

WORLD UNION
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WOUND HEALING SOCIETIES



THE ROLE OF NON-MEDICATED DRESSINGS FOR THE MANAGEMENT OF WOUND INFECTION

Biofilm and infection recognition and management
in the context of antimicrobial stewardship

Non-medicated wound dressings: Defining their role

Non-medicated wound dressings in infected wounds
or wounds at risk of infection: How to use in practice

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Wounds International
108 Cannon Street
London EC4N 6EU, UK
Tel: +44 (0)203 735 8244
info@omniamed.com
www.woundsinternational.com



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Every wound type has the potential to develop serious infection, which in some cases can lead to chronicity, bone infections, long-term disabilities or even death. Bacteria within a wound will exist in either planktonic or biofilm forms, with treatment mostly by use of topical antimicrobials or antibiotics. Alarming, there is growing concern regarding the treatment of infection, caused by the rise of antimicrobial resistance in many common bacterial pathogens and the misuse of antimicrobial agents.

Antimicrobial stewardship aims to promote the appropriate use of antibiotics and antimicrobial agents. Since the introduction of antimicrobial stewardship principles, the overall number of prescriptions for antibiotics (between 2013 and 2017) fell by 4.5%^[1]. Nevertheless, new perspectives are needed to help tackle the ongoing and very real threat of antimicrobial resistance in wounds.

Paper 1 'Biofilm and infection recognition and management in the context of antimicrobial stewardship' sets the scene on the key aspects of biofilm physiology and structure, along with the challenges and current treatment approaches to identifying and treating biofilm in wounds. A new approach offers clinicians the opportunity to reduce the overuse of antimicrobial agents in wound care and outlines the importance of antimicrobial stewardship.

Paper 2 'Non-medicated wound dressings: Defining their role' focuses on the mechanism of action of so-called non-medicated wound dressings (NMWDs) in the management of bacterial bioburden in both acute and chronic wounds, by proposing a clear definition, indications for their use and evidence that supports their effectiveness.

Paper 3 'Non-medicated wound dressings in infected wounds or wounds at risk of infection: How to use in practice' covers the use of NMWDs in practice, including when to consider NMWDs, rationale for use and shared clinical experience through specific case examples.

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Authors

Thomas Bjarnsholt, Costerton Biofilm Center, Department of Immunology & Microbiology, Faculty of Health and Medical Sciences, The University of Copenhagen, Denmark; Department of Clinical Microbiology, Rigshospitalet, Denmark

Val Edwards-Jones, Institute of Skin Integrity and Infection Prevention, University of Huddersfield, UK

Matthew Malone, PhD, FFPM RCPS (Glasg), Director of Research, South West Sydney Limb Preservation and Wound Research Academic Unit, Sydney, Australia

Karen Ousey, Professor of Skin Integrity at the Institute of Skin Integrity and Infection Prevention, University of Huddersfield, UK

Mark Rippon, Visiting Clinical Research Fellow, Huddersfield University; Medical Marketing Consultant, Daneriver Consultancy Ltd, Holmes Chapel, UK

Alan Rogers, Independent Wound Care Consultant, Flintshire, UK

Samantha Westgate, CEO, Perfectus Biomed Limited, UK

Sabine Eming, Professor of Dermatology and Head of the Interdisciplinary Wound Healing Centre, University Hospital of Cologne, Germany

Isabelle Fromantin, Wounds and Healing Expert, Institut Curie, France

Astrid Probst, Advanced Nurse Practitioner, Wound Management, Kreiskliniken Reutlingen GmbH, Reutlingen, Germany

Hans Smola, Professor of Dermatology, University of Cologne, Germany; Medical Director, PAUL HARTMANN AG, Germany

Hui-Mei Yang, Nurse Practitioner, Department of Endocrinology and Metabolism, Chang Gung Memorial Hospital Linkou Branch, Taoyuan, Taiwan, R.O.C

Jiun-Ting Yeh, Plastic Surgeon, Division of Trauma, Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital Linkou Branch, Taoyuan, Taiwan, R.O.C

Lead Reviewer

Steven Percival, CEO, 5D Health Protection Group Ltd; Director, Centre of Excellence in Biofilm Science (CEBS), Liverpool, UK; Professor (honorary), University of Liverpool, UK

Reviewers: Chairs of the WUWHS International Scientific Committee

Afsaneh Alavi, Professor, Dermatologist, University of Toronto, Toronto, Canada

Dieter Mayer, Professor, Senior Consultant of Vascular Surgery and Head of Wound Care, Switzerland

Biofilm and infection recognition and management in the context of antimicrobial stewardship

The aggregation of bacteria and fungi and their role in human health and disease has been the scope of much research over the past two decades. There has been debate around how best to define microbial biofilms and the nomenclature has varied significantly within the literature. Is surface association a necessity for biofilm formation? Is the maturity or age of a biofilm important? Do biofilms originate from planktonic cells and, if so, what triggers this? All these questions have been heavily debated. However, it does not matter whether we discuss surfaces or whether suspended aggregates are biofilms; the importance is in understanding the context and behaviour of the bacteria microorganisms. Therefore, the most important hallmark feature that distinguishes microbial biofilms (aggregates of bacteria microorganisms) from planktonic microorganisms is their significant tolerance towards antimicrobial agents and the host defence. In addition, we need to understand that single cells in an infection are not equal to exponentially growing planktonic bacteria in a shaken culture. This subsequently means that infections involving biofilms cannot be treated in a similar fashion to acute infections.

KEY ASPECTS OF BIOFILM PHYSIOLOGY/STRUCTURE AND HOW THIS IMPACTS THERAPEUTICS

Antimicrobial therapies for acute infections based on minimum inhibitory concentrations (MIC; planktonic microorganism's susceptibility to antibiotics) target rapidly multiplying planktonic microorganisms with high efficacy. Unfortunately, when these therapies are employed against biofilm microorganisms that differ markedly in both their physiology and activity, they typically fail to eradicate the problem^[1]. Indeed, a plethora of *in vitro* biofilm models have elucidated that bacterial biofilms can withstand antimicrobial concentrations 100 to 1,000 times higher than that of their planktonic counterparts^[2]. Resistance and tolerance have been reported synonymously in defining biofilm's ability to withstand much higher concentrations of antimicrobials (topical, oral and intravenous), antiseptics and disinfectants, but they infer two very different mechanisms (Box 1^[3]).

Individual bacteria can promote resistance through mobile genetic elements (such as plasmids or transposons allowing horizontal gene transfer) or by target mutations (modifying enzymes or efflux pumps). These familiar mechanisms by which individual planktonic microorganisms can resist the increased concentrations of antimicrobials do not seem to explain the enhanced protection afforded to bacteria in a biofilm. Therefore, when describing a biofilm's ability to withstand many different antimicrobial treatments, we often term this as tolerance and not resistance. Most of our knowledge on biofilm physiology has been investigated *in vitro* and has identified key areas of biofilm tolerance research:

- Reduced growth/metabolism
- Extracellular polymeric substance (EPS)
- Efflux pumps
- Altered microenvironments.

A dominating factor of biofilm tolerance seems to be due to the slow growth or dormancy of the bacteria. This is important as most antibiotic agents act on metabolic pathways in active bacterial cells. Therefore, in the case of slow-growing or dominant bacteria, antibiotics can be less effective. Another proposed contributor to biofilm tolerance is the production of a protective matrix called EPS. Costerton et al^[4] first described a process whereby bacterial cells produced 'glycocalyx', and

Box 1. Term of resistance/tolerance^[3]

Antimicrobial resistance refers to a specific mechanism of drug resistance. Tolerance refers to the decreased susceptibility and enhanced tolerance to antimicrobials in a non-specific manner.

Thomas Bjarnsholt, Costerton Biofilm Center, Department of Immunology & Microbiology, Faculty of Health and Medical Sciences, The University of Copenhagen; Department of Clinical Microbiology, Rigshospitalet, Denmark
Val Edwards-Jones, Institute of Skin Integrity and Infection Prevention, University of Huddersfield, UK
Matthew Malone, PhD, FFPM RCPS (Glasg), Director of Research, South West Sydney Limb Preservation and Wound Research Academic Unit, Sydney, Australia

proposed it provided additional benefits to microorganisms with reduced growth^[4]. The glycocalyx was defined as being a composition of polysaccharides that accounted for over 90% of a biofilm, with less than 10% being bacterial in composition^[4]. The terminology of glycocalyx was redefined in later years to EPS, as it became clear that bacterial glycocalyx were more than just polysaccharides^[5,6]. EPS is characterised as biopolymers, composed of proteins, nucleic acids, lipids and humic substances, enabling the immobilisation and cohesion of bacterial cells in close proximity. The importance of the biofilm matrix seems to play a role at least *in vitro*^[7,8]; however, the roles of matrix components are not as clearly defined *in vivo*, as it is not known what components the bacteria produce here^[9].

