SCHOLARLY REVIEW

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Approach to chronic wound infections

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Summary

Infection is the likeliest single cause of delayed healing in healing of chronic open wounds by secondary intention. If neglected it can progress from contamination to colonization and local infection through to systemic infection, sepsis and multiple organ dysfunction syndrome, and it can be life-threatening. Infection in chronic wounds is not as easy to define as in acute wounds, and is complicated by the presence of biofilms. There is, as yet, no diagnostic for biofilm presence, but it contributes to excessive inflammation – through excessive and prolonged stimulation of nitric oxide, inflammatory cytokines and free radicals – and activation of immune complexes and complement, leading to a delay in healing. Control of biofilm is a key part of chronic wound management. Maintenance debridement and use of topical antimicrobials (antiseptics) are more effective than antibiotics, which should be reserved for treating spreading local and systemic infection. The continuing rise of antimicrobial resistance to antibiotics should lead us to reserve their use for these indications, as no new effective antibiotics are in the research pipeline. Antiseptics are effective through many mechanisms of action, unlike antibiotics, which makes the development of resistance to them unlikely. There is little evidence to support the theoretical risk that antiseptics select resistant pathogens. However, the use of antiseptic dressings for preventing and managing biofilm and infection progression needs further research involving well-designed, randomized controlled trials.

What's already known about this topic?

- Infection is the most likely cause of stalled healing in chronic wounds.
- Infection in chronic wounds is a clinical decision-making process; a diagnostic would be useful for practitioners.
- Presence of biofilm cannot be detected clinically and a diagnostic is needed.

What does this study add?

- Presence of biofilm is the likely cause of persistent infection and requires maintenance debridement at dressing changes, as well as topical antiseptic intervention.
- Use of antibiotics to treat infections in chronic wounds requires strict antibiotic stewardship.

Worldwide it has been estimated that 20 million individuals have chronic wounds, and the cost of their management and treatment exceeds U.S. $31 billion a year.[1] In addition, the indirect costs associated with the management of these chronic wounds include decreased quality of life and reduced productivity. It is paramount that clinical practitioners have a thorough understanding of current diagnostic modalities and principles of chronic wound care in an effort to improve patient outcome and reduce costs, particularly in relation to the complication of infection.

Demographically, the prevalence of chronic wounds increases with age, and the risk of developing a chronic wound is higher in women than in men.[2] Unfortunately many of these wounds, such as pressure ulcers and chronic venous insufficiency with lower-limb ulceration, rarely heal expeditiously, placing a significant fiscal burden on both the patient and healthcare systems.[3] The biology of chronic wound healing processes is complex, and several factors contribute to delayed healing including chronic metabolic disease (diabetes), neurological defects, vascular insufficiency, nutritional insufficiency and age; often many of these factors will act in concert to delay the healing process, placing the wound within a state of prolonged inflammation with incomplete and disorganized healing.[4,5] Delay in healing relating to infection is common to all these wounds and is complicated further by rapidly increasing antibiotic resistance and the almost complete lack of new antibiotic groups in the research pipeline. Alternative or complementary adjuncts to antibiotic therapy have to be seriously considered to address this issue. The following discussion will address several key topics, relevant to current understanding, management and treatment of infection in chronic wounds.

Infection as an adjunctive factor in chronic wounds

Infection, with its associated excessive or inappropriate inflammation,[6] is the likeliest cause of delayed healing in acute and chronic wounds, despite the wide range of antimicrobials that are available for prophylaxis and treatment. Paradoxically, research related to infection prevention and control in wounds, and particularly to chronic wounds, lags behind the progression that has been made in the laboratory-based understanding of the pathophysiology of wound healing and the healing cascades. Textbooks continue to be published about these advances in tissue engineering, antiscarring, molecular biology, stem and progenitor cells and regeneration; the list is impressive.[7–9]

However, the clinical potential of many of these *in vitro* advances has not translated well from bench to bedside, as their clinical effectiveness or their cost is negated by various underlying pathologies and morbidities, such as diabetes, peripheral vascular disease, venous hypertension and unrelieved pressure, which cannot be adjusted for in laboratory-based models. In addition, the development of infection can be the principal cause of failure of these new adjuncts or modalities to aid stalled healing in chronic wounds. As chronic wounds in particular challenge both diagnosis and treatment, this scholarly review article will focus specifically on chronic wounds.

