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Clinical and Antibiofilm Efficacy of Antimicrobial Hydrogels

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Significance: Hydrogels have been shown to have a significant role to play in wound healing. Hydrogels are used to assist in the management of dry, sloughy, or necrotic wounds. However, recent scientific evidence has shown that biofilms delay wound healing and increase a wound propensity to infection. It is therefore essential that hydrogels incorporating antimicrobials demonstrate efficacy on biofilms. Consequently, it is the aim of this article to review the efficacy of hydrogels, incorporating antimicrobials, on wounds with specific reference to their efficacy on biofilms.

Recent Advances: Technologies being developed for the management of wounds are rapidly expanding. In particularly next-generation hydrogels, incorporating copolymers, have been reported to enable the smart release of antimicrobials. This has led to the development of a more tailored patient-specific antimicrobial hydrogel therapy.

Critical Issues: Evidence relating to the efficacy of hydrogels, incorporating antimicrobials, on biofilms within both the *in vitro* and *in vivo* environments is lacking.

Future Direction: Studies that investigate the efficacy of antimicrobial hydrogel wound dressings on both *in vivo* and *in vitro* biofilms are important. However, there is a significant need for better and more reproducible *in vivo* biofilm models. Until this is possible, data generated from appropriate and representative *in vitro* models will help to assist researchers and clinicians in evaluating antimicrobial and antibiofilm hydrogel technology for the extrapolation of efficacy data relevant to biofilms present in the *in vivo* environment.

SCOPE AND SIGNIFICANCE

MICROORGANISMS HAVE detrimental effects on wound healing by affecting healing times, a patient's recovery time, risk of infection, and costs to the health service. To help manage wound healing, dressings, in particular hydrogels, are employed. However, the efficacy of hydrogels on wound healing, and biofilms specifically, is poorly researched and discussed. Consequently, it is the intention of this article to review the hydrogel platform and report on its effectiveness on wound healing

specifically when used in the management of at-risk or already infected wounds and biofilms, based on currently available research publications.

TRANSLATIONAL RELEVANCE

Chronic wounds are tissue injuries that heal slowly or completely fail to heal. Generally, if a wound has not healed beyond 12 weeks or the same wound reoccurs in a repetitive fashion, it will be classified as a chronic wound.¹ Such wounds fail to heal due

to repeated tissue insults or underlying physiological conditions, such as diabetes, persistent infections, poor primary treatment, and other patient-related factors.² Further the risk of these wounds becoming infected is high due to the presence and colonization of endogenous and exogenous microorganisms² growing both within the planktonic and biofilm phenotypic states.

CLINICAL RELEVANCE

Hydrogel wound dressings contain water (typically between 70% and 90%)³ and have been shown to have a significant role to play in wound healing.^{4,5} They are generally utilized in the management of sloughy or necrotic wounds given their requirement for moisture. They are non-reactive with biological tissue, have a high permeability to metabolites, and are non-irritant.⁶ Hydrogels have the ability to absorb fluid thousands of times their dry weight.⁷ Since these gels are used in all wound types, their rheological profile is such that they stay in place after application to the wound and can remain *in situ* for relatively long periods of time.⁸

BACKGROUND

Enormous gaps still remain in our knowledge regarding the etiology (origin) and pathogenesis (mechanism) of chronic wounds. In general, all chronic wounds are categorized into three groups: venous ulcers, pressure ulcers, and diabetic ulcers. These three types of chronic wounds upon first inspection would appear to have little in common and have been addressed previously as separate conditions. However, examining their commonalities in more detail leads to the hypothesis that human chronic wounds may not have a unique defect individual to each group but they represent a combination of common factors.⁹ Each component of pathogenesis, including biofilm virulence, is damaging to wound healing, but collectively they completely overwhelm the natural healing response. Mustoe and colleagues¹⁰ have previously proposed this theory of unification of causes. However, the treatment of chronic wounds should be addressed on an individual basis.

The management of chronic wounds is a complex process compounded by underlying pathophysiology and neuropathies. Many chronic wounds are characterized by chronic inflammation resulting in the release of cytotoxic enzymes, free radicals, and inflammatory mediators that can cause damage to the host tissues if not properly controlled.¹¹ A state of prolonged inflammation can be initiated and augmented by a number of factors, including

excessive polymorphonucleocyte and metalloprotease levels (in particular, matrix metalloproteases [MMPs]-2 and -9), microbial wound bioburden, and more recently evidence of a virulent biofilm.¹²

A biofilm is defined as a community of microorganisms attached to a surface, or each other, which becomes encased in a self-generated extracellular matrix, referred to as the extracellular polymeric substance, which is fundamentally composed of polysaccharides, proteins, glycoproteins, extracellular DNA, and metal ions.