The exact role of biofilm tolerance *in vivo* is poorly understood; however, we know that bacterial metabolism and growth is significantly reduced. The microenvironment within the wound may play a role in reducing the growth of microorganisms. These low-oxygen areas house micro-niches of differing microorganisms and may explain how the presence of anaerobes in mixed-species biofilms exist, contribute and cooperate with aerobic neighbours *in vitro*. Studies employing microelectrodes with confocal microscopy have identified micro-domains with different biochemical environments, including alterations in pH and oxygen^[10]. These alterations in biochemical gradients have been proposed as pathways to inhibit the action of antibiotics^[11].

Recent data by James et al (2016)^[12] have provided further evidence to support a concept of a localised low oxygen tensions contributing to wound chronicity using oxygen microsensors and transcriptomics (examining microbial metabolic activities) to study *in situ* biofilms. James et al (2016) identified steep oxygen gradients and induced oxygen-limitation stress responses from bacteria, and established that metabolic activities of the biofilm and the recruitment of cells that consume oxygen for host defensive processes are the primary pathways of oxygen depletion^[12]. This supports the concept of a biofilm establishing and maintaining localised low oxygen tensions in a wound, thus contributing to chronicity.

CHALLENGES AND CURRENT TREATMENT APPROACHES TO IDENTIFYING AND TREATING BIOFILM IN WOUNDS

Prevalence of biofilms in wounds and their role in wounds

Based on the current literature, it is evident that most chronic wounds are likely to contain biofilms and biofilms appear to play a role in the lack of healing^[13-15]. However, very importantly, both clinicians and researchers should remain aware that bacteria are never the primary cause of a chronic non-healing wound. The underlying aetiology may include host-patient factors, such as diabetes, peripheral vascular disease, peripheral neuropathy, trauma and increased plantar pressure. However, once a wound is established in a person with multiple comorbidities, any infecting bacteria may contribute or overtake the primary aetiological causes to keep the wound in a non-healing state, due to the continuous inflammatory response the bacteria evoke.

Another consideration is where the bacteria comes from, both in the first instance and for re-infections. In acute wounds and breaches of the skin of healthy people, the initial inflammatory response is activated. However, if the recruitment of white blood cells/leucocytes is impaired due to factors such as venous insufficiency, bacteria from the skin and possibly the gut (e.g. by faecal contamination when showering) may get a head start and form un-phagocytosable biofilms. In addition, the incoming bacteria are unlikely to enter as free planktonic bacteria but rather as aggregates, since the bacteria on the skin and the rest of the microbiome are found as small aggregates^[16].

How do biofilms organise themselves in human tissue?

Microscopy techniques analysing biofilms in human wounds have identified the presence of both aggregated and planktonic microorganisms. Microorganisms within a wound can be on the surface or imbedded deeper within the wound bed^[17-20]. Bacterial aggregates are fairly small and range from

5–200µm in diameter^[21]. They are heterogeneously distributed in the wound bed^[22], meaning they do not form a homogenous layer of “slime” across the entire wound surface. These aggregates, in addition to single cells (planktonic bacteria), are not macroscopically visible (i.e. they are not visible to the naked eye). It is also not possible to assess the level of bioburden by the size of the wound alone or by the amount of fibrin, slough or non-viable tissue.

GENOMICS AND THE UTILISATION IN WOUND RESEARCH

Identification of causative pathogens and/or microbial communities within open wounds is vital in directing therapy. Historically, clinicians have relied upon conventional culture techniques that are now acknowledged to be selective for microorganisms that thrive under the physiological and nutritional constraints of the microbiology laboratory, and have grossly underestimated the microbial diversity of a sample. Over the last decade, we have seen an explosion in the use of next-generation DNA and RNA sequencing platforms that circumvent the requirement to grow and isolate bacteria from a nutrient-based Petri dish. In tandem with the increasing publications in this area, there has been an ever-increasing complexity of molecular and bioinformatic-based approaches, generating potentially confusing data using technical jargon that is confusing to the everyday clinician. In this section, the utilisation of genomics in the context of wounds and biofilm research will be explained in lay terminology to help readers understand the potential (and limitations) of such technologies to improve wound care.

Next-generation sequencing: clinician's guide

Next-generation sequencing refers to the overall approach to analysing DNA or RNA from a sample. Numerous sequencing-based platforms exist — e.g. Illumina, IoN Torrent, PacBio, Oxford Nanopore — with each having slightly different proprietary technologies to sequencing DNA or RNA. The one commonality of most sequencing platforms today is their ability to sequence many samples at one time and to sequence the entire genome of an organism (this is often referred to as high-throughput sequencing).

The most commonly used approaches to analysing DNA or RNA for wound research can be separated into clear categories:

- **16S ribosomal RNA (rRNA) sequencing** — alternative names: 16S sequencing, 16S amplicon sequencing, 16S rDNA sequencing
- **Whole genome (shotgun) sequencing** — alternative names: shotgun sequencing, metagenomics
- **RNA Transcriptomics** — alternative names: metatranscriptomics, RNA sequencing.

16S rRNA sequencing

This is by far the most commonly utilised approach in wound research. 16S, as it is commonly referred to, also represents the easiest of sequencing approaches. 16S rRNA is present only in bacterial DNA and not in humans, and thus represents an ideal target to identify bacteria. The 16S gene contains the taxonomic information that allows a user to identify the bacterium or a community of bacteria from within a sample, such as wound tissue or a swab. Lastly, once DNA sequences are obtained during the sequencing process, they need to be compared against millions of other sequences read from publicly available databases (e.g. Greengenes, Silva, NCBI). The sequences are then matched against a known reference and taxonomy is assigned. A major limitation of 16S sequencing is the short reads of DNA, meaning that taxonomic identification of a bacteria is often only possible to genus level (i.e. *Staphylococcus*). Therefore, the clinical utility is limited, given that current antibiotic treatment is driven by conventional culture capable of identifying the species of pathogen and antibiotic susceptibilities. Table 1 outlines other advantages and disadvantages of 16S sequencing.

Table 1. The advantages and disadvantages of 16S sequencing^[23-25]

Advantages	Disadvantages (limitations)
Inexpensive (cost now <\$50 USD)	Most commonly can only identify bacteria to the genus level (i.e. <i>Staphylococcus</i>). Therefore can be limiting for clinical purposes
The easiest of molecular approaches and can be performed rapidly	Will sequence both live and dead bacteria
Not computationally challenging	Will only identify which bacteria are present and cannot infer function or behaviour
Not reliant on culture and can identify bacteria with slow growth (biofilm) or bacteria that cannot be cultured. Thus, it can provide an extended view of the microbial communities in wounds	It is difficult to interpret the data in context with clinical care and what it means to have significantly more and different bacteria within a wound
Can be combined with powerful bioinformatic approaches to better understand microbial communities in wounds and how they respond to treatment	Data is often pooled from multiple patient samples, but this can skew data, as each individual patient may have a slightly different microbiome of clinical importance

Whole genome (shotgun) sequencing

This molecular DNA-based approach offers the opportunity for a deeper insight into the wound microbiome and its potential function. Unlike 16S sequencing, which amplifies only the 16S gene, whole genome sequencing surveys all DNA within a sample in a random “shotgun-like” approach. In this manner, it is possible to characterise not only the microbial diversity via the 16S gene, but also other genes from both host and microbe (e.g. virulence, pathogenicity or antimicrobial resistance). In essence, this approach can provide information on the armoury of genes possessed by bacteria or group of bacteria; however, whether these genes are activated in the wound bed would be unknown.

RNA Transcriptomics

In short, examining DNA provides a static picture of what a microorganism might do, whereas measuring RNA can provide insight into what a microorganism is actually doing at that specific timepoint. Bacteria can possess a repertoire of genes for varying functions, such as antimicrobial resistance; however, it does not mean that these genes will be expressed. To circumvent the need for researchers to hypothesise on the potential of a microorganism based on the presence of certain genes, RNA transcriptomics looks at the actual expression of regulated genes. This may offer opportunities to look at metabolic pathways or specific up-regulation of virulence factors during infection compared with no infection. It can also be used to look at the host response to the presence of microorganisms.

WOUND STUDIES EMPLOYING 16S SEQUENCING

There has been a plethora of wound studies that have used 16S sequencing to define the microbiome of a variety of chronic non-healing or infected wounds (Table 2). Despite the differing aetiologies of wounds affecting the lower limb, it seems the microbiome does not differ significantly. This has been highlighted by Wolcott et al (2016)^[26] who utilised 16S sequencing to analyse the composition of the bacterial communities present in samples obtained from 2,963 patients: chronic diabetic foot ulcers (*n* = 910), venous leg ulcers (*n* = 916), pressure injuries (*n* = 767), and non-healing surgical wounds (*n* = 370)^[26]. All wound samples contained a high proportion of *Staphylococcus* species (63% of all wounds) and *Pseudomonas* species (25% of all wounds), in addition to high prevalences of anaerobic bacteria, which are traditionally considered commensals, or skin flora. Furthermore, Kalan et al (2016) have also estimated that up to 80% of wounds contain fungi as well as bacteria, and that they contribute to forming polymicrobial wound biofilms^[27].

