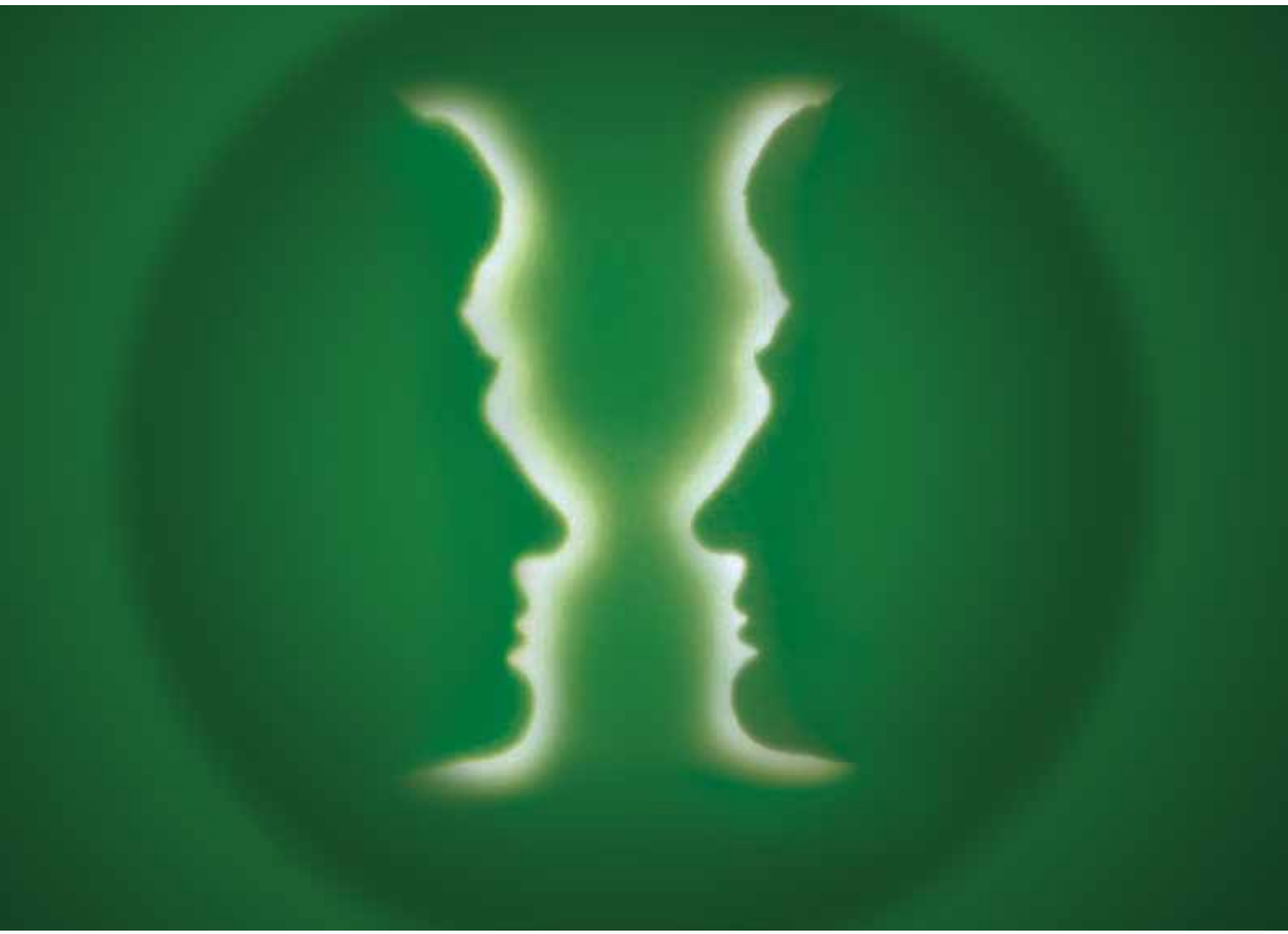
DACC antimicrobial technology:

a new paradigm in bioburden management



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Foreword

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That all open wounds are contaminated with microorganisms does not imply that infection is inevitable. However, wound infection is a major factor in delayed healing. Although there is controversy about the precise mechanisms by which microorganisms cause infection,[1] it is generally accepted that microbial expression of toxins and enzymes destroys tissue cells which delays healing. This, together with the arrival on the scene of polymorphonuclear leucocytes (PMNs), whose enzyme expression can also lyse healthy tissue cells, explains the delay in healing so often observed. The clinical objective in preventing or managing infection is to ensure the host's defences are able to outcompete microbial pathogens, leaving microbes unable to thrive and proliferate. With increasing anxiety about antibiotic resistance, interest has reverted to the therapeutic value of topical antiseptics. Not all wounds require such active measures. Contemporary indications are that 'passive' mechanisms may play a role in managing wound bioburden without resorting to 'traditional' active antimicrobials.