Wound dressings, in particular hydrogels, are a standard treatment required for the management of wounds and are used for both the donation of fluids in dry wounds and the removal of excessive levels of wound exudate in wetter wounds. Wound dressings are classified in a number of ways depending on their function: first, whether they function to help debride, treat at-risk or infected wounds, provide an occlusive environment, or absorb exudate at the wound site¹³; second, on the type of material used, that is, hydrocolloid, alginate, or collagen¹³; and third, on the physical form of the dressing, that is, an ointment, film, foam, fiber, or a hydrogel.¹⁴

Hydrogels are water-retaining, swelling hydrophilic materials made from polymers or a combination of polymers, which can be either synthetic or natural in origin. As examples poly(methacrylates) and polyvinylpyrrolidone are typically used polymers. Dressings, such as Nu-gel™ (Johnson and Johnson) and Purilon™ (Coloplast), use hydrogel alginate combinations. Hydrogels can be applied either as an amorphous gel or as elastic, solid sheets or films. Although hydrogels are very similar to hydrocolloids, hydrogels have subtle differences in action. Hydrocolloids are a type of dressing containing gel-forming agents, such as sodium carboxymethylcellulose (NaCMC) and gelatin, often in combination with elastomers and adhesives and applied to a carrier. In the presence of wound exudate, hydrocolloids absorb liquid and form a gel while hydrogels are a water containing gel already upon application. In the intact state, most hydrocolloids are impermeable to water vapor, but as the gelling process takes place, the dressing becomes progressively more permeable.¹⁵ Hydrogels are typically cross-linked and produced in free radical reactions. These are summarised schematically in figure 1.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Hydrogels

The use of hydrogels as debriding agents in diabetic foot ulcers was included in the Cochrane

Figure 1. Schematic methods used in the formation of crosslinked hydrogels by free radical reactions, including a variety of polymerizations and crosslinking of water-soluble polymers. Examples include crosslinked polyhydroxyethylmethacrylate (PHEMA) and polyethylene glycol (PEG) hydrogels.

Review by Smith.¹⁶ This review highlighted that hydrogels increased the healing rate of diabetic foot ulcers compared to gauze and standard wound care. However, it was unclear whether this effect was due to debridement or the intrinsic properties of hydrogels. Furthermore, the follow-up period to these trials was relatively short and restrictions may have occurred as a consequence of the self-application of the dressings by the patients. Yet, in other randomized control trials, hydrogels have been reported to be equal to, or superior in terms of fluid absorption and odor control¹⁷ when compared with various hydrocolloid dressings.¹⁵ This demonstrates that, when compared with a hydrocolloid dressing, a synthetic polymer hydrogel dressing performed more favorably in terms of overall clinical performance based on its ability to aid autolytic debridement; however, healing rates were comparable for the two dressings. Thomas *et al.*¹⁷ reported findings that a hydropolymer dressing outperformed a hydrocolloid dressing in terms of dressing leakage and odor control in the treatment of leg ulcers and pressure sores. An earlier study by Geronemus and Robins documented the ability of hydrogel dressings to promote reepithelialization of wounds, using a pig wound model, by up to 44% when compared with control untreated wounds.¹⁵ In a more recent study, hydrogels were found to be superior to a conservative treatment with povidone-iodine-soaked gauze, facilitating the rapid epithelialization of pressure ulcers in 27 patients.¹⁸ Also evaluated in this study was the safety and efficacy of a hydrogel dressing in comparison to a hydrocolloid dressing and wet-to-moist gauze. They found that, while each dressing was satisfactory in providing an environment favorable to healing, the hydrogel dressing proved superior in terms of; visualization of the wound, nonadhesiveness, cooling effect, ease of application, and conformability.¹⁸ A further study by

Moody reported on the use of a hydrogel dressing to treat a chronic leg ulcer for a patient who could not tolerate even reduced compression therapy due to pain; the hydrogel helped reduce the pain considerably to allow for therapy to continue.¹⁹

Many hydrogels reside in the market place, including amorphous gels and gel dressings. Examples include NuGel[®] (Johnson & Johnson), GranuGel[®] and DuoDERM[®] Gel (ConvaTec), Intrasite[®] (Smith & Nephew), and AquaForm[®] (Maersk), Prontosan[®] (B. Braun), Hydrosorb[®] (including Aquaclear; Hartmann), Purilon gel[®] (Smith & Nephew), Curafil[™] and Curagel[®] (Covidien), Hypergel[®] (Mölnlycke Health Care), Spenco 2nd Skin[®] (Spenco Medical UK Ltd.), SoloSite gel[®] (Smith & Nephew), Solugel[®] (Johnson & Johnson), and Sterigel[®] (Seton Healthcare). A major point of differentiation between products is in their absorbent properties and ability to donate fluid. There is a continuing and growing need for hydrogels containing antimicrobials for the use of those wounds that are at risk of infection, infected, or “biofilm infected.” The most commonly used antimicrobials added to hydrogels include silver, iodine, and polyhexamethylene biguanide (PHMB). The efficacy of these antimicrobial-based hydrogels on wound healing, microbes, and biofilm will be discussed.