Table 2. Wound care studies employing 16S rRNA sequencing techniques. The list is not an exhaustive reference

Wound aetiology	Literature
Diabetic foot ulcers	Johani et al, 2017 ^[20] ; Wolcott et al, 2016 ^[26] ; Kalan et al, 2016 ^[27] ; Smith et al, 2018 ^[34] ; Dowd et al, 2008 ^[44,45] ; Price et al, 2009 ^[46] ; Han et al, 2011 ^[47] ; Rhoads et al, 2012 ^[48] ; Gardner et al, 2013 ^[49] ; Gardiner et al, 2017 ^[50] ; Kalan et al, 2017 ^[51] ; Loesche et al, 2017 ^[52] ; Johani et al, 2018 ^[53] ; Suryaaletha et al, 2018 ^[54] ; Wu et al, 2018 ^[55] ; Malone et al, 2019 ^[56]
Diabetic foot infection	van Asten et al, 2016 ^[57] ; MacDonald et al, 2017 ^[58] ; Malone et al, 2017 ^[59,60] ; Johani et al, 2018 ^[61] ; Malone et al, 2019 ^[62]
Venous leg ulcers	Wolcott et al, 2016 ^[26] ; Dowd et al, 2008 ^[44] ; Price et al, 2009 ^[46] ; Wolcott et al, 2009 ^[63] ; Tuttle et al, 2011 ^[64]
Pressure injuries	Wolcott et al, 2016 ^[26]
Hidradenitis suppurativa	Ring et al, 2017 ^[65] ; 2019 ^[66]
Non-healing surgical wounds	Wolcott et al, 2016 ^[26]

Chronic non-healing wounds, or wounds with chronic infections, have complex polymicrobial communities that exist as biofilms, which has been a defining feature of wound microbiome exploration. Because biofilms have markedly reduced growth (and thus can be difficult to culture), a molecular sequencing approach can circumvent these limitations. When combined with a bioinformatic analysis, the data produced can provide an extended picture of the microorganisms involved in causing chronic infections and/or delaying wound healing.

WOUND STUDIES EMPLOYING METAGENOME (DNA OR RNA) APPROACH

Unlike 16S, both shotgun (DNA) sequencing and RNA transcriptomics are both technically and computationally challenging, and require significant bioinformatic expertise to analyse robust data sets. Perhaps this explains why, to date, there are only two studies that have employed either shotgun (DNA) sequencing^[28] or RNA transcriptome^[29]. Despite the gaps in evidence, both studies have offered exciting glimpses into the potential utility of molecular-based microbiology. Kalan et al (2019) used a whole genome (DNA) shotgun approach to identify species and strain-level differences in the microbiome of diabetic foot ulcers^[28]. This eloquent study revealed that strain-level variation of *Staphylococcus aureus* and genetic signatures of biofilm formation were associated with poor outcomes. Cornforth et al (2018) compared the transcriptome of *Pseudomonas aeruginosa* during human infection to that of *P. aeruginosa* in a variety of laboratory conditions^[29]. Several pathways, including the bacterium's primary quorum-sensing system, had significantly lower expression in human infections than in many laboratory conditions. On the other hand, multiple genes known to confer antibiotic resistance had substantially higher expression in human infection than in laboratory conditions, potentially explaining why antibiotic resistance assays in the clinical laboratory frequently underestimate resistance in patients.

THE OPPORTUNITY TO REDUCE THE OVERUSE OF ANTIMICROBIAL AGENTS IN WOUND CARE

Antimicrobial agents were originally introduced to help prevent and treat wound infection. Current advice from governing bodies, such as the National Institute for Health and Care Excellence (NICE) in the UK, states that spreading infection requires treatment with systemic antibiotics to eliminate infection, plus adjunct treatment with topical antiseptics to reduce numbers of microorganisms in the wound^[30]. Although there is copious evidence about which systemic antibiotic is appropriate for the prevention and treatment of infection^[30], the current level of evidence for the use of topical antimicrobial agents is limited.

When wound infection is diagnosed, administration of appropriate antibiotics at the onset can prevent

the infection from spreading into the deeper tissue, and possibly prevent the development of sepsis. This, along with application of topical antimicrobial agents/antiseptics, can reduce the microbial bioburden sufficiently to allow the immune system to combat the infecting microorganisms. This can be suggested to be relatively straightforward in acute wounds, where only 6% are reported to contain biofilm and a single organism tends to infect wounds^[31]. However, it is far more complicated in chronic wounds. Here, the microorganisms are often found within biofilm^[14,17,31] and it can be difficult to establish whether a single opportunistic pathogen is causing the infection or if a multitude of species from within the biofilm are interacting together. Administration of a single antibiotic (even if it is a broad-spectrum agent) will often not eradicate the biofilm or the organisms potentially causing the overt infection, because levels at the site of infection are insufficient, or the antibiotic is inactivated by accumulated enzymes in the biofilm matrix — produced by other resistant species growing alongside the pathogen (associated resistance)^[32]. **This leads to higher levels of antibiotics being required to actively combat the microorganisms within the biofilm, which frequently results in inappropriate treatment.**

For the past 70 years, we have been successfully treating infection, but the development of antimicrobial resistance (AMR) has now led to the need for antimicrobial stewardship for antibiotics and other antimicrobial agents, aiming to promote judicious use. Since the introduction of antimicrobial stewardship, there has been a reduction in antibiotic usage (by 4.5% since 2013)^[33], but there is still a long way to go. Research in the UK through surveillance has shown that 1 in 3 people will be given antibiotics in any 1 year and, in at least 20% of these cases, the antibiotics will be given inappropriately^[34]. Antimicrobial stewardship has the potential to help reverse the trend for misuse of antibiotics and to prevent further AMR development, but more needs to be done to encourage the appropriate use of antimicrobial dressings and other wound care products.

The role of antimicrobial stewardship in biofilm-based wound care

Antimicrobial stewardship is often managed by a team or a committee for a particular healthcare provider. Its remit is to provide the strategic direction, guidance, manpower, intelligence and resources for any stewardship-related activities. It is essential that every provider selects and correctly administers the appropriate antibiotic for the patient, while causing minimum harm to the individual, as well as protecting others from the risk of resistance in the future^[35].

A greater understanding of the physiology and structure of biofilms has led to a reduction of antibiotics and the introduction of biofilm-based wound care as an accepted concept for current practice^[36]. The wound is debrided, cleansed and an antimicrobial dressing used topically to reduce bioburden and to help wound healing. If there is no change in the wound after 2 weeks, a change in antimicrobial dressing should be encouraged, if considered appropriate. There is debate on whether antimicrobial agents should be used during debridement and cleansing procedures to reduce microorganism numbers, or whether water is sufficient to reduce wound bioburden^[37].

There is little definitive guidance for each step, and this is mostly dependent upon the level of training of the personnel undertaking the treatment. Appropriate dressing choice following assessment varies, and is determined by either local guidance or clinician preference. Supporting evidence on the status of the wound in terms of infection/colonisation is not always available from the laboratory^[115,38,39].

Currently, there is limited evidence as to which antimicrobial dressing should be used, or whether one antimicrobial agent will demonstrate better outcomes than another. Antimicrobial agents include honey, iodine, silver and polyhexamethylene biguanide (PHMB), and these agents are incorporated into a variety of dressing types. The initial choice of dressing depends on the physical structure (e.g. alginate, carboxymethyl cellulose, foam, gel, hydrocolloid) and the requirements of the wound. The clinician then decides if an antimicrobial is required and whether or not this will be incorporated within a dressing or in the form of a cream, ointment or gel. Unfortunately, much of the evidence is based on laboratory tests,

which, in general, lack standardisation and rely on using standards meant for the textile markets and therefore may lack credibility. Further development and standardisation of clinically relevant laboratory tests and simulated wound fluid are, therefore, needed. For example, some dressings work by allowing the antimicrobial agent to leach out into the wound bed, while others work within the dressing. The various methods can help supply *in vitro* evidence for the different claims made. Other standards are used for testing the physical properties of dressings. In this way, it is very difficult to compare different dressings. Logarithmic reduction of organisms in a given time period and “time to kill” is an *in vitro* method that is quoted and accepted by regulatory authorities, based on AATCC 100 Test Method (2019)^[40]; however, this uses planktonic organisms and not those seen in biofilms. Testing the reduction of bioburden or removal of biofilm would need to be carried out using a model to reflect the chronic wound bed. Research has been undertaken to develop such a model, using a pork explant model, which demonstrated that there was a 24-hour therapeutic window available before the biofilm reformed after disruption^[41].

Preventing antimicrobial resistance

Development of a classification scheme for advanced dressings, with and without antimicrobial agents, could potentially aid clinicians dealing with infected and non-infected wounds where there are barriers to wound healing. This approach may support the antimicrobial stewardship team in healthcare facilities and provide better guidance on effective management and appropriate use, rather than the unsubstantiated protocols often devised by wound care providers.

Antimicrobial stewardship of wound care products should be considered in clinical decision-making, aiming to prevent resistance from developing in the future. There is a need to give evidence-based advice on antimicrobial stewardship to incorporate into local guidelines, to ensure that resistance does not develop to these antiseptics, as we have seen with antibiotics. Antiseptic stewardship is considered under the umbrella of antimicrobial stewardship^[35], but currently most teams are focused solely on antibiotic usage.