An array of *in vitro* and *in vivo* studies demonstrate that a range of modern wound dressings, including alginates, hydrocolloids and Hydrofibers, promote reduction in the wound surface bioburden without a chemically active agent. Alginates have been found to retain bacteria within the dressing matrix.[2,3] Hydrocolloids create an environment that is hostile to microbial growth[4-6] and their occlusive barrier properties provide an important infection control function.[7,8] Hydrofibers immobilise bacteria, thus purportedly helping to reduce wound bioburden.[9]

A relatively new concept, hydrophobic interaction, has been introduced to the array of wound dressings that interact with the surface bioburden. At its heart is the fatty acid DACC (dialkylcarbamoylchloride) that coats dressing fibres. This physical principle provides an interesting mechanism for bacterial binding. Microbes, including fungi, are irreversibly bound through hydrophobic interaction to the DACC coating on the dressing surface, allowing them to be disposed of at dressing change. There are no 'active' antimicrobial agents involved, avoiding the risk of bacterial resistance or sensitisations. Potentially damaging endotoxin release in the wound bed is also prevented as microorganisms are removed whole rather than destroyed.

Bacterial colonisation of a wound is normal. Where healing is progressing, adjuncts such as antimicrobials are generally not indicated as this could increase the risk of selection for resistance. A strategy to support healing lies in maintaining host immunological control of the wound environment. If the wound surface bioburden is 'managed' through 'passive' mechanisms such as bacterial binding, clinicians can utilise this novel option without resorting to 'traditional' antimicrobials. Both *in vitro* and *in vivo* evidence demonstrates the efficacy of the DACC coating and resulting hydrophobic interaction in reducing the wound bioburden and facilitating healing. Recent *in vitro* evidence indicates that DACC enhances binding of MRSA and *P. aeruginosa* biofilms. Although *in vitro* findings are not necessarily representative of the clinical situation, this indication of antibiofilm activity has to be welcomed. As always, more research is required before the full implications of hydrophobic interaction can be adequately assessed but at the moment the implications for this method of managing wound bioburden are encouraging.

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Introducing a new paradigm for bioburden management

The prevention and management of infection relies largely on the use of topical antimicrobial dressings. These treatments achieve their effects by killing bacteria, but this results in the presence of bacterial cell debris in the wound and the release of endotoxins, which may prolong inflammation. An alternative approach, where bacteria and fungi bind irreversibly to the wound dressing as a result of a hydrophobic interaction and are then removed at dressing change, avoids the risk of prolonged inflammation and the potential for resistance. A further benefit is that there is no risk of toxicity to healthy tissue or systemic absorption

wound infection • hydrophobic interaction • bacteria • binding • DACC

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Wound infection is one of the main areas of concern in the management of the wound environment. Infection complicates treatment and impedes the healing process by damaging tissue, reducing wound tensile strength and inducing an undesirable inflammatory response.[1-3] Increased wound bioburden increases the metabolic requirements of the tissues, stimulates a pro-inflammatory environment and encourages the in-migration of monocytes, macrophages and leucocytes, all of which can negatively affect healing. In addition, bacteria can secrete harmful cytokines, which can lead to direct vasoconstriction and decreased blood flow to the wound[4] and cause systemic toxicity.[5] At lower levels, critical colonisation and localised, sub-clinical infection are significant factors in delayed healing,[4] which in turn increases healthcare costs and results in poor patient outcomes. Thus, controlling or preventing infection and optimising the potential for healing by maintaining an ideal wound environment and managing associated health-related issues remain central to good wound care.[6,7] This will also yield significant overall cost savings.[8]

Clinicians take active measures to eliminate bacteria and so reduce the impact of infection. This has relied on the use of topical and/or systemic chemicals to destroy bacterial colonies. However, with greater understanding of the relationship between the wound environment and its colonising microbes, and in particular the role that endotoxins released by dead and damaged bacteria may play in prolonging the inflammatory response, it is becoming clear that these methods may have implications for healing outcomes. It may therefore be time to re-evaluate and refine this approach. This supplement describes how dialkylcarbamoylchloride (DACC) technology can be used to control bioburden through the irreversible binding and deactivation of bacteria and fungi in the wound, and without the need for potentially toxic and resistance-inducing chemicals.