Silver hydrogels and biofilms

Some currently available silver hydrogels include SilvaSorb[®] (Medline), Elta Silver Gel[®] (Elta Skin and Wound Care), Silver Shield[®] and Silver-Sept[®] (Anacapa Technologies), Gentell[®] Silver Hydrogel (Gentell), DermaSyn/Ag[®] (DermaRite Industries), SilverMed[®] (MPM Medical, Inc.), ReliaMed Silver Hydrogel (ReliaMed), and Silver Genesis Colloidal Silver Hydrogel (Silver Genesis). Efficacy of antimicrobial hydrogels on biofilms will be discussed where research is available.

It has long been known that ionic silver possesses antimicrobial properties. Silver is available in a number of therapeutic preparations, including colloidal silver suspensions, a dilute salt solution (0.5% silver nitrate solution), creams, and in modern wound dressings. Preparations including silver sulfadiazine and silver nitrate are commonly used for wound infections, with antimicrobial efficacy reported on *Pseudomonas-aeruginosa*-related infections.^{20–22}

A number of studies have investigated the effectiveness of silver hydrogels in the treatment of wounds. Boonkaew *et al.* compared the antimicrobial efficacy of a novel silver hydrogel dressing compared with two commonly used dressings (Acticoat[™] and PolyMem Silver).²³ The silver hydrogel dressing was composed of 2-acrylamido-2-methylpropane sulfonic acid sodium salt with silver nanoparticles. To com-

pare the antimicrobial efficacy of each dressing, three different antimicrobial tests were used: disc diffusion, broth culture, and the Live/Dead BacLight™ bacterial viability assay against *P. aeruginosa*, Meticillin-sensitive *Staphylococcus aureus*, *Acinetobacter baumannii*, *Candida albicans*, Meticillin-resistant *S. aureus*, and vancomycin-resistant enterococci. Acticoat was reported to be the most efficacious dressing, with a zone of inhibition ranging from 13.9 to 18.4 mm. Acticoat reduced the microbial inocula below the limit of detection and reduced microbial viability by 99% within 4 h. Poly-Mem Silver™ had no zone of inhibition for most of the evaluated test microorganisms, and it also showed poor antimicrobial activity in the broth culture and Live/Dead BacLight assays. The silver hydrogel reduced most of the tested microbes below the detection limit and decreased bacterial viability by 94–99% after 24 h exposure.²³

Shuffitt *et al.* reported on the ability of SilvaSorb to deliver ionic silver and moisture to the wound bed, as a result the dressing only required changing three days after application. The increase in application time resulted in an overall reduced bioburden. This case series demonstrated a cost-effective and clinically effective method of treatment.²⁴ Glat *et al.* also presented a study on SilvaSorb (Medline Industries, Inc.) compared with silvadene (King Pharmaceuticals), a silver sulfadiazine cream, demonstrating the efficacy of SilvaSorb in the treatment of partial-thickness burns.²⁵ Recently Simcock and May conducted a study on split-skin graft reconstruction of scalp defects using a decellularized extracellular matrix biomaterial, with application of SilvaSorb after application to successfully stop infection at the site of reconstruction.²⁶

Zelen *et al.*²⁷ compared the healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®; MiMedx) versus SilvaSorb (Medline Industries, Inc.). An international review board–approved, prospective, randomized, single-center clinical trial was performed. Included were patients with a diabetic foot ulcer of at least 4-week duration, without infection, and having adequate arterial perfusion. Patients were randomized to receive SilvaSorb alone or with the addition of EpiFix. In the SilvaSorb group alone ($n=12$) and the EpiFix group ($n=13$), wounds reduced in size by a mean of $32.0\% \pm 47.3\%$ versus $97.1\% \pm 7.0\%$ ($p < 0.001$) after 4 weeks. Patients treated with EpiFix achieved superior healing rates over standard treatment alone.²⁷