Introducing non-medicated wound dressings

There are modern dressings that do not incorporate an antimicrobial agent in the dressing but use properties of the dressing material to reduce microorganisms, either through retention of the organism in the dressing away from the wound bed (thus removing organisms when the dressing is changed) or by killing microorganisms through biochemical interaction within the dressing. These dressings may have an important role to play in the prevention of infection following surgery or as part of debridement and cleansing to remove the planktonic bacteria and unbound cells^[42].

As a result of the emerging trend of bacterial resistance and the dangers to human health that undoubtedly are caused by this, there has been a tremendous effort to develop new antibiotics that can outcompete bacteria. However, it has also been stated that “*we need to consider our remaining options and develop new ones in a world where antibiotics can no longer be counted upon to cure infections. Non-antibiotic opportunities to treat serious bacterial infections exist as possible options*”^[43]. Thus, the use of wound dressings that can effectively eradicate bacteria in a physical way, while not inducing bacterial resistance, would prove to be a significant addition to the wound care clinician’s toolbox, as will be discussed in the next paper in this document.

CONCLUSION

Although we can confirm that bacterial aggregates/biofilms are present in chronic, non-healing wounds, their exact role is still not evident. They appear to disrupt the normal healing of wounds and, as such, need to be managed. There is a general consensus on the need for physical removal of slough and debris, in combination with antimicrobial treatment. However, the usage of antimicrobial agents and dressings should be evidence-based, rather than based on assumption. The field of wound care must now work towards optimising antibiotic and antimicrobial usage to avoid overuse and implement evidence-based antimicrobial stewardship in wound care.

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Non-medicated wound dressings: Defining their role

This article outlines the role that non-medicated wound dressings (NMWDs) play in the strategy of reducing wound bioburden, without the need for an active antimicrobial agent. The inappropriate use of a variety of active antimicrobial agents has resulted in the widespread development of bacterial resistance to an array of antibiotics, and a crisis in infection management across the globe. The treatment of wound infection is also a major challenge for clinicians working in this field, with many key opportunistic pathogens becoming resistant and difficult to eradicate, leading to an increase in patient suffering and higher mortality levels.

The case for the use of alternative non-active NMWDs to eradicate infection is presented in this paper as a viable alternative to “active antimicrobial agents” in the management of microbial bioburden, in both acute and chronic wounds. A definition of a NMWD to aid their differentiation from medicated wound dressings is presented, alongside their proposed mode of action and evidence that supports their effectiveness.

INTRODUCTION

Microbes and the microbiome

Microbes can be found in virtually all wounds, as diverse microbiomes comprising multiple species of bacteria and fungi^[1]. Contamination of the wound surface by microbes is the first step in presence of organisms in the wound^[2]. At this stage, the manifestation of these bacteria within the wound may be transient, but subsequently wound colonisation could occur. Wound colonisation is defined as the presence of attached and multiplying bacteria on the surface of a wound^[3]. If wound colonisation becomes too great, and virulence factors (molecules produced by microbes that increase effectiveness for infection) expressed by colonising microbes outcompetes host immune responses^[4], then the host's immune system is unable to control the microbial population, leading to the potential for local and/or systemic infection^[5,6]. Wound colonisation can affect the wound — e.g. by altering the pH — which in turn disrupts the healing process^[7,8] and the patient's overall health depending upon their status (e.g. immune status). For example, *Acinetobacter baumannii* infections are more common among immunocompromised individuals who have experienced hospital stays in excess of 90 days^[9]. In the most extreme of cases, wound colonisation can potentially lead to serious harm and even death if systemic infection occurs, especially in high-risk wounds such as burns^[10].

Commensal microorganisms living on the skin may help the body defend against infection by helping to prime immune cells^[11], although the same organisms that act as beneficial commensals can also act as opportunistic pathogens when the environment permits^[12,13]. Furthermore, the use of probiotics has been shown to be useful in preventing sepsis in experimentally induced burn wounds^[14]. Disruption of a microbiome by antibiotics may lead to impaired wound healing^[15]. There is increasing evidence that infections on external surfaces have to be treated fundamentally differently to internal infections^[15], hence the validity of investigating NMWDs as an alternative for treating infection in wounds.

Skin commensal bacteria include common aerobes such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus* spp. and *Candida albicans* and, consequently, these are common targets for antimicrobials. Organisms that require specialist growth media or extended culture periods can be

Karen Ousey, Professor of Skin Integrity at the Institute of Skin Integrity and Infection Prevention, University of Huddersfield, UK

Mark Rippon, Visiting Clinical Research Fellow, Huddersfield University; Medical Marketing Consultant, Daneriver Consultancy Ltd, Holmes Chapel, UK

Alan Rogers, Independent Wound Care Consultant, Flintshire, UK

Samantha Westgate, CEO, Perfectus Biomed Limited, UK

less easy to culture, and these include Gram positive anaerobic cocci such as *Anaerococcus*, *Finegoldia*, *Parvimonas*, *Peptoniphilus* and *Peptostreptococcus*^[16].

Wound infection

Most acute and chronic wound infections involve polymicrobial populations of aerobic and anaerobic bacteria^[17]. The detrimental effects of wound infection and the presence of biofilms can be particularly problematic in non-healing wounds — e.g. pressure ulcers, venous leg ulcers and diabetic foot ulceration. Extended wound healing and the resulting elevated levels of bacteria, combined with their virulence and/or synergistic effects, can all negatively affect the wound healing process^[18].

Active antimicrobial wound dressings

There have been a range of approaches used to assist in the reduction of the wounds microbial bioburden. Primarily, however, the use of active antimicrobials — e.g. antiseptics and antibiotics (that actively kill or inhibit bacteria) — have been the first-line treatment of wound infection for many years^[19,20]. These antimicrobial agents may be defined as:

- “a substance* that acts directly on a microbe in a way that will either kill the organism or significantly hinder development of new colonies^[21]”
- “any substance with the ability to inhibit a microorganism...[including] both antibiotics and antiseptics, irrespective of being in the form of a dressing, solution, gel or drug^[22]”

So-called medicated antimicrobial dressings contain an antimicrobial agent such as silver or iodine as a component of the dressing^[23]. These antimicrobial agents can be bactericidal (kills bacteria) or bacteriostatic (prevents bacterial growth) depending upon their concentration; at higher concentrations, bacteriostatic agents are often bactericidal against susceptible organisms^[24].

These active antibacterial agents can kill bacteria via different direct antibiotic-bacteria interactions — i.e. inhibition of cell wall synthesis or function, inhibition of nucleic acid synthesis or function and inhibition of protein synthesis (via 30S/50S subunit)^[25]. However, bacteriolytic antibiotics that result in the lysis of bacterial cells cause the release of cellular components such as endotoxins that can also be harmful to host cells^[26]. Specifically, these endotoxins can detrimentally affect cells involved in the wound healing process — e.g. inflammatory cells, fibroblasts (the major cells responsible for the production of collagen, glycosaminoglycans and proteoglycans, which are major components of the extracellular matrix) and keratinocytes (epidermal cells that produce keratin^[27-29]). Endotoxins released locally into experimental wounds stimulate the production of pro-inflammatory mediators such as tissue necrosis factor-alpha and elevate levels of damaging protein-degrading enzymes such as matrix metalloproteinases^[30]. Endotoxins have also been shown to reduce deposition and cross-linking of collagen in wounds resulting in reductions in wound strength^[31].

NMWDs

As a consequence of the development of resistance in microorganisms, new and alternative methods of managing wound infections are required. Recent advances in wound dressing development, design and chemistry have led to the appearance of wound dressings that do not contain active ingredients, but are able to eliminate wound bioburden (the number of microorganisms in a wound) without the use of an active component (e.g. silver), but act in a physical manner upon the bacteria. It is suggested that NMWDs should meet the criteria listed in Box 1.

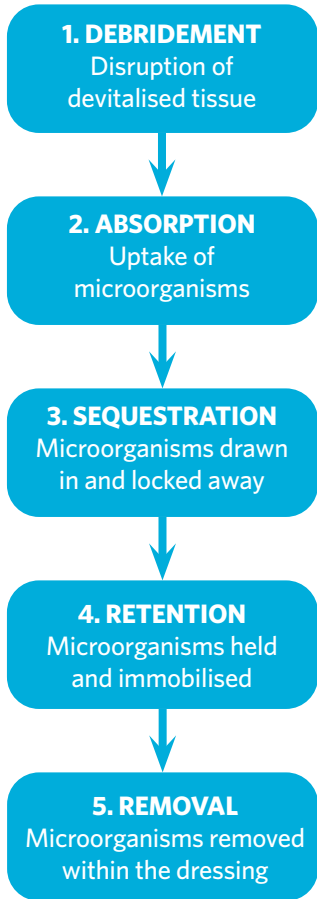
In order to differentiate them from antimicrobial wound dressings that contain active agents, these dressings have been described as NMWDs, including, for example, hydrogels, hydrocolloids, super-absorbents and carboxymethylcellulose (CMC) dressings. Although NMWDs are not new, there has been no clear definition to allow clinicians to make an informed decision when choosing an appropriate NMWD product for managing wound infection.

