i>	<i>What happens in a chronic wound</i>
Collagen	The collagen deposited becomes disorganized causing excess granulation tissue
Fibronectin	Fibronectin synthesis is decreased and is absent in chronic granulation tissue
Glycosaminoglycans	Increased levels are found in granulation tissue, most specifically hyaluronan
Elastin	Levels are decreased
Tenascin-c	Levels are elevated
Proteases	Increased levels

However, in a chronic wound, protease levels are consistently elevated such that breakdown of the ECM supersedes the synthesis of new ECM. Chronic wounds become caught in the inflammatory stage, characterized by abundant levels of proteases, which further enhances ECM breakdown (Table 2).

Relevant basic science context

pH and wounds. Healthy, intact skin has a slightly acidic pH ranging from 4.0 to 6.0. This is an important aspect of the skin's barrier function, since it regulates bacterial flora and prevents infection.²⁹ When a wound occurs, the skin's acidic milieu and pH is disrupted, exposing the more neutral pH (7.4) of the underlying tissue.² With successful healing and re-epithelialization, the skin returns to being acidic. Acute wounds have a more neutral pH and, during acute wound healing, there is a drop in pH caused by various factors, including hypoxia¹ and increased production of lactic acid.³⁰ An acidic pH environment is considered to be beneficial, by increasing fibroblast proliferation and migration and also regulating bacterial colonization. If however wound healing is delayed, then the pH will oscillate and become increasingly alkaline over time (Figs. 1 and 2).² At this stage the wound is described as chronic and the synthesis of ECM molecules becomes impaired, thus arresting the healing process. Recordings of the chronic wound environment have been in the range of pH 7.15 to 8.9³.

As wounds progress through the stages of healing, studies have shown that a shift toward an acidic pH occurs. A study of 50 patients measured the wound pH during the course of healing. Wounds presented with a pH of 8.5 or more, but as the wound began to heal pH values reduced to 8 and below.³¹ Other studies have demonstrated a difference in pH of wounds classed as being in different stages of healing. Stage-3 ulcers had a pH of 7.6 compared with stage-1 ulcers with a more acidic

Figure 1. Time course of pH of healthy skin, acute wounds, and chronic wounds showing the main differences with time. Adapted from Schneider *et al.*² To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

Figure 2. Schematic highlighting the key wound healing events and conditions that occur at various environmental pH.

and similar pH to intact skin (pH 5.4–5.6).¹² The progression toward an alkaline pH in a chronic wound and how this affects the phases of wound healing is not clearly understood.

It is reported that bacterial colonization may contribute to the shift toward an alkaline pH.² Pathogenic bacteria have demonstrated a preference to a more alkaline environment to grow and bacterial colonization and proliferation is encouraged at a higher pH.³² Therefore, when the underlying tissue is exposed, it provides opportunity for the growth of the resident skin flora, which can colonize the wound. This causes a shift in pH, making the wound environment alkaline as it develops into a chronic wound. Finding a way in which the acidic milieu of the skin can be restored would effectively reduce microbial load of the skin surface and decrease the likelihood of bacterial colonization in a chronic wound. A clinical study in 2002 demonstrated that the topical application of acidic ointments in diabetic patients significantly reduced the bacterial load on the skin surface.³³

Many researchers have shown that pH is increased in a chronic nonhealing wound environment, but there is very little research and evidence about how this change in pH ultimately affects the skin ECM. Is it the increase in surrounding pH that triggers a dysfunctional ECM and changes in the phases of wound healing or is it the alterations in ECM–cell interactions and synthesis that cause the wound to become alkaline?

A study by Lengheden and Jansson investigated the effects of pH between 7.2 and 8.4 on human periodontal ligament and embryonic lung fibroblasts *in vitro*. Growth and attachment of these

cells showed a significant decrease above pH 7.8.⁹ Cell migration and DNA synthesis were significantly reduced with an increase in pH; maximum fibroblast migration occurred between pH 7.2 and 7.5.⁹ Skin keratinocytes tolerate a much wider pH range compared with fibroblasts and show optimal migration at pH 8.5, far more alkaline than fibroblasts can tolerate.²⁹ If changes in pH can change the behavior of the skin keratinocyte and fibroblast cells, then it may also consequently modify the wound healing process. An alkaline pH could be beneficial for increased epithelial growth; however, an alkaline environment would also be more advantageous for microbial growth and infection.

Protease activity is extremely pH sensitive with peak activity between pH 7 and 8 and a significant decrease in activity in an acidic environment (Fig. 2). A balance of protease activity is essential for wound healing; an excess of proteases impedes the process of wound healing. The pH-dependent activity profiles of four proteases important in wound healing were assessed; they showed similar pH profiles, with optimum activity between pH 7 and 8.⁸ Wound fluid and chronic wound pH correlate with optimum protease activity, therefore an ideal environment for proteolytic activity. Greener¹⁰ suggested that reducing the environmental pH from 8 to 4 would significantly reduce the activity of these proteases and that reducing the environmental pH of chronic wounds would act as a way in which to control proteolytic activity and return the wound to a healing state.