Definitions of infection

Acute infection

The definition of acute infection, and inflammation, is based on the time-honoured Celsian observations of *rubor et tumor, cum calore et dolore* (redness, swelling, heat and pain). The mediaeval addition of *functio laesa* as a result of swelling or pain is now also included. The diagnosis of acute infection has always been based principally on clinical appraisal, although the support of microbiological laboratories, radiological imaging and intervention, and other modalities, is widely available. Undergraduates are taught that, in broad terms, the risk of infection in acute and chronic wounds is related to the number and virulence of infecting organisms, and adequacy of the host response. However, unequivocal identification of wound infection is challenging, and particularly difficult in patients with chronic wounds. At least half of patients with a limb-threatening infection may not manifest systemic signs of infection, and the yield of bacteria from a wound does not necessarily prove the presence of an infection.

Early identification of wound infection is important. When early, localized infection is not adequately controlled by host response or therapy it can progress to cellulitis, lymphangitis with lymphadenopathy, bacteraemia, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) and organ failure, sepsis and death (Tables 1 and 2).

Infection in chronic wounds

The diagnosis of infection in chronic wounds is not so straightforward (Table 3). Attempts to facilitate this have come through 'expert opinion' and use of a Delphi assessment.[10–12] Underlying comorbidities, exhibited in diabetic foot, venous and arterial leg ulcers, and malignant ulcers, obtund the host response and promote the formation of a biofilm and risk of infection. A holistic approach to this with appropriate attention to underlying relevant systemic and local pathologies is the key to the understanding and management of infection in chronic wounds, not reliance on antimicrobials. The bioburden in chronic, open wounds presents as a continuum from contamination through colonization to local and systemic infection (which is just as potent in leading to SIRS, MODS and mortality as in acute wounds). Although a precise definition has not been agreed on, a prelocal, or covert, preinfection phase has been referred to as 'critical colonization'.[13] The progression or lack of control of critical colonization may relate to uncontrolled biofilm formation.[14]

The role of biofilms

All bacteria have evolved the facility for self-preserving, parasitic relationships through the formation of biofilms; their role

Table 1 Systemic inflammatory response syndrome (SIRS). Manifestation of any two of the clinical components constitutes SIRS

Component	Value
Pyrexia	> 38 °C (or < 36 °C)
Tachycardia	> 90 beats per min
Tachypnoea	> 20 breaths per min (or $PaCO_2$ < 4.2 kPa)
White blood cells	> 12 × 10^9 cells L^{-1} (or < 4 × 10^9 cells L^{-1})

Table 2 Sepsis, multiple organ dysfunction syndrome and septic shock

Sepsis is systemic inflammatory response syndrome with documented infection	
Severe sepsis, or sepsis syndrome, with evidence of organ dysfunction has these features:	
Cardiovascular	Systemic vascular resistance < 800 dyne s^{-1} cm^{-3} or blood lactate > 1.2 mmol L^{-1}
Respiratory (acute respiratory response syndrome)	Increasing positive-end expiratory pressure, PaO_2/FiO_2 < 30; PaO_2 < 9.3 kPa
Renal (acute tubular necrosis)	Urine output < 120 mL per 4 h, rising urea or creatinine
Central nervous system	Glasgow coma scale < 15 without sedation
Gastrointestinal	Stress ulceration, ileus, hepatic dysfunction
Haematological	Coagulopathy, thrombocytopenia
Metabolic	Insulin resistance
Septic shock is severe sepsis refractory to fluids and requires inotropes to maintain mean arterial blood pressure	

FiO_2, fraction of inspired oxygen.

in clinical infection has been recognized only over the last 20 years.[15–17] Biofilms are present on at least 70% of chronic ulcers and are also present in acute wounds where they cause a risk of delayed infection; this is a particular complication of major joint replacement. Late infection, caused by coagulase-negative staphylococci, often with multiresistance,[18] is almost certainly mediated through this route.[19] Persistent and relapsing skin and soft-tissue infections might also be caused by this mechanism.

Biofilms are made up of a complex protective glycocalyx, produced by bacterial communities, which protects them from host defences and antimicrobial therapy, whether it is administered topically (antiseptics) or systemically (antibiotics). Within a biofilm bacteria are able to communicate through 'quorum sensing', while being sustained and protected within their slimy matrix, through channels that permit nutrient, gas and chemical signal molecule ('autoinducers') exchange.