*incorporating disinfectants, antiseptics and antibiotics

Box 1. Suggested criteria for the ideal NMWD for infected wounds or wounds at risk of infection

- Effective against a broad range of pathogenic bacterial species, including (most importantly) those demonstrating resistance or the propensity for developing resistance
- Reduces microbial load without selecting for, or perpetuating, the spread of antibiotic-resistant organisms
- Does not induce bacterial resistance
- Does not damage the bacteria in such a way that their components can cause further damage (e.g. endotoxins causing sensitisation)
- Does not damage localised tissue or induce a systemic response in the patient
- Easy to use and apply to the wound
- Have a minimal environmental impact (e.g. disposal should not detrimentally impact the environment)
- Cost-effective.

Figure 1: Mechanism of action of NMWDs for infection prevention and management



Definition

NMWDs, as suggested from the name, do not contain any active antimicrobial agent. For a NMWD to diminish the impact of bacteria (e.g. infection) they must reduce wound bioburden via a mechanism(s) other than active killing — for example, by physical means only.

For the purpose of this paper, the authors suggest a NMWD be defined as “a wound dressing that does not contain any active/pharmaceutical component, but reduces bacterial load via alternative methods” including:

1. Removing the devitalised tissue within which bacteria may reside and which are outside the normal host immune response surveillance system^[32,33]
2. Maintaining a low bioburden level by the absorption, sequestration (taking temporary possession), retention and removal of bacteria at the wound site.

As these modes of action for reducing wound bioburden rely on physical methods and chemical interactions, the use of NMWDs on all types of wounds prior to overt clinical signs of infection is recommended^[34]. A number of clinical studies have shown that NMWDs have a positive impact on the wound by reducing infection, either without or as an adjunct to antimicrobial agent use^[35].

NMWDs: mechanism of action

NMWDs, as described above, are able to effectively reduce wound bioburden, without selecting for antimicrobial-resistant organisms. Figure 1 highlights that optimal antimicrobial mode of action involves multiple steps taking place in a coordinated manner, while each part individually is still able to reduce bacterial numbers.

1. DEBRIDEMENT

The process of debridement is an early step in wound management and, ultimately, wound bed preparation. It involves the removal of sloughy/necrotic tissue or foreign material that accumulates on the surface of chronic wounds and is generally colonised by bacteria^[36]. This tissue, because it is isolated from the host’s blood supply, allows the population of bacteria within to be protected from immune surveillance and inflammatory cell attack of the host^[37,38]. In addition, chronic slough provides an environment in which resident bacteria can easily proliferate and develop into a biofilm^[39]. Thus, the body is unable to manage this microbial bioburden and there is the opportunity for unhindered bacterial growth. As well as the potential for this devitalised tissue-resident population of bacteria being the source of microorganisms responsible for a subsequent wound infection, the release of bacterial toxins may result in an intensification of wound inflammatory reactions, which may delay healing^[40]. A basic principle indicates that removal of necrosis and slough from the wound is necessary for the preparation of the wound bed and for subsequent healing progression to occur^[41-44].

There are several debridement methods available to clinicians, which include, mechanical, autolytic, enzymatic and surgical^[45]. Each method has its own advantages and disadvantages, which help to determine the most appropriate method for any given clinical situation^[42,46,47]. Whichever mechanism is used, debridement results in the disruption of devitalised tissue containing a large proportion of the wound’s bacterial load, and this disruption aids in subsequent removal of the bioburden, as evidenced in recent experimental studies^[48,49].

A number of NMWDs support debridement (Table 1). For example, hydrocolloids, hydrogels and hydro-responsive wound dressings (HRWDs) debride via autolysis, promoting a moist wound environment, breaking devitalised tissue by the body’s own enzymes that are produced by tissue cells. This moist environment provides optimal conditions for the body’s natural enzymes to encourage wound debridement. In the case of HRWDs — dressings based upon a chemically inert superabsorbent polyacrylate material, which is ‘triggered’ (i.e. the hydro-responsive nature of the dressing is optimised) by Ringer’s solution — wound debridement is promoted by the softening and detachment of the devitalised tissue

by the availability of the Ringer's solution. As previously stated, hydrocolloids and hydrogels promote debridement by softening slough and necrosis. However, these dressings are not in themselves non-medicated antimicrobial dressings, in that they are unlikely to reduce wound bioburden without additional intervention.

Table 1. Examples of NMWDs that support debridement

Gauze (wet-to-dry)	Kammerlander et al, 2008 ^[74] ; Armstrong and Price, 2004 ^[87]
Films	Lisle, 2002 ^[88] ; Powers et al, 2013 ^[89]
Hydrogels	Williams, 1994 ^[90] ; Vernon, 2000 ^[91] ; Scanlon, 2002 ^[92] ; Burki et al, 2009 ^[93] ; Ivins, 2014 ^[94] ; Hedger, 2013 ^[95] ; Gethin et al, 2015 ^[96]
Hydrocolloids	Gethin et al, 2015 ^[96] ; Lydon et al, 1988 ^[97] ; Romanelli, 1997 ^[98] ; Burgos et al, 2000 ^[99] ; Szewczyk & Jawień, 2005 ^[100]
HRWDs	Ousey et al, 2016 ^[83] ; Paustian, 2003 ^[85] ; Cooper, 1998 ^[101] ; Scholz et al, 1999 ^[102] ; Mähr, 2003 ^[103] ; Mwipatayi et al, 2005 ^[104] ; Kaspar et al, 2008 ^[105] ; Mancini et al, 2018 ^[106]

2. ABSORPTION OF WOUND EXUDATE AND BACTERIA

The production of wound exudate is a natural part of the healing process and, under normal circumstances (e.g. acute wound healing), it is beneficial, providing growth factors and other nutrients important for the growth phase. However, in chronic wounds (and some compromised acute wounds), excessive production of wound exudate provides a significant clinical challenge with respect to its removal and management. Wound exudate contains a variety of planktonic (free-floating) bacteria (including bacteria released from disrupted biofilm) and, because of the free-floating nature of these bacteria, they are carried with wound exudate into wound dressings with significant absorptive capacity^[48]. The levels of bacteria removed from the wound site and taken into the dressing are dependent on the volume of exudate absorbed^[48]. As a result, wound bacteria — and occasionally, the damaging bacterial proteinases (e.g. many pathogenic bacteria secrete a range of proteases of the serine, cysteine, and metallo type^[50]) — are removed from the wound environment^[48,51]. In some cases where absorptive capacity is low, or exudate retention is poor, bacterial uptake is transient and there may be release of bacteria back to the wound surface, unless they are bound within the matrix of the dressing^[34].

Wound dressings should be selected to fit the needs of the wound. Factors such as the amount of exudate produced per 24-hour period, consistency of the exudate, the size of the wound and dressing wear time need to also be considered when selecting the most appropriate dressing. For absorption of exudate and bacteria, several wound dressings have been developed with the specific aim of managing high levels of wound exudate production (Table 2). Some of these dressings absorb better than others — for example, polyurethane foams have a higher absorptive capacity than hydrofibers, alginates and hydrocolloids when examined in laboratory tests^[52]. However, with foams, fluid retention can be poor, leading to leakage of exudate through (strikerthrough) or from around the dressing edges — this occurs when the absorptive capacity of the dressings has been overcome.

Table 2. Examples of NMWDs exhibiting absorption of bacteria, MMPs and endotoxins into the matrix of the wound dressing

Foams	Krejner and Grzela, 2015 ^[107]
CMC dressings	Newman et al, 2006 ^[58] ; Walker et al, 2003 ^[63]
Superabsorbent polymer (SAP)-containing dressings	Eming et al, 2008 ^[86] ; Wiegand et al, 2011 ^[108] ; Wiegand and Hipler, 2013 ^[109,110] ; Wiegand and White, 2013 ^[111]
Dialkylcarbamoylchloride (DACC)-coated dressings	Bowler and Davies, 1999 ^[64] ; Ljungh et al, 2006 ^[73] ; Ronner et al, 2014 ^[81] ; Wadström et al, 1985 ^[112] ; Butcher, 2011 ^[113] ; Brackman et al, 2013 ^[114] ; Geroult et al, 2014 ^[115]
HRWDs	Rippon et al, 2018 ^[34,48] ; Bruggisser, 2005 ^[60] ; Ousey et al, 2016 ^[83]

Poor exudate management can cause maceration of the peri-wound skin and wound tissue^[53] and has a negative impact on the patient’s wellbeing — e.g. soiling of clothes, delays in healing^[54,55]. SAP-containing dressings demonstrate excellent exudate-absorbing capacity with a high fluid retention and are used to manage wounds with moderate-to-high levels of wound exudate production, without the risk of exudate leakage and maceration^[56,57].