Impact of prolonged inflammation on healing

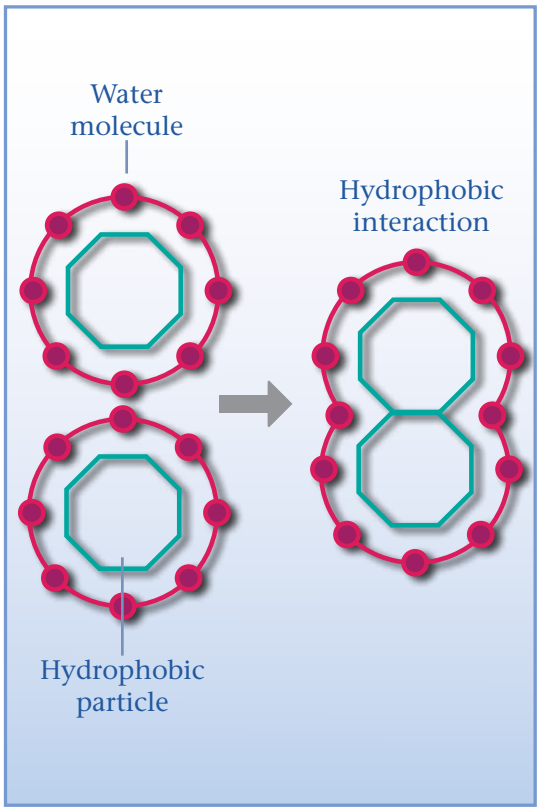
The physical removal of bacteria from the wound helps to remove the stimulus for continued dysfunctional neutrophil activity. Neutrophils and macrophages are essential to health; they target and destroy pathogenic microbes by phagocytosis and lyosomal enzyme breakdown and play a key role in growth factor production. However, neutrophils can have a negative effect on wound healing; high levels become highly destructive.[9-11] For example, an excess of MMP8 and neutrophil elastase in a wound is a direct consequence of dominant neutrophil activity from either chronic inflammation or over-zealous antibacterial responses, and leads to the degradation of growth factors and damage to extracellular matrix proteins.[12,13] The body has a number of control mechanisms to limit the opportunities for neutrophils to assemble, accumulate and become over-aggressive. All too often, circumstances conspire to override these safety mechanisms, allowing the neutrophil onslaught to continue unabated for too long.[9,14] Sustained neutrophil infiltration prevents wound healing

because of the continuing proteolytic and oxidative havoc it wreaks and a hypoxic state will continue[15] chemically signalling further neutrophil recruitment. Therefore, effective wound management should seek to avoid eliciting a prolonged inflammatory state.

The role of bacterial debris

The aim of all antimicrobial approaches to bioburden management is to reduce bacterial load. The traditional interpretation of 'antimicrobial' is to assume biocidal action — but what direct effect does the death of bacteria within the wound have on the healing cascade? Obviously, the destruction of pathogenic organisms reduces the bacterial load and therefore reduces exotoxin levels. However, the death and disruption of bacteria within the wound results in the release of endotoxins and the dumping of cell debris, leading to further inflammatory events locally and possibly systemically, even septic shock.[16] Therefore, treatment modalities that reduce wound bacterial numbers and proliferation rates without inducing bacterial death and the release of these toxins may be preferable to long-term wound health. Such bacterial sequestration, be that from mechanical retention or binding, is a feature of some dressing materials. However, the method by which this is attained and its clinical effectiveness requires further understanding.

Fig 1: The principle of hydrophobic interaction



Bacterial sequestration

Wysocki claims that the capacity of a dressing is to absorb and retain (i.e. sequester) bacteria is an important function, particularly in chronic wounds.[17] However, few dressings — mainly Hydrofiber and alginates — sequester bacteria into the dressing matrix, and then only as a mechanical by-product of their mechanism of action. Hydrofiber dressings absorb fluid directly into their fibres, which swell, entrapping moisture and bacteria.[18] Alginates exhibit varying degrees of absorbency and gelling properties when in contact with wound fluid, resulting in the formation of a weak gel.[18] While the clinical significance of this is yet to be demonstrated, it is likely to be of value in reducing bioburden in colonised wounds.[19] However, if the binding of bacteria could be more effectively facilitated as a primary dressing function, then it would offer clinicians an alternative method of managing bioburden.

