Restoring balance: biofilms and wound dressings

Abstract: Biofilms are responsible for stimulating and maintaining wound inflammation, increasing infection risk and delaying wound closure. Appropriate biofilm management is required to fight against local and systemic infection and to restore balance to the wound environment. The most effective way to remove biofilms involves the use of mechanical techniques, with the wound dressing representing an important component of this strategy. Wound dressing fibres, such as polyacrylate fibres, have been shown to be effective in affecting biofilm architecture by disrupting the biofilm matrix. This helps enhance the efficacy of antimicrobials, such as silver. Focusing an antibiofilm strategy on active agents alone does not constitute a sustainable approach to biofilm management. Furthermore, adding too many active chemicals into a wound can be highly detrimental to the wound bed, and potentially may have both short- and long-term biological concerns. Particular attention on the characteristics and key features of wound dressings is discussed in this paper. The aim of the paper is to review the ideal characteristics of wound dressings, in conjunction with antimicrobials, that are considered a fundamental part of an antibiofilm strategy and growing requirement for enhanced wound healing.

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biofilm • antimicrobial • wound dressing • infection • silver

From a cellular, microbiological, biochemical, mathematical and physical perspective, a chronic wound is a 'chaotic system'. Helping to restore a chronic wound to a more ordered and balanced state, similar to an acute wound, should help to enhance wound healing. New technologies employed in wound care must help the patient's wound healing process and decrease disorder. To stabilise a chronic wound, different interventions and procedures are required to ensure a positive outcome i.e. infection prevention. To do this, management of the patient, the pathobiology of the wound and its indigenous microbiome is needed.[1]

In a wound, microorganisms reside in two distinct states, the planktonic (or free floating state) and the sessile (or attached state),[1,2] which are phenotypically dissimilar[3,4] but are not mutually exclusive as they do not occur in isolation. Typically, within any environment that contains surfaces (biotic or abiotic), liquid/moisture, nutrients and microorganisms, both microbial phenotypic states will exist together.[5]

Biofilms are defined as communities of microorganisms that are attached to a surface (biotic or abiotic), or each other (forming an aggregate), and become encased within a matrix of extracellular polymeric substance (EPS). The formation of a biofilm is a natural phenomenon and forms part of the routine microbial growth lifecycle.[1] It has important implications in microbial evolution and selection.[1] Biofilm formation is beneficial to microorganisms as it provides a 'safe haven' for microbial survival, microbial resuscitation, genetic transfer and nutrient availability, ensuring the long-term survival of the indigenous microbiota. Within the human body, biofilms are generally within a mutualistic or commensal relationship with the host. An example of a commensal relationship includes the skin or gastrointestinal (GI) tract.[6] However, despite a commensal relationship, dysbiosis in these environments are known to occur leading to certain medical conditions, for example inflammatory bowel disease.

Attached microbes can also reside for many weeks on dry surfaces demonstrating moisture is not necessarily imperative for biofilm survival in the short term. A good example of biofilm persistence on a dry surface has been reported for *Acinetobacter baumannii*, a prevalent bacteria in hospital environments.[7] *In vitro* research has shown that high biofilm-forming strains of *Acinetobacter baumannii* have an increased survival rate on dry surfaces (36 days) when compared with low biofilm-forming strains (15 days) ($p < 0.001$).[7] Evidence of the formation and survival of biofilms in dry areas has implications within the wound environment, signifying that necrotic tissue, and even dry wound dressings, could represent a reservoir of microbes and biofilms.[2]

The presence of biofilms in unexpected and unwanted places such as chronic wounds can often, but not always, lead to problems including inflammation and infection. Consequently, if the host's immune system is unable to stabilise and control biofilms, external interventions are needed to reduce the biofilm's pathogenicity and remove them from areas of concern.

The study, science and management of biofilms is referred to as biofilmology. In medicine, biofilmology is still in its infancy and more so in acute and chronic

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wounds. Biofilms represent a growing area of interest due to their impact on delayed wound healing and infection.[8,9] However, clinical evidence on the role biofilms play and the effects they have on wound healing, presently lacks robustness and consensus. If we consider the small number of clinical case studies to date, it is suggested that biofilm, in conjunction with a number of other pathophysiological factors, can increase a wound's microbiological load and matrix metalloproteinase (MMP) levels, reduce levels of growth factors, and increase inflammation resulting in a delay in wound healing.[10,11]

Strategies involved in the management of biofilms in wounds are complex and require a systematised plan of action. Of particular concern is the fact that sessile microbes growing within biofilms are inherently more recalcitrant to antimicrobials when compared with their planktonic counterparts.[12,13] The management of biofilms involves control of:

- Planktonic microbes (if you can reduce the number this may help to reduce attachment and biofilm formation)
- Biofilm(s) in the wound bed
- Biofilm(s) in the wound dressing
- Biofilm(s) in slough
- Necrotic tissue
- Disseminated biofilms

which adds further dynamics necessary to an effective antibiofilm strategy.[2,14]