When in this state they are sessile and called persister cells, and are relatively metabolically inert and protected. However, when conditions are appropriate they can undergo a phenotypic change, with a rapid expression of new proteins,[20] and become planktonic and free of the biofilm. Their change from sessile to planktonic state is supported by fluctuations in bacterial cell population density, which correlates directly with production and release of autoinducers serving as signals to other bacteria to regulate gene expression (for example), which then may influence bacterial virulence and development of resistance against antibiotics, motility or even new biofilm production. Hence, bacteria embedded in biofilms may use 'quorum sensing' communication to regulate a broad spectrum of activities. Once active, and released from biofilm in their planktonic state, microorganisms may lead to infection by becoming invasive into adjacent tissues. However, it is only in this planktonic state that they can be recognised through harvest and culture, which is the basis for conventional microbiological reporting. Even use of the Levine technique or biopsies for conventional microbiological harvest only reveals presence of planktonic bacteria; such techniques are ineffective in demonstrating the presence of bacterial persister cells in biofilm.[21]

Table 3 Characteristics of infection in chronic wounds

Abnormal granulation tissue (excessive 'vascular' hypergranulation)
Bleeding from friable granulation tissue at the wound surface
Epithelial bridging and pocketing in granulation tissue
Wound breakdown and enlargement
Changes in colour of the wound bed from red to green/yellow or black
Increasing inflammatory signs and abscess formation
Increasing pain
Increasing odour
Increased exudate and maceration of surrounding skin
Delayed healing (beyond expectations)

The value of bacterial colony counts in biopsies, originally found useful for the diagnosis of infection in burns, must now be considered as being mythical for the diagnosis of infection in chronic wounds. The organisms involved in chronic wound biofilms are polymicrobial and need sophisticated molecular techniques for recognition.[22,23] They also pose an additional therapeutic challenge, as the polymicrobial nature of related infection is not recognized, and microbiological laboratory results give poor clinical guidance.[24]

While biofilms persist on, and exist within, chronic wounds, they can induce a prolonged, inappropriate, inflammatory host response (through stimulation of neutrophils and macrophages) to cause a prolonged release of nitric oxide, inflammatory cytokines and free radicals, and activation of immune complexes and complement, leading to a delay in healing.[15,25,26] This delay is not an inert biological process; quite the reverse, inflammatory processes and healing cascades may become excessive and out of phase. This concept, which helps to explain why chronic wounds fail to heal, is not new,[27–30] but does suggest that biofilms should be removed and suppressed from reforming. It is also possible that biofilms may turn an acute wound into a chronic one, which might be particularly relevant in diabetic foot ulcers.

Biofilms cannot be seen with the naked eye, although they are almost certainly present in chronic wounds, particularly when there is delayed healing. A diagnostic guideline to recognize likely biofilm presence in chronic wounds has been proposed:[31–33] (i) microbiological evidence of a localized or foreign-body-associated infection; (ii) confocal or scanning

electron microscopic evidence of microbial aggregation/glycocalyx from wound biopsies; (iii) recurrent infection in a chronic wound with organisms that are clonally identical; (iv) documented history of persistent infection despite the correct dose and duration of an appropriate antimicrobial; (v) presence of local or systemic signs and symptoms of infection (Tables 1 and 2) that resolve after appropriate antimicrobial therapy but recur after termination of therapy; and (vi) a chronic wound bed that is heavily exuding or covered with 'fibrinous' or necrotic material that needs repeated debridement (Table 3).

It has been suggested that maintenance debridement be undertaken at every dressing change, particularly when healing is stalled and certainly when signs of chronic infection are present.[34–38] Its success presumably relates to the delay in reformation of the biofilm. Maintenance debridement can be undertaken with a minimal skill set, and often without the need for analgesia [other than oral analgesics or topical EMLA® cream (AstraZeneca UK Ltd, Luton, U.K.)], using conventional scalpel and scissors, or a ring curette.[39] The use of a 'soft brush' has proven effective, akin to daily brushing of teeth, and can be used as a substitute by the more faint hearted.[40] More sophisticated use can be made of negative-pressure wound therapy (NPWT) or high-pressure irrigation techniques, but they are more expensive and need considerably more training, particularly with the need for attention to the infection/control aspect of using high-pressure irrigation or hydrotherapy devices in a treatment room.[41] Biofilm debridement from chronic wounds is probably, at best, only suppressive, which is why maintenance debridement is effective.