3. SEQUESTRATION

The term sequestration comes from the Latin word *sequestrare*, which essentially means taking something and locking it away. The term has been used to describe the mechanism whereby exudate, debris and bacteria are drawn into the core of the dressing and held within a wound dressing matrix^[58,59]. As bacteria uptake progresses, the sequestration of these components within the wound dressing results in their reduction in the wound environment, so limiting their damaging effects^[34].

An early indication of the sequestration of bacteria by wound dressings was with CMC dressings^[58] and HRWDs^[60]. This property has been demonstrated in a variety of experimental studies^[58,60,61]. Retention of bacteria by wound dressings was highlighted by Tachi et al (2004), examining the retention of bacteria by alginate and CMC dressings^[62]. *S. aureus* or *P. aeruginosa* were inoculated to rat skin ulcer model wounds and either alginate or CMC dressings were applied. After 12 hours, total viable bacterial counts within the dressings and bacterial counts of microbes released from the dressings were calculated^[62]. The results demonstrated that the CMC dressing was more effective at retaining both types of bacteria. Previously, Walker et al (2003) showed that, following hydration of the CMC dressing, the bacteria appeared to be physically trapped within the structure of the dressing as a result of the formation of a cohesive gel^[63]. Several other dressing types have been suggested to show sequestration of bacteria (Table 3).

Table 3. Examples of NMWDs with evidence of sequestration of bacteria	
DACC-coated dressings	Bowler and Davies, 1999 ^[64] ; Ljungh et al, 2006 ^[73] ; Ronner et al, 2014 ^[81] ; Wadström et al, 1985 ^[112] ; Butcher, 2011 ^[113] ; Brackman et al, 2013 ^[114] ; Geroult et al, 2014 ^[115]
HRWDs	Rippon et al, 2018 ^[34,48] ; Bruggisser, 2005 ^[60] ; Ousey et al, 2016 ^[83,84]
Hydroconductive	Edwards-Jones et al, 2014 ^[66]
CMC dressings	Newman et al, 2006 ^[58] ; Tachi et al, 2004 ^[62] ; Walker et al, 2003 ^[63] ; Bowler and Davies, 1999 ^[64] ; Waring and Parsons, 2001 ^[116]
SAP-containing dressings	Butcher, 2015 ^[67]
Others	Desroche et al, 2016 ^[61] ; Westgate and Cutting, 2012 ^[117]

4. IMMOBILISATION AND RETENTION

The immobilisation (stopping the microbes from moving) and retention (prevention of movement back out of dressing) of bacteria within the core of a dressing is an important step in reducing wound bioburden (Table 4). The sequestration of microbes provides the opportunity for bacteria to then be immobilised and retained within the dressing, reducing the likelihood for wound infection by preventing a return of bacteria back into the wound. This ability to sequester and retain bacteria within the dressing varies across the different wound dressing types and this variable response is dependent upon the nature of the constituent fibres and their three-dimensional structure^[34,48,58,62,64-68].

Table 4. Examples of NMWDs exhibiting immobilisation and retention of bacteria	
DACC-coated dressings	Ronner et al, 2014 ^[81]
HRWDs	Rippon et al, 2018 ^[34,48]

The ability of materials within dressings to aid in the absorption and sequestration of bacteria indicates that these dressings physically remove bacteria from the wound (Table 5), thus reducing bacterial load without resorting to any bacterial killing^[65]. Bacteria that are physically retained by adherence to the dressing material and within the confines of a wound dressing are easily removed when the dressing is changed. Repeated application and removal of these dressings is accompanied by a regular reduction in the level of bacteria found within the wound bed^[34,48].

Table 5. Examples of NMWDs exhibiting removal of bacteria with dressing

DACC-coated dressings	Ljungh et al, 2006 ^[73]
HRWDs	Rippon et al, 2018 ^[34,48]

Organisms held in the core of the dressing are retained separately from the dressing's wound contact layer. Clinicians are able to handle the used dressing with increased safety as organisms are held within the matrix of the dressing. There is also a reduced potential for spread of pathogenic organisms (including antimicrobial-resistant organisms) from the dressing.

Examples of NMWDs that exemplify one or more of the above mechanisms of action

Carboxymethylcellulose (CMC): Early studies have exemplified how CMC in some wound dressings can sequester and enable retention of bacteria^[58]. Newman et al (2006) investigated the effect of two dressings (CMC versus alginate) on bacterial immobilisation^[58]. It was shown using a scanning electron microscopic technique that bacterial immobilisation in a CMC was more apparent than in the alginate. Specifically, the CMC wound dressing immobilised exudate containing bacterial populations within its cohesive gel structure. Subsequent analysis identified that bacteria appeared to be predominately immobilised within a gel-like matrix formed by the CMC wound dressing^[63]. Immobilised bacteria were not visible near to the surface of the continuous gel formed by the CMC wound dressing and the bacteria appeared to be absorbed deep into the cohesive gel structure, with no bacteria visible on non-hydrated fibres near to the gelled area. The authors concluded that the ability of the CMC wound dressing to form a cohesive gel structure, thereby immobilising potentially pathogenic bacteria, could complement existing practices in wound management^[63]. Using confocal laser scanning microscopy, Newman et al (2006) supported previous findings in that when a Hydrofiber® dressing (Aquacel) was hydrated, its fibres swelled quickly, reducing interstitial spaces, resulting in the formation of a cohesive gel that immobilised the bacteria. Furthermore, bacteria stained as live for up to 20 hours, did not show any increase in numbers^[58]. More recent studies have suggested that CMC may have some intrinsic anti-biofilm properties^[69,70] that may be related to pH modifications^[71].

Dialkylcarbamoylechloride (DACC): DACC is a fatty acid that has been used as a coating for dressing fibres and which facilitates microbial binding (including fungi) via a hydrophobic interaction. It is reported that microbes become irreversibly bound to the dressing surface through hydrophobic interactions via DACC and are then removed from the wound at dressing change^[72]. The importance of cell surface hydrophobicity (CSH, a measure of water-repelling properties) on the binding of microbes to DACC-coated dressings were investigated in laboratory studies^[73], and a number of studies have highlighted the potential benefit of DACC-coated dressings to lower surface bioburden of wounds^[72,74-76]. The wound contact layer is coated with dialkylcarbamoylechloride (DACC) that mediates the irreversible binding of bacteria^[73]. Bacteria can switch between hydrophobic ('water hating') and hydrophilic ('water loving') phenotypes in response to changes in their environmental conditions — e.g. temperature, available nutrients^[77]. Therefore, microbes' ability to bind to DACC may be variable depending on the wound conditions. However, clinical studies in surgical site infections (SSIs) have shown that most bacteria responsible for SSIs have high CSH^[78,79] and the effect of DACC-coated dressings on bacterial cell numbers may reduce SSI rates^[80]. Once bacteria are bound or 'trapped' in the dressing, the microbes appear to be inactivated, as bacteria bound to the dressings do not multiply^[73], and can then be removed at each dressing change, resulting in a reduction in the bacterial load of a wound. DACC-coated dressings do not release any chemically or pharmacologically active substances and

rely on a physical mode of action, using the hydrophobic coating (DACC) to reduce bacterial load^[73]. DACC-coated dressings have been shown *in vitro* to bind to organisms that are antibiotic resistant^[72,81]. A systematic review summarises the role of DACC-coated dressings in the management and prevention of wound infection^[82].

Hydro-responsive wound dressings (HRWDs): HRWDs comprise of a range of wound dressings that can deliver or absorb moisture depending on the environmental fluid balance, and which optimise the moist wound environment and promote autolytic debridement^[83]. Microbial sequestration is achieved via the absorbent core of HRWDs, which are composed of superabsorbent polyacrylate that can manage large amounts of fluid as a result of the chemical properties of the polyacrylate^[84]. HRWDs contain Ringer's solution, which has partially hydrated the polyacrylate material. The dressing core's combination of polyacrylate and Ringer's solution results in the binding of proteins (and bacteria) contained in the wound exudate to the SAP^[85,86]. Laboratory studies have demonstrated the presence of large numbers of bacteria within the matrix of a HRWD^[34,48] (HydroClean®). Clinically, these dressings have been shown to be very effective in reducing signs and symptoms of infection^[35]. Electron micrographic images have shown sequestration and immobilisation of microorganisms to HRWDs^[60].

Hydro-conductive wound dressings: Hydro-conductive wound dressings rely on the physical process of how fluids move through porous structures contained within the materials that compose the dressing. The promotion of bulk fluid flow within the dressing, which is as a result of the use of LevaFiber Technology, draws debrided devitalised tissue and bacteria into the dressing. A study undertaken evaluating a hydroconductive dressing for the absorption, sequestration and retention of bacteria showed the dressing was able to absorb a significant level of fluid with a corresponding 90% reduction in bacterial numbers over a 24-hour period. Scanning electron microscopy demonstrated bacterial sequestration within the fibres of the dressing^[66].