Wound dressings, in particular, are known to support the growth of biofilms and act as bioreactors. Subsequently, microbes will continually disseminate from the dressing to the wound bed, further increasing the wound's bioburden.[15] Consequently, what is introduced onto, or into the wound, can have important effects on microbial interactions, ecological shifts in microbiology (dysbiosis) and may directly or indirectly increase microbial virulence and pathogenicity.[1] Many agents can induce ecological shifts in the chronic wound's microbiome and increased biofilm formation. This concept has been reported in other medical areas such as dentistry.[16,17]

Selected modifications of materials used in wound dressings have been shown to have a pivotal role to play in both inhibiting and killing the microbes attached to them[18] and in preventing microbial spread with the potential to reduce biotic and abiotic biofilms.[19] Specific modifications have included electrostatic modifications and the impregnation of actives, for example, dialkylcarbamoyl chloride (DACC)-coated dressings and enzymes, which can alter a dressing's physical and chemical properties. Wound dressings composed of chitosan, for example, are considered to have inherent bacteriostatic ability.[20,21] Such an approach has been beneficial in the treatment of wounds that have focused specifically on planktonic bacteria.

As well as microbes, inflammation,[22,23] elevated MMPs[24] and other factors, all have a significant role to play in prolonging wound healing rates, increasing the risk of infection and the development of problematic biofilms. Reducing elevated levels of both human and microbial proteases will help to reduce the breakdown of the extracellular matrix (ECM) proteins and growth factors, and potentially make a more hostile environment for microbes and biofilms.[23] A wound dressing that is able to sequester excessive amounts of degrading human and microbial enzymes will help effective wound healing.

The characteristics and key features of wound dressings are discussed within this paper, with a focus on how they might influence microbial adhesion and biofilm development. Furthermore, the concerns, relevance and significance of adding actives to these platforms for biofilm prevention and control will also be briefly reviewed.

Aim

The aim of this paper is to review the ideal characteristics of wound dressings, in conjunction with antimicrobials, that are considered a fundamental part of an antibiofilm strategy and a growing requirement for enhanced wound healing.

Biofilms and the 'chaos theory'

Within the human body there are many biofilms. These reside in areas such as the skin, the GI tract, and the oral cavity. In the majority of cases, these biofilms represent stable and balanced entities, which are generally rendered 'benign' by the host's immune system and can, in fact, be beneficial to the host.[25] Providing the host's immune system is 'healthy', the commensal relationship between the host and biofilm remains in a stable and balanced state.[26] However, the biofilm is very sensitive to small changes and will adapt accordingly to ensure the survival and protection of the indigenous microbiota. Small changes or perturbations to the biofilm can lead to many biological and chemical changes, which can affect microbiological behaviours, and their eradication and immunological clearance.

Biofilms and wounds

The concept of biofilms in wounds was, in principal, proposed in 2001[27] and in more detail in 2004,[28] but it was not until 2008 that biofilms were identified in wounds.[29]

As discussed, the wound environment supports planktonic and sessile states. As microbes within the sessile state grow and multiply, they begin to form biofilms. The formation of a biofilm goes through a simple process of adhesion (reversible followed by irreversible), EPS production, microcolony formation, further EPS production, 'immature' biofilm formation, 'mature' biofilm formation, detachment/dispersion and microbial re-attachment. An 'immature' biofilm is often defined as a biofilm that has grown for up to 24 hours, and a mature biofilm as having grown for over 24 hours, within the *in vitro* environment only. Biologically and architecturally, within the *in vivo*

Table 1. Criteria for an effective wound dressing

Pre-biofilm concept criteria	Post-biofilm concept criteria
Facilitation of debridement (when necessary)	Extracellular polymeric substance breakdown (antibiofilm)
Maintenance of thermal insulation	Microbial sequestration and immobilisation within the wound dressing
Reducing scar formation	Antimicrobial
Removal of excess wound exudate	De-sloughing/cleaning
Does not shed fibres and is non-toxic	Absorption of excessive exudate
Non-adherent, comfortable with intimate contact	Matrix metalloproteinase modulation
Manage wound bioburden	Moist environment known to promote healing
	Enhancement of cell proliferation

environment, a biofilm would be significantly different at 24 hours and 48 hours when compared with biofilms within the *in vitro* environment.