In a recent comprehensive comparative study on biofilms, Phillips *et al.*²⁸ used an *ex vivo* porcine skin explant, *P. aeruginosa* biofilm model to com-

pare and contrast currently available antimicrobial dressings. The dressings that were evaluated included Cadesorb®, IdoFlex™, Alisite®, Acticoat®, Medihoney®, Curity™, Tegaderm®, SilvaSorb, Prontosan™, Triadine™, and Aquacel®. The biofilm was subjected to pretreatment with gentamicin for 24 h to gain antibacterial resistance. The study was conducted over a 24 h time period. The study concluded that the ability of antimicrobial wound dressings to kill mature biofilms varies widely with time of exposure, number of applications, moisture level, and release profile. However, the researchers did conclude that taking into account the large degree of variables SilvaSorb and IdoFlex were the most effective in reducing the mature biofilm by a log of five.²⁸

Iodine hydrogels and biofilms

Vogt *et al.*²⁹ undertook a monocentric, randomized, observer-blinded, phase III study of a poly (N-vinylpyrrolidone) (PVP)–iodine preparation hydrogel containing a 3% iodine concentration (Repithel®) to study the effect on epithelialization in patients receiving meshed skin grafts. Grafts of 167 patients (donor site defects, burn wounds, or chronic defects) were dressed either with Repithel ($n=83$) covered with a gauze (Jelonet), or Jelonet-gauze only ($n=84$) until healing. The grafts that received Repithel healed significantly earlier (9.4 vs. 12.4 days; $p < 0.0001$) and faster than controls, as measured by neo-epithelialization of mesh holes between days 7 and 11 ($91.20 \pm 22.8\%$ vs. $82.3\% \pm 28.6$, $p < 0.001$).²⁹ Further, Beukelman *et al.*³⁰ tested PVP-ILH, Repithel, on its ability to reduce the inflammatory response. The study showed that PVP-ILH reduced the amount of free superoxide anions and helped promote “normal” wound healing.³⁰

Mishra and Chaudhary tested numerous hydrogels that had incorporated povidone-iodine (PVP-I) showing that its release could be tailored by hydrogel composition leading to improved wound healing.³¹ Homann *et al.* demonstrated the efficacy of a novel PVP-I-loaded liposome hydrogel in a randomized controlled trial compared with silver sulfadiazine cream treatment. The liposome PVP-I hydrogel resulted in significantly faster, complete healing of the burn wounds compared with silver sulfadiazine cream (9.9 ± 4.5 vs. 11.3 ± 4.9 days; $p < 0.015$). Local tolerability was also noted to be good; handling and change of dressing were also rated as easy.³²

PHMB hydrogels and biofilms

The antimicrobial activity of PHMB owes itself to its molecular shape and charge. Where PHMB causes an irreversible loss of essential cellular

components due to damage caused to the cytoplasm membrane. PHMB has also been found to prevent the efflux pump and so the microbe is unable to reduce the levels of antimicrobial present within it.³³ Therefore, microorganisms are not known to adapt to PHMB and no known resistance has yet been documented.³⁴

The precise mechanism of action of PHMB on bacteria still remains unclear.³⁴ An example of a PHMB-containing hydrogel is Suprasorb X+PHMB®.³⁵ Bruckner *et al.*³⁶ performed a study on 40 patients, each suffering from delayed wound healing for at least 3 weeks, and signs of critical colonization/infection to determine the efficacy of Suprasorb X+PHMB. The progress of wound healing was evaluated by a colorimetric method. In 32 out of 40 patients, the share of granulation tissue was increased, as a result of sufficient reduction of bacterial colonization (granulation tissue start point is $12\% \pm 18\%$ and endpoint is $79\% \pm 24\%$ in 27 ± 25 days; $n=40$). However, in five patients no progress was measured, all of these wounds were infected with *P. aeruginosa* with signs of biofilm formation.³⁵

Consultants³⁶ undertook a cohort study to evaluate the clinical efficacy of a polyhexanide-containing biocellulose dressing, Suprasorb X+PHMB (Lohmann and rauscher GmbH), for the eradication of biofilms in nonhealing wounds. The study consisted of 28 patients, aged over 18 years, who presented at an outpatient wound clinic with nonhealing, locally infected, and/or critically colonized wounds of various etiologies that showed clinical signs of biofilm. The patients were prospectively followed for a maximum of 24 weeks or until healing for analysis of safety and efficacy endpoints.