The process of preparation of a chronic wound bed, for optimal healing, is taken from plastic surgical practice, in which a recipient wound site is made as receptive as possible to receive a split-thickness skin graft. This has been taken up and used as part of the TIME concept.[12] The acronym stands for Tissue assessment and debridement, Infection/Inflammation, Moisture imbalance and Edge of wound assessment. The framework has been taken up widely for the assessment and management of chronic wounds. In open wounds, where infection and biofilms can be controlled by antimicrobial therapy (topical antiseptics and systemic antibiotics) and debridement, healing is likely to progress successfully by secondary intention with adequate wound and dressing care alone – coupled of course with attention to holistic care and correction of underlying disease processes.

Use of antiseptics to prevent and manage bioburden in chronic wounds

Antiseptic agents differ from antibiotics in three perspectives: antiseptics are used topically and cannot be given systemically, they have more than one mechanism of action, and their bacteriostatic/bactericidal activity occurs within a matter of seconds rather than minutes. The use of antiseptics at dressing changes to complement wound cleaning, irrigation and debridement reduces bacterial burden and suppresses biofilm formation and reformation, ideally without impacting adversely on the wound healing process.[42] In ideal conditions antiseptic agents should possess a broad antimicrobial spectrum, demonstrate persistence within the wound bed, not be unduly inactivated by blood or tissue protein, be noninjurious to eukaryotic cells and possess minimal allergenicity.

Presently several antiseptics are available for clinical use,[4,43,44] and include phenolics, hydrogen peroxide, hexachlorophane, cetrimide, benzalkonium salts, potassium permanganate, dilute hypochlorite preparations (such as 0·025% Dakin's solution), iodophor compounds (including povidone and cadexomer iodine), chlorhexidine gluconate, triclosan, silver-releasing compounds, and polyhexamethylene biguanide, polyhexanide and octenidine.

Povidone iodine, chlorhexidine and octenidine are used as skin antiseptic agents to reduce the microbial burden on the surface of the skin (preadmission shower and perioperative skin preparation) prior to surgery. While povidone iodine is both potent and broad spectrum, its antimicrobial activity can be diminished in the presence of blood or tissue protein.[43] Furthermore, several studies have suggested that povidone iodine can exert a cytotoxic effect, delaying or inhibiting wound healing.[45,46] Several animal and human studies have investigated the efficacy and safety of chlorhexidine on wounds, and it has been found safe with little or no adverse effect on wound healing.[47–49] In 2011, the U.S. Food and Drug Administration approved a chlorhexidine 0·05% antiseptic solution for wound cleansing and irrigation. Depending on the application time this concentration of chlorhexidine has been documented to reduce the bioburden of both Gram-positive and Gram-negative healthcare-associated pathogens by a factor of five to six logs.[50,51]

Cadexomer iodine promotes the absorption of fluids, exudate, debris and bacteria from the wound bed while at the same time facilitating the slow controlled release of iodine at nontoxic levels.[52,53] Silver ions are effective against most common healthcare-associated pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and multidrug-resistant Gram-negative bacteria.[54,55] Silver is a good example of an antiseptic agent that exerts antimicrobial activity at multiple sites in the bacterial cell. The multiple mechanisms of action involve binding (silver) to and disrupting the bacterial cell wall, damaging intracellular and nuclear membranes, and poisoning the respiratory enzymes and denaturing both DNA and RNA.[56,57] While silver is an effective, broad-spectrum antiseptic, some investigators have reported that silver may be toxic to keratinocytes and fibroblasts.[58,59] However, these reports should be tempered with current clinical evidence suggesting that silver-impregnated dressings do not adversely impact wound healing. A controversial paper[60] has suggested that silver dressings do not enhance healing in chronic venous ulcers and that they are not cost–effective. Silver dressings were introduced to control chronic wound bioburden, and they have been independently claimed to be effective for this purpose; procurement manag-

ers should perhaps ignore the results of this VULCAN study.[61,62]

These antiseptic properties have also been used successfully as an adjunct to NPWT and chronic wound cleaning/irrigation techniques. Polyhexamethylene biguanide has proven effective for NPWT instillation, but other antiseptics such as cadexomer iodine and silver as irrigants or in dressings are also effective in control of bacterial colonization and biofilm formation.[37,61–65] The use of such topical antimicrobials is more effective after the biofilm has been disrupted by debridement.[66]