EPS is a major component of both the young (24 hours) and older (>24 hours) biofilms, forming 75–90% of a biofilm volume.[30] It is composed of polysaccharides, proteins, glycoproteins, lipids, metal ions and extracellular DNA (eDNA). The biofilm's matrix is very important and should be a consideration i.e. removal, as part of an antibiofilm strategy.[31] The dispersive stage of a biofilm has critical implications for spreading infection. Such an approach helps to disseminate microbes to different sites helping them to spread. If dissemination is to sites that the microbes are in a commensal relationship with this is not considered an issue, provided the microbes and the immune response are maintained in a balanced state.[32] However, if these microbes develop in unfamiliar regions of the body, then problems such as inflammation begin to develop. Within the biofilm state, microbes are often able to withstand the interventions imposed on them, such as the host's immune response and antimicrobials.[33]

If we are to manage biofilms when they become detrimental to human health, it is important to consider that microorganisms growing within a biofilm are significantly more tolerant to general biocides and, more specifically, to antiseptics and antibiotics when compared with planktonic bacteria.[34] A collation of evidence to support biofilm tolerance to antimicrobials has been recently reviewed elsewhere.[35] While there are various theories that support biofilm tolerance, it is thought that the matrix of the biofilm forms part of the defence. Consequently, the breakdown of the matrix of the biofilm should therefore be an integral part of any antibiofilm strategy.[31,36]

Effective wound dressings

The ultimate aim of a wound dressing is to help facilitate timely wound repair and closure. There are a number of criteria that a wound dressing is expected to fulfil[37] and a small number are shown in Table 1. However, with growing concern about biofilms in wounds and their impact on wound healing, these criteria need updating. In particular, understanding how the features and characteristics of the wound dressing itself can help to prevent and control biofilms[2] is a significant need. There is a plethora of wound dressings available including as examples polyurethane hydrophilic foams, alginates, polyurethane films, carboxymethylcellulose, chitosan, hydrogels and hydrocolloids. Each have their own inherent varying features and benefits. Furthermore, the wound dressing itself can represent an environment that is supportive and conducive for the proliferation of microorganisms and the development of biofilms; conceptually speaking, a bioreactor.[15]

To help gain order in a chaotic wound system, particularly when biofilms are present, the ideal characteristics of an effective wound dressing is discussed. It should be noted that some of these lack concrete and robust data for clinical significance and therefore acceptance.

Exudate management

An important element during the wound healing process, which is part of the inflammatory response to tissue injury, that has a role to play in both enhancing and decreasing wound healing, is high levels of exudate. Exudate contains many components including a diverse range of white blood cells which help to reduce planktonic microbes and biofilm within the wound. Exudate also contains various nutrients including serum protein, glycoproteins and sugars, and leukocytes, proteases, serum proteins, sodium chloride, calcium ions, protease inhibitors, growth factors, and clotting factors such as platelets and fibrin. It represents a bathing fluid significant to the sustainability and longevity of the biofilm, microbial dissemination rates and MMP activity.

The production of high volumes of exudate is relevant to chronic wound pathology. Within the exudate, increased levels of proteases have been detected such as MMP, which are thought to be linked to the presence of infection and inflammation due to excessive tissue breakdown.[38]

Intimate contact

In vitro studies of intimate contact and wound contouring have been observed for many wound dressings. This is where the wound dressing may contour with the surface of a material or the wound bed, as observed on gelling fibrous dressings such as an alginate wound dressing. However, the clinical significance and relevance of this to wound healing and its effects on antimicrobial performance remain vague at best. Consequently, the value of this to wound healing warrants more robust and clinical study. A recent study by Desroche et al.[39] demonstrated the importance of a direct contact method in helping to control biofilms.

Matrix metalloproteinases modulation

MMPs are a subfamily of zinc-metalloproteinases that are produced in humans[38,40] and are synthesised within a variety of cell types, including fibroblasts and epithelial cells. Their primary function is to degrade ECM components such as collagens, elastin and fibronectin. Another, equally important, role of MMPs is the cleavage of substrates to release growth factors and chemokines, resulting in cellular processes such as chemotaxis and vasculogenesis. Through the cleavage of the ECM components, MMPs play a vital role in the immune response towards infection, by effectively facilitating the migration of immune cells to the site of injury and infection.[41,42] While the activation of MMPs in physiological wound repair is essential, elevated MMP activity within chronic wounds associated with reduced wound closure and increased degradation of ECM has been well documented.[43,44] In this scenario, MMPs can cause infection-related pathology at increased levels or decreased levels of their inhibitors, causing host tissue damage. Examples of infections whereby elevated MMP levels may adversely affect the host include hepatitis B, mycobacterial infection and endotoxic shock.[45] *In vitro* studies have highlighted the importance of microbial-host interactions and the stability of the wound environment. Okamoto and colleagues[46] reported the activation of host pro-MMP-1, MMP-8 and MMP-9 by *Pseudomonas aeruginosa* and *Vibrio cholerae*-derived proteases.