CONCLUSION

The presence of bacteria in wounds can have a detrimental effect on the healing response, delaying the healing of (acute) wounds that would otherwise heal in a timely manner, or exacerbating the problems of difficult-to-heal chronic wounds. Currently, the use of active antimicrobial agents in wound dressings is a mainstay of local wound management for the treatment of wound infection. The over-reliance of antimicrobials and the inappropriate use of specific antimicrobial classes such as antibiotics has led to a worrying increase in antibiotic resistance of bacteria. Effective alternative methods of managing wound infections are required in order to counter deficiencies in antimicrobial treatment due to antibiotic resistance and to limit the spread of resistance.

NMWDs — dressings that do not contain any active/pharmaceutical component and reduce bacterial load via alternative mechanisms — offer an ideal option in the drive to promote antibiotic stewardship by providing effective treatment for the reduction of wound bioburden in a physical manner, without contributing to the crisis of antibiotic/antimicrobial resistance.

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Non-medicated wound dressings in infected wounds or wounds at risk of infection: How to use in practice

Sabine Eming, Professor of Dermatology and Head of the Interdisciplinary Wound Healing Centre, University Hospital of Cologne, Germany

Isabelle Fromantin, Wounds and Healing Expert, Institut Curie, France

Astrid Probst, Advanced Nurse Practitioner, Wound Management, Kreiskliniken Reutlingen GmbH, Reutlingen, Germany

Hans Smola, Professor of Dermatology, University of Cologne, Germany; Medical Director, PAUL HARTMANN AG, Germany

Hui-Mei Yang, Nurse Practitioner, Department of Endocrinology and Metabolism, Chang Gung Memorial Hospital Linkou Branch, Taoyuan, Taiwan, R.O.C

Jiun-Ting Yeh, Plastic Surgeon, Division of Trauma, Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital Linkou Branch, Taoyuan, Taiwan, R.O.C

Cellulitis, erysipelas, abscess, surgical site infections (SSIs), and chronic wounds with signs of infection represent a continuum of soft tissue infections. As previously discussed, age, poor glycaemic control in people with diabetes and obesity predispose the individual to localised and spreading infections^[1-3].

SSIs, which are acute wound infections, can appear at any time, with reporting at 30 days, and 90 days in the instance of prosthetic material implantation, after surgery. In 1992, the United States Centers for Disease Control and Prevention (CDC) defined clinical criteria for diagnosis of SSI^[4,5]. Positive bacterial culture results are one criterion; however, negative culture results still do not exclude an SSI diagnosis. Clinical signs of infection are key diagnostic parameters^[5]. Localised erythema, swelling, heat, purulent drainage, pain or tenderness are clinical signs for superficial incisional SSIs. If deeper layers are involved, dehiscence of the wound and fever (>38°C) are additional signs^[5].

At the opposite end of the wound spectrum, in chronic wounds, clinical signs of inflammation become less reliable in diagnosing infection. This is highlighted in several consensus documents that expertly collate the available evidence and clinical expert knowledge^[6-8]. A study by Gardner et al (2001)^[8] illustrates the difficulties with diagnosing an infection in chronic wounds. The authors investigated 36 chronic wounds, with infection defined as 10⁵ CFU/per gram of viable wound tissue or wounds containing *β-hemolytic Streptococcus* in tissue biopsies, and concluded that, with a specificity of 100%, increasing pain and wound breakdown were good indicators^[8]. However, this still leaves a large grey zone where other indicators of chronic wound inflammation are suggestive of infection, but not conclusive.

INFLAMMATION AND THE LOCAL WOUND ENVIRONMENT

The role of inflammation in the presence of bacterial infection is discussed in the first paper of this document. Of practical interest for the clinician are mechanisms for resolving inflammation, which permit the wound to progress to healing. From animal wound healing models, the concept of different polarisation of macrophages has been proposed^[9,10]. Early-phase macrophages predominate during inflammation, responding to pathogen-derived signals (pathogen-associated molecular patterns) or signals from necrotic tissue (damage-associated molecular patterns)^[10], and these fight pathogens and remove necrotic tissue. The resolution of inflammation and progression to granulation tissue formation depends on macrophages with late-phase polarisation. In humans, macrophage stages seem to be more nuanced and less clearly classed into either early-phase or late-phase macrophages. Still, our current knowledge supports the concept that pathogen- and necrotic tissue-derived factors prevent the emergence of late-phase macrophage-like cells and thus healing.

INFECTION AND NON-PRODUCTIVE INFLAMMATION IN WOUNDS

In all wounds, different levels of inflammation are observed at each phase of healing and, without microbiological investigation, this can make it difficult to differentiate inflammation from infection.

The inflammatory response needs to be recognised as a significant contributing factor to tissue damage in infection. This is by the synthesis of excessive protease levels such as matrix metalloproteases, elastase, plasmin (which degrade newly formed granulation tissue) and, most importantly, growth factors^[11-17], as well as reactive oxygen and nitrogen radicals that can prolong inflammation further. Bacteria in the wound bed can fuel non-productive inflammation.

This type of inflammatory response is best illustrated in wounds based on autoimmune disease. In these wounds, tissue damage is, to a large extent, the result of overshooting immune cell activation. Clinically, these wounds share many characteristics of local infection. This has important implications for management, as pathogenic bacteria are not the cause of non-healing, and therefore treatment needs to consider immunosuppression as a means to manage excessive inflammation^[18,19].

Over-prescription of antibiotics and antimicrobials

In the non-specialised wound care setting, the rate of systemic antibiotic prescription is suggested to be high^[20,21]. When patient treatment follows specialist recommendations or when patients are transferred to specialist wound care centres, antibiotic usage is likely to be reduced and reserved for only those patients who meet certain criteria^[20].

These data suggest that clinicians, in the non-specialist setting, may have a lower threshold in diagnosing infection, and therefore prescribe antibiotics unnecessarily^[20,21]. Less is known about the use of antimicrobial wound dressings, although in recent years silver dressings have become the subject of debate. Sibbald et al have investigated a high-release silver dressing on a variety of chronic wounds^[22,23] and noted a marked improvement in wound healing, although quantitative wound biopsies showed no decrease in bacteria numbers^[22]. Moreover, as with other antimicrobial-releasing dressings, the discussion is still open as to whether local cytotoxic effects are present and whether this has a negative influence on healing^[24].

On a global level, it is interesting to note that, in those geographies where silver dressings are reimbursed on a limited scale only, clinicians appear to achieve similar success rates^[25]. They may substitute silver dressings with another topical antiseptic preparation such as PVP-iodine or systemic, sometimes topical, antibiotics. Nevertheless, it can be suggested that antimicrobial dressings are overused in patients where inflammatory signs are present in and around the wound. From prescription data, Hussey et al (2019) have shown a huge increase in silver dressing prescriptions since 1997^[26]. Although, when a Scottish Intercollegiate Guidelines Network (SIGN) guideline was published, the number of prescriptions subsequently decreased^[27].

The use of non-medicated dressings for managing severe inflammation, infection and biofilm

Wounds with covert or overt signs of infection are diagnosed as infected according to the clinician's experience and setting. In addition, it is important to identify whether there is biofilm in the wound (Box 1). Scoring systems^[1,4,7,8,28] have become an instrumental and helpful guide for clinicians to reach an accurate diagnosis. If an infection has been diagnosed or biofilm is suspected, an effective wound infection/biofilm management protocol should be implemented to manage the infection, reduce microbial load, and to determine if systemic antibiotic treatment is necessary^[6,29,30].

Non-medicated wound dressings (NMWDs) may be considered in some circumstances, as an alternative to antimicrobial dressings, to handle high exudate levels and a corrosive wound exudate composition. Moreover, autolytic (endogenous) debridement can facilitate the removal of damaged tissue and support the effects of surgical debridement. Finally, an optimal dressing should provide relief for the wound from excessive levels of proteases in the wound exudate, which may destroy growth factors and newly formed granulation tissue constituents. This approach would support the principles of antimicrobial stewardship programmes and avoid the misuse and overuse of medicated treatment. Figure 1^[6,31] outlines factors to consider when using NMWDs for the management of excessive inflammation/wound infection/biofilm.

Case studies using NMWDs as an alternative to antimicrobial dressings

Examples of NMWDs for infected or at-risk-of-infection wounds have previously been outlined in this document. One class of NMWDs, polyacrylate superabsorber-containing dressings, known as SAP-containing dressings, are composed of cellulose and dry polyacrylate superabsorber polymers in their core. They present as dry dressings, can absorb large amounts of wound exudate^[32], bind bacteria^[33,34], inactivate excessive protease levels^[35] including proteases from *Pseudomonas aeruginosa*^[36], quench reactive oxygen species^[37] and perform under compression. They are suitable for wounds with copious amounts of wound exudate production.

Box 1. Clinical signs and symptoms indicative of potential biofilm*^[6]

- Failure of the wound to respond to appropriate antibiotic treatment
- Recalcitrance to appropriate antimicrobial treatment
- Recurrence of delayed healing on cessation of antibiotic treatment
- Delayed healing despite optimal wound management and health support
- Increased exudate/moisture.

*Note: biofilm is present in the majority of chronic wounds and should be suspected in all wounds failing to heal.