Bacterial adherence and hydrophobicity

The principle of hydrophobic (lacking an affinity for water molecules) interaction is a key mechanism for bacterial attachment. In order for invading pathogens to initiate an infection, they need to adhere to underlying damaged tissues.[20,21] Doyle, in a review of literature, showed there is a relationship between hydrophobicity and infection.[22] Microbes can attach to exposed extracellular matrix (ECM) components of a wound by hydrophobic and charge interactions and with receptor-like cell surface proteins called hydrophobins.[23]

Hydrophobic interactions take place when cells expressing cell-surface hydrophobicity (CSH) come into contact with each other. When two hydrophobic molecules come into contact with each other in an aqueous environment they increase the entropy (the disorder of molecules, or the tendency for a reaction to proceed in a particular direction)[24] and expel water molecules[24,25] between them. In this way, they aggregate and are held together by the surrounding water molecules (Fig 1).

A large number of pathogens commonly found in wounds have been shown to express CSH, with

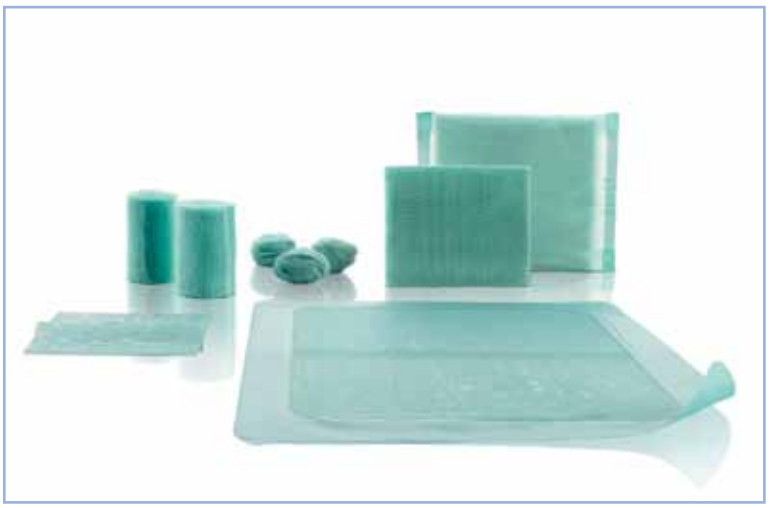


Fig 2: Cutimed Sorbact dressings

the majority expressing high or moderate CSH.[26] Binding to the ECM appears to provide the microbe with enhanced protection from host defence mechanisms. They then produce enzymes and toxins, which enable them to spread rapidly within tissue in order to obtain nutrients (thus initiating the signs of infection) or inactivate host defence mechanisms. The expression of CSH is, therefore, an important mechanism of microbial attachment.[22] Bacteria such as *Peptostreptococci* and other anaerobes express high CSH.[22,27–29] However, strains of the same species may vary in their CSH.[30] The expression of different toxins may thus influence the overall expression of CSH by an individual strain.

CSH expression is often a reaction to stress conditions such as starvation and environmental factors. These conditions may exist in many chronic wounds where there may be a paucity of nutrients and oxygen due to poor tissue perfusion or competition from other bacterial species.

In a study, Ljungh and Wadström grew microorganisms in a number of different simulated wound environments.[26] Cultures incubated in 5% CO_2 at 37°C resulted in expression of increased CSH compared with growth on blood agar media incubated in air. The growth phase also influences CSH expression; some bacteria form spores during starvation or other stress conditions.

The spores of *Bacillus subtilis* express higher CSH than dormant cells.[31] This is probably a general property of bacterial spores, which are much more resilient than planktonic bacterial forms to environmental challenges such as desiccation and chemical attack (including many antiseptics), making their control and eradication more problematic.

New paradigm

As wound bacteria express CSH, a dressing that is highly hydrophobic may therefore be preferential as it would physically bind bacteria to the dressing fibres, which could then be removed from the wound when the dressing is changed. This bacterial binding effect is already well established[32] and so is of particular interest in wound care. However, it is not commonly referred to as an antimicrobial treatment because the microorganisms are not killed by the hydrophobic interaction.