The incorporation of substrates, such as collagens, within wound dressings has been shown to help bind and act as a 'sacrificial' material for both MMPs and bacterial collagenases.[47] Therefore, the modulation of MMPs and the associated deleterious effects of elevated MMP levels within the wound environment may be addressed by the addition of a favourable substrate for excess host-derived MMPs and bacterial proteases.[47] High MMP levels and the associated deleterious effects within the wound environment should be addressed by therapies directed at modulating MMPs. Some modern dressings and procedures that modulate MMPs may be effective in improving healing rates.[48]

Sequestration, immobilisation and biofilm binding

In scientific terms, sequestration is defined as the trapping (irreversible or reversible) or isolation of a molecule, chemical or biological agent. Within this paper we refer to biofilm binding as the trapping of a molecule, chemical or biological agent found within or on the biofilm. Binding onto or within a wound dressing is not microorganism-specific but is important for helping to reduce the microbial bioburden of the wound bed. When we refer to sequestration in relation to wound dressings, we refer to the potential sequestering of components such as enzymes,[49] growth factors, reactive oxygen species (ROS), microorganisms and biofilms within the wound dressing.

Sequestration and immobilisation of microbes has been reported in the literature.[50] Evidence of microbial sequestration has been reported via real-time microbiological studies in alginate dressings.[51] While alginates have been reported with this capability, so have carboxymethylcellulose fibres as well as polyabsorbent fibres. Polyabsorbent fibres found in products such as UrgoClean and UrgoClean Ag have been found to have gelling properties with high absorbent capabilities. Their ability to swell in various solutions have enabled them, not just to trap planktonic microbes but also sessile cells which help to immobilise microbes. Such a concept, using natural physical concepts of electrostatic interactions, was identified by Wiegand and colleagues.[52]

Immobilisation is defined as 'limiting the movement' or 'making incapable of movement'. Immobilisation represents an important role of a wound dressing. Immobilising microbes within the wound dressing will help to reduce their growth and development which, in turn, will help to potentially achieve bacteriostatic claims for non-antimicrobial wound dressings. Having wound dressings that can immobilise microbes may help to enhance the antimicrobial kill by concentrating the microbes and enabling an increased contact time, enhancing the performance of the incorporated antimicrobials. However, it is also important to appreciate that microbes, if immobilised, may reduce their growth rate and cellular division. This effect may lead to a reduced antimicrobial effect. Therefore, the significance and role of immobilisation and enhanced antimicrobial performance needs further investigation.

While there are research papers demonstrating sequestration,[53] within a clinical setting, the overall clinical effects and benefits of sequestration are not well understood. Investigation into the effects of sequestration on wound closure and whether there are enhanced effects of antimicrobial treatments needs exploring.

Selective adhesion/removal of microbes

There are a number of wound dressings that claim selective removal of microbes from the wound bed.[54] This has been reported to be achieved by changing the hydrophobicity and hydrophilicity of the wound dressing fibres. Some fibres in wound dressings have

been shown to have interactions with microorganisms which may help to remove them from the wound bed. A recent study by Cooper et al.[50] demonstrated hydrophobic interactions between wound dressing fibres coated in DACC and meticillin-resistant *Staphylococcus aureus* (MRSA). While an interesting concept, it is well known that microbes are able to alter their hydrophobicity and hydrophilicity, depending on the environment they are found in. This approach of two hydrophobic surfaces interacting may therefore have limitations in a dynamic environment such as a wound. Furthermore, microbial attraction and detachment are linked to electrostatic interactions, Van der Waals forces (DLVO theory) and zwitterions. These all have a role to play in encouraging the adhesion and removal of microbes from a biofilm. Within the biofilm, microbes are generally covered in polysaccharides which provide an overall negative charge, but this will change depending on the metal ions within the biofilm.[55] Moreover, bacteria generally co-aggregate and often co-adhere to surfaces.[56] This will affect the overall net surface charge and therefore the hydrophobicity and hydrophilicity of the surface.

Polyacrylate fibres in wound dressings, which are overall negatively charged, can attract positively charged ions. Most bacterial cells (again, environment pending), in particular Gram-negative microbes, have an overall net negative charge due to the presence of polysaccharides (predominate OH-groups) which are present either as a capsule or glycocalyx, found firmly attached to the bacteria, and a slime layer which is loosely attached to the microbe. Both polysaccharide components have different chemical and physical properties, each of which have a role to play in the attachment of bacteria to surfaces and also surface charge. Consequently, charged fibres in and on wound dressings may have the potential to selectively remove polysaccharide components of a biofilm, and also those microbes with an overall net negative environment. Such has been demonstrated with *Staphylococcus aureus*,[57] in particular MRSA.[58] It is highly likely that there are electrostatic interactions between the negatively charged components of the polyabsorbent fibres and some of the major components of the biofilm matrix i.e. metal ions such as calcium and magnesium.

As microbial adhesion plays a significant role in the pathogenicity of microbes and adhesion to wound dressings, and therefore wound healing, there is a focus on biomaterials that can resist microbial adhesion.[54] For any biomaterial and wound dressing there is competition between microbial adhesion to the surface and the attachment of human cells. If microbial cells attach to dressings before tissue/cellular attachment, the immune response will not be able to reduce microbial colonisation and therefore biofilm formation on these devices. This concept has been referred to as a 'race for the surface'.[59–61] Many strategies have been employed to reduce microbial adhesion including:

- Altering the physicochemical properties of the device
- Incorporating antimicrobials.