Evolution of wound size was conducted with tracings and standardized digital photographs as well as for determining healing rates. At 24 weeks, 12 wounds (75%) had healed (complete epithelialization with no drainage). Of those wounds that had not closed, the mean wound area had reduced by 61% by week 24. Ten patients (63%) had a good reduction in biofilm presence, 5 (32%) scored moderate, and 1 (6%) had no reduction noted at week 24, concluding that the PHMB-containing biocellulose dressing seems to be suitable for lightly-to-moderately exuding wounds.³⁶

Spits and Van Gent³⁷ conducted a similar study to evaluate the clinical benefits, primarily tolerability and reduction in pain levels, associated with the use of a PHMB-impregnated biosynthetic cellulose dressing (Suprasorb X+PHMB) on pediatric heel lacerations in particular. A PHMB-impregnated biocellulose dressing was applied and left *in situ* until epithelialization occurred. A cork splint

was used for 3 days to prevent *pes equinus* and to let the ankle joint rest. Change in wound size (cm^2), incidence of local infection, wound bed characteristics, and pain levels (measured on a 0–10 pediatric pain scale) were assessed at 3-day intervals during the 14-day treatment period. Satisfaction with the dressing was also evaluated. Twenty children (mean age = 5.6 ± 1.33 years) were recruited into the study and included in the analysis. The mean baseline wound area was $8.60 \pm 6.57 \text{ cm}^2$. The mean time to complete wound closure was 12.95 ± 7.69 days with a mean total of 4.70 ± 1.56 visits. The mean pain score was 9.55 ± 0.69 , compared with 0.15 ± 0.37 on day 14 ($p < 0.003$). At the second visit (after 3 days), 17 of the 20 children were reported to be free of pain. No cases of local infection were noted. The evaluation also showed that it was well tolerated and achieved good healing outcome.³⁷

Galitz *et al.*³⁸ compared the potency of pain and the microbial reduction of chronic wounds in a controlled, randomized, multicentric comparative study over a period of 28 days on 21 patients using BWD-PHMB and a typical silver dressing as a comparison. The results of which were inconclusive in terms of reduction in microbial burden. The pain in changing dressings was noted to be reduced when using the Suprasorb X+PHMB dressing. Haemerle *et al.* compared treatment of a polyhexanide-containing biocellulose wound dressing (BWD+PHMB) to silver dressings (Ag) in 38 painful, critically colonized or locally infected wounds. Although BWD+PHMB and Ag were effective in reducing pain and bacterial burden, the BWD+PHMB was stated as being significantly faster at removing the critical bacterial load from the colonized wounds.³⁹

Lenselink and Andriessen,⁴⁰ however, conducted a study on the efficacy of Suprasorb X+PHMB on patients visiting an outpatient clinic with nonhealing wounds of various etiologies that showed clinical signs of biofilm inhabitancy.^{40,41} Suprasorb X+PHMB dressing changes took place two to three times per week, depending on the wound condition and exudate production, and patients were followed until healing. Reduction of the biofilm was scored on a three-point scale (good/moderate/poor). Reduction in wound size was also scored on a three-point scale, using planimetry and photographs. Interestingly 60% of the 25 patients included in the study had a good reduction in biofilm size and a good reduction in wound area. These results indicated that Suprasorb X+PHMB has the ability to reduce biofilm burden in patients with chronic wounds.⁴⁰ Further, Lenselink and Andriessen performed a similar study in 2011⁴² that reinforced the efficacy of Suprasorb X+PHMB toward biofilm eradication. Twenty-eight patients,

again from an outpatient wound clinic with non-healing, locally infected, and/or critically colonized wounds of various etiologies that showed clinical signs of biofilm were included in the study. Sixteen patients (9 women), with a mean age of 60.9 ± 21.6 years, were included in the analysis. The patients were prospectively followed for a maximum of 24 weeks or until healing for analysis of safety and efficacy endpoints. Wound size was conducted with standardized digital photographs for determining healing rates. After 24 weeks, 75% had healed (complete epithelialization with no drainage) and of those wounds that had not closed, the mean wound area had reduced by 61% at week 24, 63% had a good reduction of the biofilm, 32% scored moderate, and one had no reduction noted at week 24.⁴²

New-generation hydrogels and biofilms

Hydrogels containing endopeptidase enzymes, which are used to cleave denatured proteins and superoxide-dismutase-containing hydrogels, have demonstrated positive effects on wound healing. Further, a biphosphonate-functionalized hydrogel was reported to inhibit the action of MMPs in chronic wound fluid.⁴³

Lee *et al.*⁴⁴ reported on the development of novel biodegradable hydrogels from vitamin E-functionalized polycarbonates for antimicrobial applications. These hydrogels were formed by incorporating positively charged polycarbonates con-

taining propyl and benzyl side chains with vitamin E moiety into physically crosslinked networks of “ABA”-type polycarbonate and poly(ethylene glycol) triblock copolymers. *In vitro* antimicrobial studies revealed that the more hydrophobic [VE/BnCl(1:30)]-loaded hydrogels generally exhibited better antimicrobial/antifungal effects compared with their counterpart VE/PrBr(1:30) as lower minimum bactericidal concentrations (MBCs) were observed in *Staphylococcus*, *Escherichia coli*, and *C. albicans*. Similar trends were observed for the treatment of biofilms where VE/BnCl(1:30)-loaded hydrogels displayed better efficiency with regards to eradication of biomass and reduction of microbe viability of the biofilms. These hydrogels also displayed excellent compatibility with human dermal fibroblasts with cell viability >80% after treatment with hydrogels loaded with cationic polymers at minimum biocidal concentrations (MBCs).⁴⁴