The use of a dressing material with a high CSH represents an important paradigm shift in antimicrobial thinking and management as it provides a means of reducing the microbial load without the need for chemically active agents. This therefore avoids both the risk of cytotoxic reactions, bacterial resistance[33] and systemic absorption.[34]

DACC

DACC is a hydrophobic (water repellent) fatty acid derivative that can be used to coat dressing materials, resulting in a dressing with highly hydrophobic properties. Rather than being physically trapped within the dressing matrix, the microorganisms are irreversibly bound to the dressing's surface using the principle of hydrophobic interaction. Once bound to the dressing, bacteria and fungi are rendered inert and so are prevented from proliferating or releasing harmful exotoxins and endotoxins. At each dressing change, microorganisms are therefore removed from the wound bed

Fig 3: Cutimed Sorbact gel

along with the dressing, thereby constantly reducing the bacterial load.

Cutimed Sorbact dressings

DACC is a main component of the bacterial binding wound dressing, Cutimed Sorbact (BSN medical Ltd, Hull). This is a primary wound interface dressing and is effective when in close contact with the wound bed in a moist environment. The product is most commonly seen as a green acetate swab (Fig 2) and a green coloured cotton ribbon. Swabs are available in a folded flat sheet format or a 3D ball suitable for packing wounds. For wounds with no or low levels of exudate, there is an amorphous hydrogel-coated swab (Cutimed Sorbact gel) (Fig 3) and for wounds with higher levels of exudate, Cutimed Sorbact dressing pads and Cutimed Sorbact Hydroactive with a hydropolymer gel sheet matrix are available — both with a coated acetate wound contact layer and highly absorbent cores. If required, Cutimed Sorbact swabs may be used in conjunction with secondary absorbent products and devices such as compression bandages. However, care should be taken to avoid contact with oily emollients as this can reduce the effectiveness of the hydrophobic action.

DACC, and specifically the Cutimed Sorbact product range as the pioneer of this technology, offers a real alternative to traditional approaches to bioburden management by utilising the natural binding characteristics of bacteria and avoiding many of the limitations and drawbacks associated with the alternative antimicrobial interventions.

Such binding means it is safe to use the dressing for longer than the 2-week period advocated for active topical antimicrobials in the Wounds UK Best Practice Statement.[35] It can also, therefore, safely be used as a prophylaxis.

Traditional approaches to bacterial control: antibiotics

The presence of spreading infection is potentially life- and/or limb-threatening and so requires aggressive treatment. Individuals demonstrating clinical signs of systemic infection should have blood cultures taken to identify the causative organism and assess for differential diagnosis; appropriate systemic antibiotic therapy should be implemented immediately.[6,36,37]

Antibiotics are administered orally, intravenously and, in some cases, topically. Most reduce bacterial numbers by targeting bacterial functions or growth processes.[38] Most have a narrow band of effectiveness, with particular antibiotics needed to treat particular bacteria species or strains; as such, they might be considered one of the first 'designer drugs'. However, there can be problems with their use:

- Systemic antibiotics treat the whole patient, not just the wound. Therefore, they can affect normal wound flora, leading to unpleasant side effects and systemic complications such as *Clostridium difficile* infections
- Systemic antibiotics require an adequate blood supply to reach the point of infection and so may be ineffective in treating wounds with a high necrotic burden or patients with underlying arterial insufficiency
- Antibiotic resistance has become a serious problem in wound care.[5] Easterbrook[39] and WUWHS[6] suggest that widespread and often indiscriminate use of antibiotics is a major factor in the emergence of drug-resistant bacteria
- Bacterial resistance has reduced the treatment options for many systemic infections. The development of new antibiotic options is urgently needed, but there appear to be no new antibiotic preparations in development. This is a potential time-bomb for both emerging nations and the developed world[40]
- Topical antibiotics can provoke delayed hypersensitivity reactions[41]
- Systemic antibiotics have limited effect on biofilm colonies.[42-44]

Therefore, due to the limited efficacy of systemic antibiotics and the need to reserve them for serious infections, they are not recommended for wounds that only show signs of local infection.[36]

Traditional approaches to bacterial control: antiseptics

Recent guidelines on the management of wound infection[6,37] have suggested that topical antimicrobial dressings may help reduce wound bioburden. Products incorporating iodine, silver, honey and, latterly, polyhexamethylene biguanide (PHMB) are considered by many to be the first line of treatment in the management of bioburden, particularly in chronic wound care. They provide a high antimicrobial concentration at the site of infection,[5,45] have bactericidal effects against multi-resistant organisms such as meticillin-resistant *Staphylococcus aureus* (MRSA),[46,47] do not interfere with the protective bacterial flora in other parts of the body and are less likely to produce an allergic

reaction. However, their use has to be targeted and measured.[35-37] These recommendations have been developed following new concerns regarding the use and misuse of topical antimicrobial dressings.