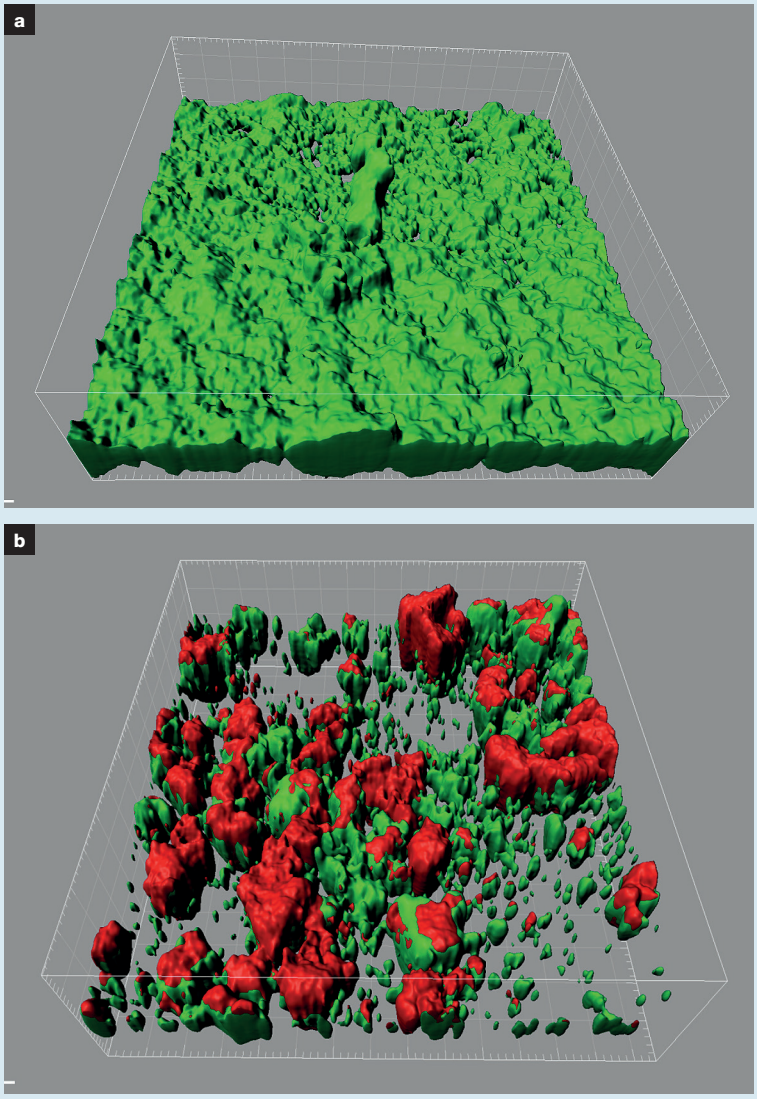
As discussed, one method for reducing bacterial adhesion involves altering the physicochemical properties of the biomaterial so that interactions between the surface and microbe are unfavourable. Surface hydrophilicity has been shown to correlate to reduced microbial adhesion[62] for example, hydrophilic polyurethanes.[63] Other investigations have worked on the principal that at neutral pH the surface charge of bacteria is negatively charged.[62] Harkes et al.[64] investigated the adhesion of *Escherichia coli* to polymers, each of which had different zeta potentials. The researchers reported an increase in bacterial adhesion with an increase in surface charge of the polymers. As well as surface charge, numerous studies have looked at the surface-free energy of a surface and the effect this can have on preventing bacterial adhesion.[65] Roosjen et al.[65] found that when the surface tension of the media in which the bacteria were grown was less than the surface-free energy of bacteria, a correlation was observed i.e. bacterial adhesion was reduced when lower surface-free energy was evident. As with any surface, when a protein conditioning layer forms on a surface, this significantly alters the surface chemistry with serious implications for microbial adhesion within an *in vivo* environment.[54] Studies have shown that hydrophobic bacteria can adhere preferentially to hydrophobic surfaces even when low surface energy is evident.[66]

Biofilm binding

Several wound dressing fibres have been shown to effectively bind to the EPS preventing biofilm formation and also aiding their removal. A recent study of Desroche et al.[39] demonstrated the effectiveness of polyabsorbent fibres in binding to and removing sections of biofilm matrix (Fig 1a and 1b). A silver-containing dressing with polyabsorbent fibres and an antimicrobial silver matrix demonstrated the capability to produce at least a 4 log reduction in the number of sessile cells after 24 hours and during seven days contact with a mature MRSA biofilm. These results demonstrate the effectiveness of the combination of certain wound dressing fibres and the silver ions, and their ability to affect biofilm structures.[39]