Antiseptics are unlikely to cause bacterial resistance, although there is a theoretical risk of selection of resistant organisms, but to date no antiseptic-resistant human pathogen causing untreatable infection has emerged.[67] The mechanism of action of antiseptics is through toxicity to several aspects of bacterial metabolism: disruption of efflux pumps, damage to cell walls and cytoplasmic processes, and nuclear disruption.[12,68] A European directive,[69] after consideration of the antiseptic triclosan, reported that there was no cause for concern related to this hypothetical risk of antiseptic resistance/selection, provided antiseptic use was realistic and controlled. By contrast, antibiotics have selective antimicrobial activity and their overuse or misuse risks resistance, which is transmissible and a major concern to public health.[70] The tissue toxicity to antiseptics, based on experimental and mostly *in vitro* experiments, has probably been overstated, although disinfectants have a limited use.[68]

The current level of medical evidence suggests that antiseptics are an important component of our 'current therapeutic armamentarium' for chronic wound care. A major advantage of using an antiseptic for the treatment and management of a chronic wound, compared with antibiotic therapy, is the reduction of a risk of causing the emergence of a drug-resistant pathogen, which in turn may lead to increased patient morbidity and resource utilization.

Microbiology and use of antibiotics in chronic wound care

Loss of skin integrity exposes the subcutaneous tissues to microbial contamination and colonization; the resulting inflammatory response is enhanced by the presence of foreign bodies (such as sutures or retained dressing materials) or tissue devitalization. The organisms that colonize these damaged tissues often form a diverse, polymicrobial community that, as discussed earlier, often leads to biofilm formation. The diversity of this polymicrobial community has a profound impact on the intrinsic biology of the chronic wound, as this heterogeneous population often fosters a mutual symbiosis, exacerbating the out-of-phase, inappropriate and excessive inflammatory component of the chronic wound process.[71] The development of a polymicrobial infection, involving both aerobic and anaerobic bacteria, is facilitated by a low oxygen tension, leading to a reduced redox potential within the wound bed. The synergistic relationships that exist between these various microbial populations, especially involving fungi, are associated with a higher probability of recalcitrant infection.[43,72]

Historically, antibiotics have been administered systemically and topically in the treatment of chronic wound infections. The list of antibiotics that have been used systemically is large, spanning virtually all antimicrobial classes, including the beta-lactams, aminoglycosides, macrolides, quinolones, lincosamides, nitroimidazoles and selective sulfonamide agents, or combinations of these. The list of topical antibiotic agents that have been used is substantially smaller and includes mupirocin, fusidic agents, neomycin, polymyxin and bacitracin.[43] A systematic review has assessed the clinical and cost–effective efficacy of systemic and topical antibiotic agents in the treatment of chronic skin wounds.[73] The authors of this review suggested that there was insufficient evidence to support any 'routine' use of systemic antibiotics in specific chronic wounds, such as diabetic ulcers. Antibiotic therapy should be viewed as one component of a multifaceted 'targeted' strategy addressing both wound biology (repair) and microbial pathogenicity and used for specific indications. Simply moving on to another antibiotic in the diminishing list that remains ought to be resisted and accompanied by increased attention to this multifaceted strategy.

Therapeutic efficacy in the treatment of an infected, chronic wound is dependent on four interrelated factors: (i) antimicrobial tissue concentrations at the site of the infection; (ii) the presence of ischaemia or tissue necrosis, which impairs drug distribution; (iii) microbial flora of the chronic wound and (iv) intrinsic and extrinsic antimicrobial resistance. Tissue pharmacokinetic studies conducted in one of the author's (C.E.E.'s) laboratory found wide variations in antibiotic tissue concentrations within chronic diabetic foot ulcers; in most cases the antibiotic levels did not reach the minimum inhibitory concentration required for inhibiting or killing elective wound pathogens.[74] In addition to the previously noted characteristics of a microbial biofilm, antibiotic penetration into chronic wounds was restricted, if not totally prevented, in the presence of a bacterial biofilm.[75] A case in point is vancomycin, which is documented as having poor penetrance into staphylococcal biofilms. Ironically, vancomycin is the drug of choice for MRSA and other device-related staphylococcal infections.[76,77]