Other hydrogels have been reported with promising results, which include oxygen-generating hydrogels,⁴⁵ thermoresponsive hydrogels,⁴⁶ semi-interpenetrating networks hydrogel silver nanocomposites,⁴⁷ and hydrogels incorporating synergistic agents for enhanced antibiofilm activity.⁴⁸

SUMMARY

Within this review a host of hydrogels as a platform containing a variety of antimicrobials in

Antimicrobial	Hydrogels currently available
Silver	SilvaSorb [®] (Medline) Elta Silver Gel [®] (Elta Skin and Wound Care) Silver Shield [®] Silver-Sept [®] (Anacapa Technologies) Gentell [®] Silver Hydrogel (Gentell) DermaSyn/Ag [®] (DermaRite Industries) SilverMed [®] (MPM Medical, Inc.) ReliaMed Silver Hydrogel (ReliaMed) Silver Genesis Colloidal Silver Hydrogel (Silver Genesis)
Iodine (PVP-I)	Repithel [®]
Polyhexamethylene biguanide (PHMB)	Suprasorb X + PHMB [®] (Lohmann and rauscher GmbH)

Figure 2. Currently available antimicrobial-incorporated hydrogel wound dressings.

the treatment of acute and infected wounds have been addressed, with references to the past, current, and future use of this type of wound dressing. It is difficult to formulate an opinion on which antimicrobial-containing hydrogel is the obvious choice for future treatment of wounds. However, it is fair to say that the choice of hydrogel is highly biased toward the type of patient and underlying pathologies, wound type, and location. Further the choice of antimicrobial hydrogel will also depend on the virulence and microbiology of the biofilm and the amount of exudate being produced by the wound. What is clearly evident and highlighted in this article is that there is presently a lack of good scientific evidence regarding the efficacy of antimicrobial hydrogels on biofilms and healing rates. This area was reviewed recently by Valle and colleagues⁴⁹ who concluded that they did not identify any studies that assessed wound healing rates in a meaningful manner. Not only for hydrogels but for composite dressings, specialty absorptive dressings, contact layer dressings impregnated gauzes, or dressings with debriding agents. Concluding this was due to the high risk of bias, inconsistent results, selective outcome reporting, and/or imprecise estimates. Consequently significant clinical- and biofilm-related research is urgently needed on hydrogels and their effectiveness in wound care. The treatment of acute and infected wounds have been addressed, with references to the past, current, and future use of this type of wound dressing'. Figure 2 has the currently commercially available antimicrobial-incorporated hydrogel wound dressings summarised.

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TAKE-HOME MESSAGE

- Hydrogels are used to assist in the management of dry, sloughy, or necrotic wounds.
- More comparative studies between wound dressing platforms are needed with standardized procedures being put in place to facilitate more meaningful conclusions to be drawn from literature in the future.
- Some initial biofilm studies that involve some antimicrobial hydrogels show good efficacy.
- Significant clinical- and biofilm-related research is urgently needed on antimicrobial hydrogels.

ABOUT THE AUTHORS

Simon Finnegan obtained his Biological Chemistry MChem in 2010 from the University of Sheffield, United Kingdom and has now undertaken a DTC-TERM PhD position at the University of Sheffield. Designing novel silicone wound contact layers to be used in wound dressings in collaboration with Scapa healthcare.

Professor Steven L. Percival holds a PhD in microbiology and biofilms, a BSc in Applied Biological Sciences, Post graduate Certificate in Education, diploma in Business Administration, an MSc in Public Health, and an MSc in Medical and Molecular Microbiology. Was a senior university lecturer in medical microbiology, Head of the Biofilm Research Group and later the positions of Director of R&D and Chief Scientific Officer at Aseptica, Inc., and senior clinical fellowships at the Centres for Disease Control, Atlanta, and Leeds Teaching Hospitals Trust. Held senior management R&D and innovation positions at Bristol Myers Squibb, Conva Tec, Advanced Medical Solutions Plc. Held an honorary Professorship in the medical school at West Virginia University. In 2011, joined Scapa Healthcare Plc as Vice President of Global Healthcare R&D and was awarded an honorary Professor in the Institute of Ageing and Chronic Disease and the Surface Science Research Centre at the University of Liverpool, United Kingdom.