Based on the evidence,[67] numerous fibrous dressings have demonstrated their ability to effectively remove barriers to wound healing, such as slough, which has been shown to have positive outcomes to wound healing.[68] Dressings with polyabsorbent gelling fibres combined with silver have demonstrated effects on *in vitro* biofilms.[68] These polyabsorbent fibres have been shown to have the ability to cause the breakdown of the biofilm matrix, a process referred to as 'mechanical disruption', which helps to enhance the ingress and diffusion of silver ions into the wound bed. The significance of mechanical disruption has been demonstrated previously in a study by Alhede et al.[69] which shows antibiotic efficacy on biofilm to be

Fig 1. Confocal laser microscopy image demonstrating a biofilm (green labelled cells–viable cells). Untreated biofilm (**a**). Confocal laser microscopy images of meticillin-resistant *Staphylococcus aureus* biofilm treated with UrgoClean Ag. Red-labelled cells—dead cells (bactericidal activity of Ag+); Clear zones—destructuring of the biofilm (synergic effect of Ag+ and polyacrylate fibres) (**b**)



enhanced following mechanical disruption of biofilms when compared with use of the antibiotic alone and a non-distributed biofilm.[69]

Looking at the speed of disruption of biofilms, Desroche et al.[39] demonstrated the disruption of *in vitro* biofilms of MRSA and *Pseudomonas aeruginosa* after 24 hours of exposure (Fig 1 and 2). The antibiofilm activity was evaluated using the *in vitro* model described by Desroche et al.[39] Both antimicrobial wound dressings were applied on mature biofilms of MRSA or *Pseudomonas aeruginosa* for 24 hours and the sessile cells were counted as previously described. The polyabsorbent silver wound dressing which combines polyacrylate fibres and a silver lipidocolloid matrix demonstrated higher antibiofilm activities than the CMC dressing which combines ionic silver, ethylenediaminetetraacetic acid (EDTA) and BC (Aquacel Ag+Extra) after 24-hours of exposure.

Antimicrobials in wound care and efficacy on biofilms

Numerous antimicrobials are used in chronic wound management for wounds which are at risk of infection or are locally infected. Unfortunately, the antimicrobial performance data, necessary for regulatory approval of wounds dressings, relies on evaluation within models used to demonstrate efficacy on microbes within the planktonic state.[70,71] As part of a combined antibiofilm approach, device-active combination,[72] antimicrobials are considered of paramount importance. However, it is evident that all antimicrobials have many negative and positive effects. Each also have different efficacies in different environments, and many factors such as pH can affect their performance.[73] Antimicrobials, such as polyhexamethylene biguanide (PHMB), silver and iodine, are used routinely for the treatment of at risk and infected wounds.[74,75] Numerous studies and reviews have been published on the use of silver and PHMB on different chronic wound types,[68,76–81] and the concerns with silver resistance has been documented.[79] However, systemic risks to the overuse of high levels of silver is presently unclear. The use of silver as a broad spectrum antimicrobial in wound dressings is common. Percival et al. [82] showed varying degrees of inhibition of the growth of 115 clinical wound isolates such as *Candida albicans*, yeasts, MRSA, vancomycin-resistant *Enterococci* and *Enterococcus faecium*. Corrected zones of inhibition (CZOI) showed that *Enterobacter cloacae* and *Acinetobacter baumannii* were the most tolerant to ionic silver, whereas strains of *Staphylococci, Viridans streptococcus* and *Candida albicans* showed the highest sensitivity. Furthermore, selected isolates that were grown in biofilm form showed increased tolerance to silver when compared with their planktonic counterparts.[82]

The use of antimicrobial-containing dressings, such as those containing ionic silver, has correlated with reduced surgical site wound complications following revascularisation when compared with conventional, non-antimicrobial dressings, stressing the importance of early microbial management in wound care.[80]

Some wound dressings with polyabsorbent fibres combined with silver are known to have specific cleaning abilities. This allows the wound dressing itself to clean slough, exudate and microbes from the wound and for the silver to enter the wound bed. Cleaning the wound with appropriate desloughing wound dressings is an important approach to an antibiofilm protocol of care in biofilm management.

Wound dressings containing antimicrobials, including silver, have a broad spectrum of activity against microbes and are generally designed to kill

microorganisms within the wound dressing itself. However, it has been reported that significantly higher levels of silver are required to treat the microbes growing within biofilms when compared with killing microbes within the planktonic phenotypic state.[83] Mahami et al. reported that to kill microbes growing within a biofilm four times the levels of silver was required when compared with microbes growing within the planktonic state.[81] Despite numerous *in vitro* studies demonstrating the efficacy of silver on microbes,[84] the clinical studies available highlight the fact that silver may not necessarily be effective in more biological situations.[85] Commercially available antimicrobials have demonstrated variations in their ability to prevent biofilm formation.[86]

Antimicrobials containing wound dressings have been shown to be effective against mono-species and polymicrobial biofilms *in vitro*.[87] Percival et al. used confocal microscopy and live/dead staining to show the effectiveness of sodium carboxymethylcellulose with 1.2% ionic silver against biofilms produced in a glass chamber slide, with the death of 90% of the bacteria within the biofilm evident after 24 hours.[87] Mulley et al. have reported the inactivation of the antibacterial and cytotoxic properties of silver ions by biologically relevant compounds such as glutathione, cysteine and human blood components.[88] The surge in the use of silver not only in wound care but also in the prevention of healthcare-associated infections (HCAIs) needs to be carefully considered as testing should include the implication of biological components.