Chronic wounds often become colonized and then infected with healthcare-associated pathogens that express multidrug resistance, such as MRSA, vancomycin-resistant enterococci and pseudomonads.[78] It is reported that up to 50% of chronic leg ulcers in hospitalized patients are colonized/infected with MRSA, while more than one-third of *Pseudomonas aeruginosa* isolates are resistant to ciprofloxacin (a fluoroquinolone).[79] As a practical matter of note, the presence of subtherapeutic antimicrobial activity within a chronic wound bed rapidly promotes the emergence of resistant microbial populations. *Staphylococcus aureus* and pseudomonads, which are potent biofilm producers, may be considered potent pathogens in chronic wounds, and their presence alone may justify antibiotic therapy. While expert opinion may suggest that antibiotics can have an important role in the treatment of clinically

Table 4 When should antibiotics be used for chronic wound infection?

Increasing bioburden (critical colonization out of control)
Cellulitis
Lymphangitis and lymphadenopathy
Osteomyelitis
Bacteraemia
Systemic inflammatory response syndrome and life-threatening sepsis and multiple organ dysfunction syndrome
Definite pathogens (β-haemolytic streptococci)
Large numbers (critical colonization/infection)
Host defences (immunosuppression, diabetes)

infected chronic wounds, the optimal choice of agent and duration of therapy is at present unresolved.[78]

As a practical guide the following three recommendations are prudent when contemplating antibiotic therapy involving chronic wounds (Table 4).[4,78,80] (i) Systemic antibiotics should be reserved for clinically infected wounds or ulcers; (ii) antibiotics selected for use should reflect the current microbial epidemiology of chronic wound infections within the specific clinical setting, bearing in mind the increased prevalence of antimicrobial resistance within this patient population (with use of local hospital formularies for the best, narrow-spectrum choice of antibiotic ideally based on sensitivities); and (iii) topical agents should be used only to reduce the wound bioburden and critical colonization, and not to treat infection. In addition, antiseptics can be used in conjunction with antibiotics.

As indicated above, microbiological data play an important role in selection of the appropriate therapeutic regimen, especially in an environment where the prevalence of resistant strains is high. But a cautionary note is warranted, *in vitro* susceptibility data from wound isolates cannot always predict therapeutic success in the clinical arena, as *in vitro* (planktonic) and *in vivo* (sessile) conditions are variable. Some antibiotics, such as linezolid, daptomycin, rifampicin and possibly ceftaroline, can penetrate biofilms.[54,81,82] In addition, laboratory testing does not reflect the diminished metabolic activity that is reflective of microbial populations existing within an extracellular biofilm matrix. Often the minimal inhibitory concentration required to neutralize a microbial biofilm population is well beyond the concentration that is clinically (and safely) achievable.[83]

In conclusion, the indication for antibiotic therapy along with an optimal treatment strategy is often poorly defined. Inappropriate use of systemic antibiotics, in our current era of 'antibiotic stewardship', places the patient at risk for acquisition of resistant microorganisms. Good antibiotic stewardship is needed to minimize this risk of healthcare-associated infections and antibiotic resistance. However, systemic antibiotics are warranted when the degree of wound infection exceeds the efforts of local bioburden control, suggesting that systemic antibiotic therapy is appropriate for treatment of invasive tissue infection and sepsis, as outlined in Table 4.[84] Overuse or misuse of antibiotics may be encouraged if microbiological swab cultures include sensitivities; it is easy to fall into this trap when outpatient antibiotic therapy is available.

The future

The use of diagnostic criteria that could hasten the recognition of the presence of biofilm in a chronic wound, at the patient's bedside, and give proof of presence or adequate suppression after treatment would be welcome.[28,85] Such a bedside diagnostic is being developed for detection of excessive metalloproteinase presence in nonhealing chronic wounds, but has been linked with the promotion of metalloproteinase scavenger dressings.[86] A biofilm diagnostic will likely be based on polymerase chain reaction technology, which would help to 'fingerprint' which microorganisms are present in wounds and in what numbers, despite a negative conventional swab and microbiological analysis. Other diagnostic strategies might include detection of signalling molecules or bacterial products, or the use of host cell lines. Diagnostics could also aid in deciding on the best method of general and maintenance debridement (including new technologies), monitoring of wound progress and how often debridement would be needed, and specific targeting with antimicrobials.[87,88] The suppression of a wound biofilm, once accurate diagnostics are available, may come with the development of quorum sensing inhibitors or other antibiofilm modalities.[16,89–91] The translation of these ideals is likely to be a long time in coming.

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