REFERENCES

- Wu L, Brucker M, Gruskin E, Roth SI, Mustoe TA. Differential effects of PDGFBB in accelerating wound healing on aged versus young animals: the impact of tissue hypoxia. *Plast Reconstr Surg* 1997;99:815.
- Robson MC. Wound infection: a failure of wound healing caused by an imbalance of bacteria. *Surg Clin North Am* 1997;77:637.
- Martin L, Wilson CG, Koosha F, et al. The release of model macromolecules may be controlled by the hydrophobicity of palmitoyl glycol chitosan hydrogels. *J Control Release* 2002; 80:87.
- Mulder GD. Cost-effective managed care: gel versus wet-to-dry for debridement. *Ostomy Wound Manage* 1995;41:68.
- Trudigan J. Investigating the use of Aquaform Hydrogel in wound management. *Br J Nurs* 2000; 9:943–948.
- Wichterle O, Lim D. Hydrophilic gels for biological use. *Nature* 1960;185:117.
- Rosiak JM, Yoshii F. Hydrogels and their medical applications. *Nucl Instrum Methods Phys Res B Beam Interact Mater Atoms* 1990; 151:56.
- Weller C, Sussman G. Wound dressings update. *J Pharm Pract Res* 2006;36:318.
- Robson MC, Mustoe TA, Hunt TK. The future of recombinant growth factors in wound healing. *Am J Surg* 1998;176:80.
- Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plastic and reconstructive surgery*, 2006;117:35–41.
- Willenborg SKJ, Ranjan R, Krieg T, Eming SA. Chronic wounds and inflammation. *Adv Wound Care* 2010;1:259.
- Yager DR, Nwomeh BC. The proteolytic environment of chronic wounds. *Wound Repair Regen* 2002;7:433.
- Pudner R. Amorphous hydrogel dressings in wound management. *J Comm Nurs* 2001;15:43.
- Falabella AF. Debridement and wound bed preparation. *Dermatol Ther* 2006;19:317.
- Geronemus RG, Robins P. The effect of two new dressings on epidermal wound healing. *J Dermatol Surg Oncol* 1982;8:850.
- Smith J. Debridement of diabetic foot ulcers. *Cochrane Database Syst Rev* 2001;4:003556.
- Thomas S, Banks V, Bale S, et al. A comparison of two dressings in the management of chronic wounds. *J Wound Care* 1997;6:383.
- Kaya AZ, Turani N, Akyüz M. The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. *J Wound Care* 2005;14:42–44.
- Moody A. Use of a hydrogel dressing for management of a painful ulcer. *Br J Comm Nurs* 2006; 11:12–17.
- Harrow J. A comparison of the effects of two hydrogels upon the proliferation of three micro-organisms of importance for chronic wound care. European Wound Management Association, Granada, Spain, 2002.
- Jones V, Milton T. When and how to use hydrogels. *Nurs Times* 2000;96:3.
- Templeton, S. Management of chronic wounds: the role of silver-containing dressings. *Prim Intent* 2005;13:170.
- Boonkaew B, Kempf M, Kimble R, Supaphol P, Cuttle L. Antimicrobial efficacy of a novel silver hydrogel dressing compared to two common silver burn wound dressings: Acticoat™ and PolyMem Silver. *Burns* 2004;40:89–96.
- Shuffitt V, Hoskinson S, Matsumoto C. CWOCA Wound Care Program, Maui Memorial Medical Center, Wailuku, HI. Silver antimicrobial hydrogel eradicates bioburden and hastens discharge for acute care facility.
- Glat PM, Kubat WD, Hsu JF, et al. Randomized clinical study of SilvaSorb (R) gel in comparison to silvadene (R) silver sulfadiazine cream in the management of partial-thickness burns. *J Burn Care Res* 2009;30:262.
- Simcock J, May BC. Ovine forestomach matrix as a substrate for single-stage split-thickness graft reconstruction. *Eplasty* 2013;13:e58.
- Zelen CM, Serena TE, Denozieri G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J* 2013;10:502.
- Phillips PL, Yang Q, Davis S, et al. Antimicrobial dressing efficacy against mature *Pseudomonas aeruginosa* biofilm on porcine skin explants. *Int Wound J* 2013 [Epub ahead of print]; DOI: 10.1111/iwj.12142.
- Vogt PM, Reimer K, Hauser J, et al. PVP-iodine in hydrosomes and hydrogel—a novel concept in wound therapy leads to enhanced epithelialization and reduced loss of skin grafts. *Burns* 2006;32:698.