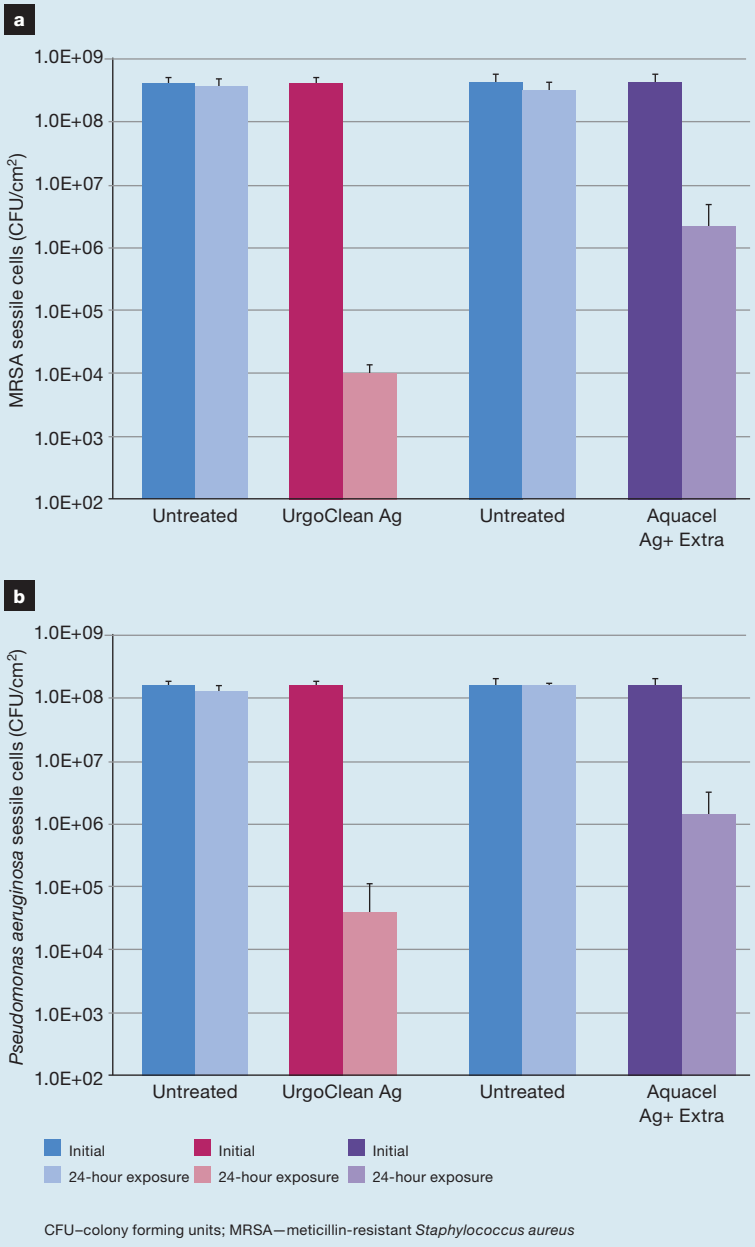
Antibiofilm wound dressing strategy

Wound dressings are porous and most will allow microbes to diffuse and move easily from the wound dressing to the wound and from the wound into the wound dressing. As nutrients and shelter are provided by the wound dressing, this will provide an ideal environment for microbial growth and development. In an antibiofilm strategy, the wound dressing and the wound bed need to be equally considered with the wound dressing itself a risk factor in biofilm development. To mitigate and reduce risk, frequent dressing changes may therefore be of paramount importance where an individual's physiology and pathobiology makes them a high risk for problematic biofilm development.

In the food industry and dentistry it is found that preventing and managing biofilms relies on a multifactorial approach.[89,90] This strategy is important in wound care as we are dealing with at least five different biofilms in a wound's ecosystem.[2] Wound dressings, and the components/actives they contain, are designed, or should be designed, to help produce an environment, both within the wound dressing and the wound bed, that is supportive of the healing process.