Silver dressings

Silver-based products have been successfully used in burns[48-50] and as an antimicrobial in general wound care,[51,52] with skin discolouration (argyria) and irritation being the only visible side effects.[53] However, all of the various antimicrobial modes of action of silver lead to bacterial cell death and breakdown. These are summarised as:

- Interference with bacterial electron transport
- Binding to bacterial DNA, thereby impairing cell replication
- Binding to the cell membrane, causing structural and receptor function damage
- Forming insoluble, metabolically ineffective cell compounds.[54,55]

In addition, question marks have been raised over the long-term use of these dressings, especially in infants.[34] In recent times, there have been concerns about silver toxicity[56,57] and the systemic uptake and deposition of silver in organs such as the liver and kidney has been noted.[34,58,59] To date, little is known of the long-term consequences for patient safety. Added to this, there are fears over the emergence of silver resistance.[60,61] It would therefore seem that, at least in academic circles, questions exist over its continued widespread clinical use. This has been further enhanced by concerns over its cost-effectiveness,[62-64] yet in the UK silver dressings represent one in seven of all wound dressing prescriptions,[65] with a high cost implications.

Iodine

Iodine-based products have been used in wound care for many years. Like all antiseptics, iodine simultaneously affects multiple sites in microbial cells. The binding of iodine to bacterial proteins results in the denaturing of the microbe through oxidation and the prevention of hydrogen bonding. The bacterium's membrane structure is further compromised by the reaction of iodine with fatty acids. These changes affect the structure and function of both enzymes and structural proteins. In addition, iodine prevents hydrogen bonding within the nucleus. Hence, following exposure to iodine, changes in cell walls, membranes and cytoplasm result in cell disruption and rapid death,[66] as well as exposure of bacterial debris in the tissues.[67]

There is an ongoing debate on iodine's antimicrobial efficacy. Cooper indicates that not all iodine-based products are the same and the chemical interaction between the carrier and the wound environment alters the availability of the element and therefore its effect.[67] Some forms of iodine are

	Silver	Iodine	PHMB	Honey	DACC
Bacterial cell wall	Chemical binding, causing structural and receptor damage	Disrupts cell proteins, damaging the cell wall	Disrupts cell wall	High osmolarity affects integrity of cell wall	Hydrophobic binding. No disruption of cell wall
Bacterial function	Chemical binding disrupts DNA replication	Denatures protein, inactivates enzymes, disrupts nucleic function	Disrupts membranes, interfering with metabolism, and targeting cytoplasmic components causing cell death	Reduces available water, thereby disrupting cellular activity. Some forms have additional antimicrobial activity	Reduces cell proliferation without causing cell death
Systemic	May be systemically absorbed	May be systemically absorbed	No evidence of systemic absorption	No systemic absorption	No systemic absorption
Overall effect	Bacteriocidal with debris left in wound	Bacteriocidal with debris left in wound	Bacteriocidal with debris left in wound	Bacteriocidal with debris left in wound	Bacteriostatic with removal of bacteria at dressing change. No cell debris

Table 1. Summary of the effects of topical antimicrobial dressings

unstable and there have been questions regarding its toxicity to host tissues and the ensuing effect on patient comfort.[68,69] As stated above, exposure to iodine results in rapid cell death, with leakage of selected cellular materials.[70] Providone-iodine is not as effective as some other biocides in eradicating *S. epidermis* within *in vitro* biofilms,[71] but cadexomer iodine provides enough iodine for biofilm suppression without causing significant host damage.[72,73]

PHMB

Although the use of PHMB in German-speaking Europe and in the US is thought to be widespread, it is a relatively new addition to the wound management armoury in the UK. PHMB is a synthetic polymer that is structurally similar to innate antimicrobial peptides (AMPs). These similarities mean that PHMB can enter bacterial cell membranes and kill bacteria in a similar way to AMPs.[74] The primary targets appear to be the outer and cytoplasmic membranes. PHMB is thought to adhere to and disrupt target cell membranes, causing them to leak potassium ions and other cytosolic components,[75-78] resulting in bacterial cell death. There is also evidence that PHMB binds to bacterial DNA and other nucleic acids,[79] damaging or inactivating them. PHMB therefore disrupts the bacteria, causing their death, and results in the release of cell content and debris into the wound.