- Beukelman CJ, Van Den Berg AJ, Hoekstra MJ, Uhl R, Reimer K, Mueller S. Antiinflammatory properties of a liposomal hydrogel with povidone-iodine (Repithel®) for wound healing *in vitro*. *Burns* 2008;34:845.
- Mishra A, Chaudhary N. Study of povidone iodine loaded hydrogels as wound dressing material. *Trends Biomater Artif Organs* 2010; 23:122–128.
- Homann HH, Rosbach O, Moll W, et al. A liposome hydrogel with polyvinyl-pyrrolidone iodine in the local treatment of partial-thickness burn wounds. *Ann Plast Surg* 2007;59:423–427.
- Körber A, Seipp HM, Hofmann S. Efficacy of different wound dressings on artificial plaques of fibrin. *EWMA J* 2008;8:261.
- Werthen M, Davoudi M, Sonesson A, et al. *Pseudomonas aeruginosa*-induced infection and degradation of human wound fluid and skin proteins *ex vivo* are eradicated by a synthetic cationic polymer. *J Antimicrob Chemother* 2004; 54:772.
- Bruckner M, Schwarz C, Otto F, Heillinger J, Wild T. Evaluation of cellulose and polyhexamethylene biguanide (Suprasorb® X+PHMB) in therapy of infected wounds. Exudate management, pain reduction, cost effectiveness—successful treatment of chronic wounds. Lohmann & Rauscher 2008; 30:27–30.
- Consultants A. A cohort study on the efficacy of a polyhexanide-containing biocellulose dressing in the treatment of biofilms in wounds. *J Wound Care* 2011;20:534.
- Spits H, Van Gent M. Clinical evaluation of a PHMB-impregnated biocellulose dressing on paediatric lacerations. *J Wound Care* 2011; 2:280.
- Galitz C, Hämmerle G, Signer M, et al. Polyhexanide versus silver wound dressings first interim results of a controlled, randomized, prospective, multicentric study. Poster Presentation, European Wound Management Association Conference, Helsinki, 2009.
- Haemmerle G, Signer M, Mittlboeck M. Comparison of PHMB-containing dressing and silver dressings in patients with critically colonised or locally infected wounds. *J Wound Care* 2012;21:12.
- Lenselink E, Andriessen A. Clinical effectiveness of polyhexanide on biofilms in wounds. EWMA Congress, Geneva, 2010.
- Schierl CF, De la Garza M, Mustoe A, Galiano RD. Staphylococcal biofilms impair wound healing by delaying reepithelialization in a murine cutaneous wound model. *Wound Repair Regen* 2009;17:354.
- Lenselink E, Andriessen A. A cohort study on the efficacy of polyhexanide containing biocellulose dressing in the treatment of biofilms in wounds. *J Wound Care* 2011;20:534–538.
- Reimer K, Vogt PM, Broegmann B, et al. An innovative topical drug formulation for wound healing and infection treatment: *in vitro* and *in vivo* investigations of a povidone-iodine liposome hydrogel. *Dermatology* 2000;201:235.
- Lee AL, Ng VW, Wang W, Hedrick JL, Yang YY. Block copolymer mixtures as antimicrobial hydrogels for biofilm eradication. *Biomaterials* 2013;34: 10278.
- Queen D, Coutts P, Fierheller M, Sibbald RG. The use of a novel oxygenating hydrogel dressing in the treatment of different chronic wounds. *Adv Skin Wound Care* 2007;20:200.

46. Jones DS, Lorimer CP, McCoy CP, Gorman SP. Characterization of the physicochemical, antimicrobial, and drug release properties of thermoresponsive hydrogel copolymers designed for medical device applications. *J Biomed Mater Res B Appl Biomater* 2008;85:417.
47. Murthy PK, Murali Mohan Y, Varaprasad K, Sreedhar B, Mohana Raju K. First successful design of semi-IPN hydrogel–silver nanocomposites: a facile approach for antibacterial application. *J Colloid Interface Sci* 2008;318:217.
48. Percival SL, Hammerslag B. Treatment of Biofilms. 01/2010; Patent: EP 2525662.
49. Valle MF, Maruthur NM, Wilson LM, et al. Comparative effectiveness of advanced wound dressings for patients with chronic venous leg ulcers: a systematic review. *Wound Repair Regen* 2014;22:193–204.

Abbreviations and Acronyms

IPN = interpenetrating networks
MBC = minimum biocidal concentration
MMP = matrix metalloprotease
NaCMC = sodium carboxymethylcellulose
PEG = polyethylene glycol
PHEMA = polyhydroxyethylmethacrylate
PHMB = polyhexamethylene biguanide
PVP-I = povidone-iodine
PVP = poly(N-vinylpyrrolidone)