With any antibiofilm strategy it is important to understand the interaction between the dressing as a biomaterial and the microbes in a wound, and may help to inhibit the development of a biofilm. Focus should be placed on both wound dressing characteristics and the active ingredients it contains. Adding more chemicals into a wound may not necessarily be the best approach to controlling biofilms. While this concept is appropriate for hard surfaces, for example in the food industry i.e. detergent, surfactant, chelating agent and

Fig 2. Antibiofilm activity of *Staphylococcus aureus* (**a**). Antibiofilm activity of *Pseudomonas aeruginosa* (**b**). The antimicrobial wound dressings were applied on mature biofilms of MRSA or *Pseudomonas aeruginosa* for 24 hours and the sessile cells were counted as previously described[39]



CFU–colony forming units; MRSA—meticillin-resistant *Staphylococcus aureus*

antimicrobial, this may not be the most appropriate approach in wound care; in the food industry and dentistry the chemicals used are regularly washed away. In wound care the approach of adding different, non-complexing agents into a wound may lead to issues, such as cytotoxicity, for cellular healing and immunological suppression. It would be important to demonstrate, from a risk-benefit perspective, that there is significant benefit and improved clinical outcomes over existing technologies.

With increasing evidence of problematic biofilms in chronic wounds, there is a major trend towards developing next generation drug-device combination wound dressings with antibiofilm ability.[14] However, more emphasis seems to be placed on the antimicrobials and actives that elute out of the wound dressing and less on the synergy and additive effect of the platform-active combination. The platform itself represents a significant and functioning entity necessary for effective management of the patient's wounds and is therefore significant to wound healing. Appropriate antimicrobials must be 'fit for purpose' and continue to be used in these next generation antibiofilm wound dressings. When used as part of an antibiofilm strategy they must be able to kill microbes both within, and external to, the wound dressing, and be effective on planktonic microorganisms as well as sessile microbes growing within the biofilm.

By cleaning the wound of excessive exudate, slough and microorganisms combined with antimicrobial and antibiofilm efficacy, some wound dressings have been found to be effective in local infections and biofilm management. Indeed, polyabsorbent fibres have been shown to breakdown the microbial biofilm matrix that form on and within the wound, thus permitting the silver ions to kill microorganisms inside the biofilm.

It is not possible to supply just one technology that is able to effectively prevent biofilms, kill the microbes within the biofilms, break up the EPS, prevent reattachment of microbes, and then remove and lock away the dislodged microbes. The future of wound care requires a combination of therapies which function in synergy. The most important approach to the biofilm management of a wound is the planned approach, in conjunction with a risk assessment, with the wound dressing-active combination a significant part of the strategy. The ideal requirements for an effective wound dressing for managing biofilms is shown in Table 1. Some wound dressings, and the actives they contain, are specifically designed to kill planktonic microbes but may not be the best approach to biofilm management.

Safety and health concerns

A number of antimicrobials used today in the management of wounds are becoming associated with growing safety and health concerns in other industries.[91] In October 2013, the European Union issued commission regulation 944/2013 reclassifying polyhexamethylene biguanide hydrochloride (PHMB) as a category 2 carcinogenic agent under the classification, labelling and packaging (CLP) regulations. Category 2 classification signifies that the agent is suspected of causing cancer. A number of retailers have now eliminated the use of PHMB from their products.[92] The US Food and Drug Administration (FDA) in 2016 issued a final ruling highlighting that over-the-counter (OTC) consumer products containing certain active ingredients, such as Triclosan, can no longer be marketed.[92] This was due to the fact that manufacturers could not demonstrate that the ingredients were safe for long-term daily use. The FDA has deferred rulemaking on safety concerns for one year on other agents such as benzalkonium chloride, benzethonium chloride and chloroxylenol (PCMX).[93]

Limitations

Limitations of this review included a lack of evidence in a number of areas and the review approach was non-systematic.

Conclusion

Evidence is mounting that suggests the more pathogenic and problematic biofilms are a major concern in wound healing.[9,11] It is critical that antimicrobials and antibiofilm technologies used in wound care are more efficacious and less cytotoxic.

Despite health concerns over other antimicrobials, silver is still considered to be safe, at certain concentrations, and still has an important and significant role to play in wound care. Provided it is used as part of a combination therapy, in conjunction with an appropriate wound dressing material, it is evident that positive clinical outcomes can be achieved.[94] However, as with all antimicrobials they have to overcome the concerns associated with poor efficacy when biological material, including biofilm, slough and necrotic tissue, is evident.[2] To enhance an antimicrobial's efficacy, wound dressings must be effective at removing materials that have a biological demand for the antimicrobial to ensure that maximum performance is achieved. It is well known that the more biological an environment the lower the antimicrobial performance.

Numerous dressings that contain absorbent fibres combined with silver have been reported to have an ability to prevent *in vitro* biofilms, and reduce inflammation, an indirect marker for biofilm presence (less problematic biofilms often only cause a subclinical effect). Some wound dressings have been shown to exhibit inherent capabilities that enable them to clean the wound by removing slough, soaking up exudate, binding and removing the matrix of the biofilm, sequestering microbes, and making available effective levels of silver. Such features and benefits make an ideal combination that demonstrates efficacy on biofilms[39] and forms an important part of any antibiofilm management strategy. JWC

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