Relevant basic science context

Biofilms in chronic wounds. Wounds are colonized with bacterial biofilms,³⁴ which further contribute to the chronicity and failure to heal of chronic wounds. It is now recognized that bacteria aggregate together on a surface or an air/liquid interface and exist in the form of a biofilm and not as free-living planktonic bacteria.³⁵ This makes open wounds a great environment for bacterial attachment, with a moist surface and plenty of nutrition for biofilm growth.³⁵ Biofilms are complex communities of aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix (EPS) made up of proteins, lipids, and polysaccharides.^{34,35} Once formed, biofilms form a protective surrounding environment, forming a complex structure that allows transfer of nutrients and waste products. Within a biofilm, bacteria modify their phenotypes, resulting in altered production of virulence factors. These factors, in addition to the surrounding layer of EPS, make biofilms very difficult to remove and eradicate as

they are highly resistant to conventional antibiotic therapy.³⁶

Many studies have now highlighted the presence of bacteria and biofilms within acute and chronic wounds, which may delay the healing process. More specifically, not just one bacterial organism, but a community of several, such that polymicrobial interactions potentially play a crucial role in wound healing. James *et al.*³⁷ have shown direct evidence of the presence of biofilms in human chronic wounds using light and scanning electron microscopy. Sixty percent (30 out of 50) of the chronic wounds examined revealed the presence of biofilms, whereas only one of the acute wound specimens presented with a biofilm.³⁷ Further molecular analyses confirmed that these biofilms contained a diverse polymicrobial community of microorganisms.³⁷ Evidence of bacterial biofilms in equine chronic wounds has been reported with 61.5% (8 out of 13) of equine wounds showing the presence of a biofilm.³⁸ Further, bacterial isolates obtained from these wounds showed a significantly higher biofilm-forming potential than isolates obtained from uninjured skin.³⁸ Gram-positive cocci were the most common bacteria observed in all chronic wound samples,³⁷ which associates with staphylococci organisms being known as good biofilm formers. The polymicrobial nature of biofilms within a chronic wound has also been confirmed with multiple species identified, the most common being *Staphylococcus aureus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*.^{37,39}

Effect of biofilms on fibroblasts and the ECM. There is still much debate around whether biofilms delay wound healing. It is likely that within a chronic wound, biofilms colonize the dermal layers and have a detrimental effect on skin fibroblast and keratinocyte cells. The synthesized products from planktonic and biofilm bacteria (planktonic/biofilm conditioned media) have recently been shown to have effects on human epithelial keratinocytes⁴⁰ and dermal fibroblasts *in vivo*.⁴¹ *S. aureus*-planktonic- and biofilm-conditioned media significantly reduced keratinocyte and fibroblast cell viability and migration. Biofilm-conditioned media induced higher levels of TNF- α compared with planktonic-conditioned media.⁴¹ Whereas planktonic-conditioned media was responsible for an increase in interleukin-6, transforming growth factor- β 1, MMP-1, and metalloproteinase-3 compared with biofilm-conditioned media.⁴¹ What effect biofilms have on the synthesis of ECM from fibroblasts is unclear. The presence of some bacteria in a wound seems to have a positive effect in inducing an inflammatory re-

Table 3. The optimum growth pH for the most prevalent microorganisms isolated from wounds

Wound-associated microorganisms	Optimum pH for growth
<i>Staphylococcus aureus</i>	7.0–7.5
<i>Enterococcus faecalis</i>	7.0–9.0
<i>Pseudomonas aeruginosa</i>	6.6–7.0
Coagulase-negative staphylococci	7.0–7.5
Anaerobic bacteria	6.0–7.0
<i>Escherichia coli</i>	6.0–7.0
<i>Klebsiella</i> spp.	5.5–7.0
<i>Candida</i> spp.	7.0–8.0

sponse for the process of normal wound healing. Some researchers have found that very low levels of bacteria in fact accelerate wound healing and the formation of granulation tissue.⁴² However, an increase in bacterial load within a wound has the opposite effect. An increase in the production of bacterial enzymes results in excess granulation tissue and scar formation.³⁵ Therefore, increased microbial density within a wound could correlate with chronicity.

Effect of pH on biofilms. Various environmental factors affect the growth of bacteria, including temperature, pH (Fig.2), dissolved gases, osmotic pressure, and water availability. Most bacterial organisms grow best around pH values of 6.5–7.0; however, some thrive in very acidic (e.g., *Acetobacter*) or very alkaline conditions (e.g., *Candida*). Organisms grow at a range of pH defined as three cardinal points: (1) the minimum pH, below which the organism cannot grow; (2) the maximum pH, above which the organism cannot grow; and (3) the optimum pH, at which the organism grows best. Each microbial species has its own pH range in which it grows best (Table 3).