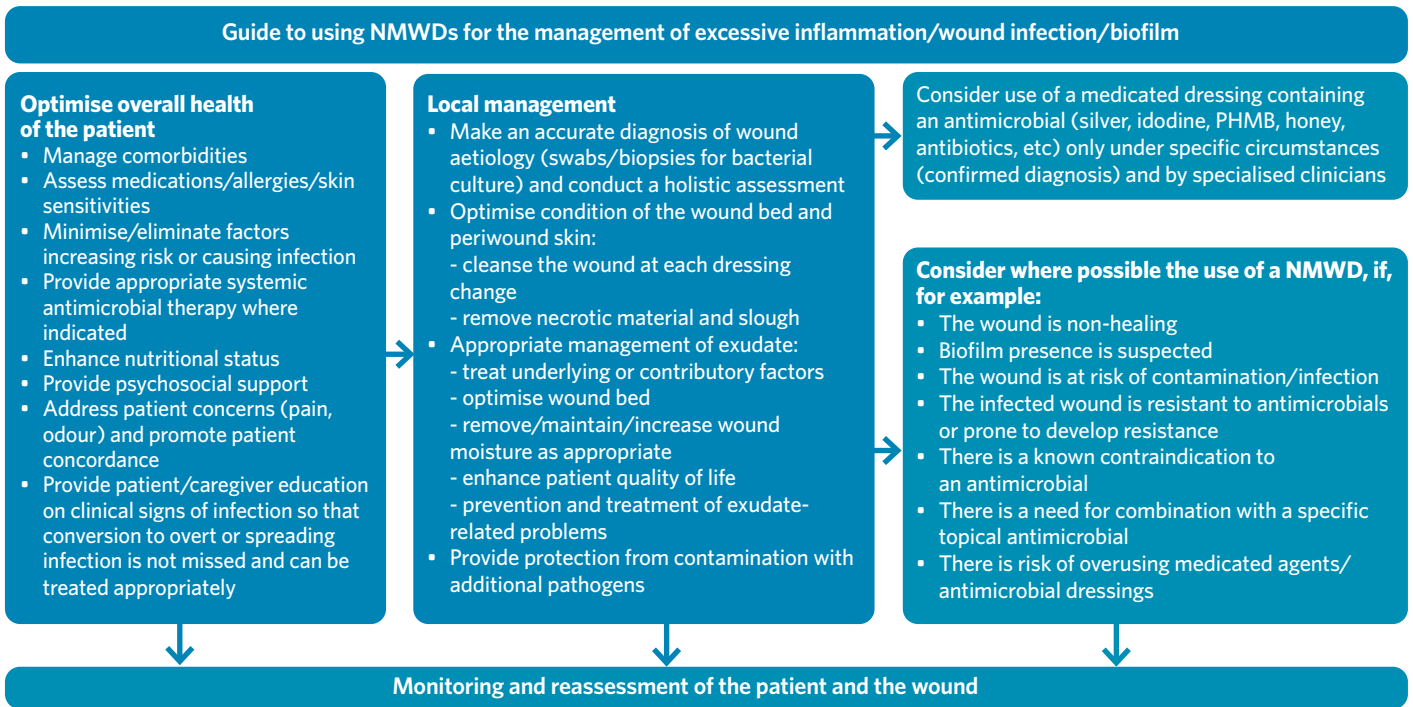


Figure 1: Factors to consider when using NMWD for the management of excessive inflammation/wound infection/biofilm^[6,31]

As outlined in the preceding paper, hydro-responsive wound dressings (HRWDs) contain Ringer’s solution-preactivated polyacrylate superabsorber polymers (HydroClean® family). The role of Ringer’s solution is to provide a bridge between the dressing and the wound bed that allows diffusion and exchange of soluble constituents. HRWDs have the functional properties of the polyacrylate superabsorber polymers mentioned above and can also be used under compression^[38].

Cases 1-3 provide practical examples where NMWDs have been used in different care settings. In the cases selected, HRWDs with Ringer’s solution-preactivated polyacrylate superabsorber (HydroClean®) have been used to kick-start healing.

Case study 1. Courtesy of Astrid Probst



Figure 2. Initial assessment

A 54-year-old male presented with a right-sided fracture on the proximal femur and a fatigue stress fracture of the left femur. He had an abscess on the left lower leg in December 2018 and was treated in another hospital.

Management strategy

At initial assessment (Figure 2), the patient presented with three wounds, measuring 4.5cm (length) x 1.5cm (width); 8.5cm (length) x 2.2cm (width) x 1cm (depth); and 3.5cm (length) x 1cm (width). Larval therapy was initiated, with the aim of cleaning the wound bed, followed by cold atmospheric plasma (CAP)^[39] and application of a hydroresponsive wound dressing (HydroClean® mini) and an absorbent dressing pad (Zetuvit®Plus Silicone) as a secondary dressing.



Figure 3. +4 days of treatment with Hydroclean® mini

Commentary progress

After using larval therapy, the wound was much cleaner. The combination of this and the HRWD seemed to prevent infection and restore moisture balance (Figure 3). After 9 days of treatment, the wound bed was much cleaner and appeared to be on the right trajectory for healing; therefore, the patient was discharged from hospital and treatment continued in the home setting.

Case study 2. Courtesy of Hui-Mei Yang and Jiun-Ting Yeh^[40]



Figure 4. Initial assessment

A 55-year-old male with a 10-year history of diabetes and previous episodes of peripheral neuropathy and insensate foot, presented with a diabetic foot ulcer (Figure 4). Post-radical debridement and skin grafting had been used to treat diabetic foot ulceration on the lateral foot 4 years previously. Ulceration had occurred following trauma from a sharp object, which had lacerated the sole of his foot. The small lesion was at the margin of the skin graft and the other lesion on the heel area. The wounds were noted to have had repeated infection and were deep to calcaneous bone.

Management strategy

The patient was admitted to hospital and the wound was treated with radical debridement and sequestrectomy on the calcaneous bone. He received IV antibiotics after debridement for 2 weeks. This led to a larger wound, treated initially with normal saline wet gauze; however, the wound showed no signs of progression and 2 days later a HRWD was selected (HydroClean®).



Figure 5. Day 41

A HRWD was selected for management of a very deep and highly exudating wound in a patient at high risk of infection. It was felt that this dressing would absorb, sequester and immobilise harmful bacteria and proteases, while promoting rapid formation of granulation tissue. After 12 days of treatment, the wound started to reduce in size and depth, and a smaller HRWD was used (HydroClean®mini).

Commentary progress

After 26 days, the wound decreased from 4 cm (length) x 2.3 cm (width) x 3 cm (depth) to 1.8 cm (length) x 0.5 cm (width) x 0.2 cm (depth) without any complications, and the patient was discharged from hospital. The wound showed good production of new granulation tissue, which continued to improve during the course of treatment (Figure 5). Treatment continued at home with a HRWD (Hydrotac®) as the wound continued to progress to healing.

Case study 3. Courtesy of Isabelle Fromantin



Figure 6. Initial assessment

A 49-year-old female patient presented with breast swelling, following a partial mastectomy for breast cancer. The breast was tense and painful, with nipple necrosis evident and a temperature of 38.3°C, without shiver, recorded. Slight inflammation was also visible near the nipple (Figure 6).

Management strategy

At initial assessment, the surgeon drained 160ml of brown lymph and consulted the Wound Care Unit about further course of action. Amoxicillin was prescribed for 8 days.

As infection was suspected, quick sharp debridement of moist necrosis on the nipple was performed. However, standard local protocol indicated to dry out the necrosis and wait 8-10 days to distinguish healthy tissue and necrotic tissue. Promoting granulation tissue in this area can prove challenging, as there is a lot of adipose tissue, with poor vascularisation. This is proven to be even more difficult when moist necrotic residue is present.



Figure 7. Day 7

There were three main goals during the course of treatment: to continue autolytic debridement after mechanical debridement, reduce the number of microorganisms at the wound site and promote healthy granulation tissue. A HRWD (HydroClean® advance) was selected and covered with a polyurethane film dressing; zinc oxide paste was also applied to the periwound skin for protection. Dressing changes were performed daily.

Commentary progress

After a few days, the wound bed was clean (Figure 7) and the decision was made to continue with current treatment, until epithelialisation had been achieved. A non-adhering dressing was then used as the wound continued to progress to healing.

CONCLUSION

If a wound has excessive non-productive inflammation, is infected, or biofilm is suspected, then NMWDs may be considered as an alternative to antimicrobial dressings and, if necessary, in conjunction with other antimicrobial agents, to aid in the overall management of the infection and contribute to reducing the level of bacterial bioburden.

Inflammation is a marker of wounds that are infected or at risk of infection. Thus, imbalanced or non-productive inflammation requires the clinician to diagnose the underlying disease accurately, to initiate the correct systemic treatment, to consider surgical debridement to remove non-viable tissue and, if required, immunosuppression for autoimmune disease. Dressings under these conditions need to be able to absorb high levels of exudate and minimise local inflammation, in order to promote granulation tissue. A major advantage of using a NMWD is that these non-medicated dressings avoid cytotoxicity of antimicrobial substances, promoting safety in daily practice.

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