Growth of free-floating planktonic bacteria is affected by changes in pH, so does pH, therefore, have any effect on biofilm growth and formation of these microorganisms within a wound setting? If so, does a biofilm benefit from alkaline conditions known to occur in a chronic wound? Or is it the growth of biofilms that contributes to the alkalinity and nonhealing state of chronic wounds.

To date no studies have specifically looked at wound-derived bacteria and the effect of pH on their growth and formation of a biofilm within a wound. Some studies have looked at the role of pH in dental plaque biofilms⁴³ and in urinary tract infections.⁴⁴ A brief study by Hostacka⁴⁵ was carried out to look at the effect of pH on the most common pathogens associated with healthcare-associated infections. These included *P. aeruginosa*, *Klebsiella* spp., and *Vibrio cholera*. Their biofilm-forming ca-

TAKE-HOME MESSAGES

- The presence of biofilms, proteases, defective ECM, and change in pH make chronic wounds very difficult to treat.
- pH has a role to play in wound healing.
- pH could be used as a simple tool to quickly recognize a nonhealing wound.
- Targeting the pH and making the wound environment acidic could benefit the healing process.

capacity is considered to be the main reason for their persistence and why conventional antimicrobial treatments failed to eradicate them.⁴⁵ Results showed that increasing pH correlated with an increase in biofilm production by all microorganisms analyzed. Significantly higher biofilm production was observed at pH 7.5 and 8.5 compared with pH 5.5.⁴⁵ Initial growth (0–6 h) of planktonic *S. aureus* showed a decrease in pH 8.5 compared with pH 7.2.⁴⁶ Both specific *S. aureus* and *S. epidermidis* strains failed to adhere to a surface in alkaline conditions and biofilm biomass formation was significantly reduced at pH 8.5 compared with pH 7.2.⁴⁶ Another study showed that very acidic (pH 3) and very alkaline (pH 12) conditions resulted in *S. aureus* not being capable of successfully forming a biofilm compared with neutral pH conditions.⁴⁷ Earlier studies have demonstrated an enhanced adherence of a specific *S. aureus* strain in alkaline conditions compared with acidic conditions. This could relate to the high incidence of biofilms within alkaline chronic wounds. The differences reported on variations between pH and biofilm development demonstrate evidence that variation between the same species of bacteria exist. Therefore, even a bacterium with the same name, that is, *S. aureus*, isolated from one patient from one environment will not be equivalent to a *S. aureus* isolated from a different patient or environment. This is often an overlooked yet fundamental research need in wound microbiota studies.

SUMMARY

Chronic wounds are very complex with many factors involved, including changes in pH, presence of biofilms, defective ECM synthesis, and an increase in proteases. Is it just the presence of one factor that is the main cause of a chronic wound such that this should be concentrated on from a research and clinical perspective? Or is it the presence or change in one of these factors that begins a downstream chain reaction to negatively affect all other factors, which exacerbates the

healing process? Further research is required to clarify how these effects individually and together contribute to the delay in wound healing, and then chronic wound treatment can be better directed. Although more research is required to further investigate the role of pH in healing and nonhealing wounds. It is important to remember that a chronic wound has a very complex environment. All aspects of the nonhealing wound (defective ECM, pH, microbial invasion, and excess proteases) need to be taken into account when investigating or clinically treating a chronic wound.

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At the time of this writing Steven L. Percival was employed by Scapa Group Plc.

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Professor Steven Percival holds a PhD in microbiology and biofilms, a BSc in Applied Biological Sciences, Postgraduate Certificate in Education, diploma in Business Administration, an MSc in Public Health, and an MSc in Medical and Molecular Microbiology. Early in his career, Steven held R&D positions in the Department of Biotechnology, British Textile Technology Group (BTTG) Plc, followed by 6 years as a senior university lecturer in medical microbiology and later the positions of Director of R&D and Chief Scientific Officer at Aseptica, Inc., and senior clinical fellowships at the Centers for Disease Control, Atlanta, and Leeds Teaching Hospitals Trust, Leeds. More recently, Steven held senior R&D positions at Bristol Myers Squibb, ConvaTec, Advanced Medical Solutions Plc and held an honorary Professorship in the medical school at West Virginia University. In 2011, Steven joined Scapa Healthcare Plc as Vice President of Global Healthcare R&D and in 2012 was awarded the position of honorary professor at the University of Liverpool. He has written over 300 scientific publications and conference abstracts on biofilms, antimicrobials, wounds, and infection control and has authored and edited seven textbooks. Steven has provided over 100 presentations globally at conferences, universities, and hospitals. He is an editor of the *Journal of Medical Microbiology* and holds a number of honorary and advisory board roles.

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Abbreviations and Acronyms

ECM = extracellular matrix
 EPS = extracellular polysaccharide matrix
 GAG = glycosaminoglycan
 HA = hyaluronan
 MMP = matrix metalloproteinase
 PG = proteoglycan
 TGF- β = transforming growth factor- β
 TIMP = tissue inhibitor of metalloproteinase
 TNF- α = tumor necrosis factor- α