Honey

Honey has been used in wound care for millennia, but in recent years there has been resurgence in interest in honey-based wound-care products for the management of wound bioburden[53] though its exact mode of action is not yet fully understood. Honey is hyperosmolar and hygroscopic, and so restricts access of environmental water to bacteria and other organisms,[80] leading to cell disruption and death. However, this effect is lessened as the honey becomes more diluted by wound exudate.[81]

A secondary antimicrobial property is the generation of hydrogen peroxide; this is slowly released by glucose oxidase, which is activated as the honey is diluted by exudate.[82] Some honeys, particularly *Leptospermum* or manuka honeys, retain their bactericidal properties even without the presence of hydrogen peroxide.[83,84] Mavric et al.[85] and Adams et al.[86] have identified that, in manuka honey, this is attributable to methylglyoxal. This form of honey appears to interrupt the cell division of *S. aureus* and damages the cell membranes of Gram-negative bacteria.[87] The antibacterial properties of honey therefore appear to affect the cellular activity of bacteria, although these properties vary according to its source. However, regardless of their precise action, all honey-based products leave bacterial debris within the wound.

Table 1 summarises the antimicrobial effects of the topical antimicrobial dressings. It shows that DACC offers a different mechanism and approach to the control of wound bioburden, when compared with other topical dressings. However, it is important to evaluate its effectiveness in bacterial binding in the laboratory situation and assess whether this can be transferred to the clinical situation.

Binding of microorganisms with DACC: evidence from *in vitro* and animal studies

Over more than 30 years, multiple *in vitro* studies have demonstrated the effective binding of microorganisms to DACC-coated wound dressings.

In one of the earliest, Wadström et al., in a series of comparative studies using a laboratory and a porcine animal wound model, tested the ability of a variety of dressing materials to influence bacterial colonisation.[88] Samples of a DACC-coated dressing, a cellulose dressing (Cutimed Sorbact without DACC) and Actisorb (Johnson & Johnson, Skipton UK [correct at the time of the study]) were exposed to three different strains of bacterium: *Staphylococcus epidermidis* strain S-1-1030 (a hydrophilic control), *Staphylococcus aureus* Cowan 1 and strain 402-2006 (both hydrophobic to differing degrees).

The DACC-coated sample showed greater bacterial uptake than the other products tested.[88]

In the subsequent animal experiments, standardised wounds were produced on the subject animals. Half the wounds were exposed to heat from a copper plate to simulate a burn injury. All the wounds were then inoculated with cultures of *S. aureus* strain SA 113 (83A). The wounds were dressed with a sample of a non-coated cellulose dressing, a DACC-coated cellulose dressing, Debrisan, or Actisorb 30 to 60 minutes after inoculation. All dressings were changed daily for the duration of the trial. Wounds (both burn and non-burn) treated with the DACC dressing showed no signs of infection while all the comparators displayed continuous suppuration. Healing was noted by day 5–6 in the non-burned wounds and 7–8 in the burned wounds.[88]

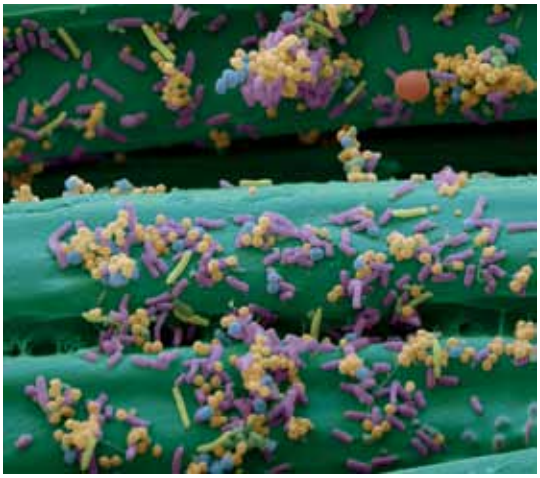


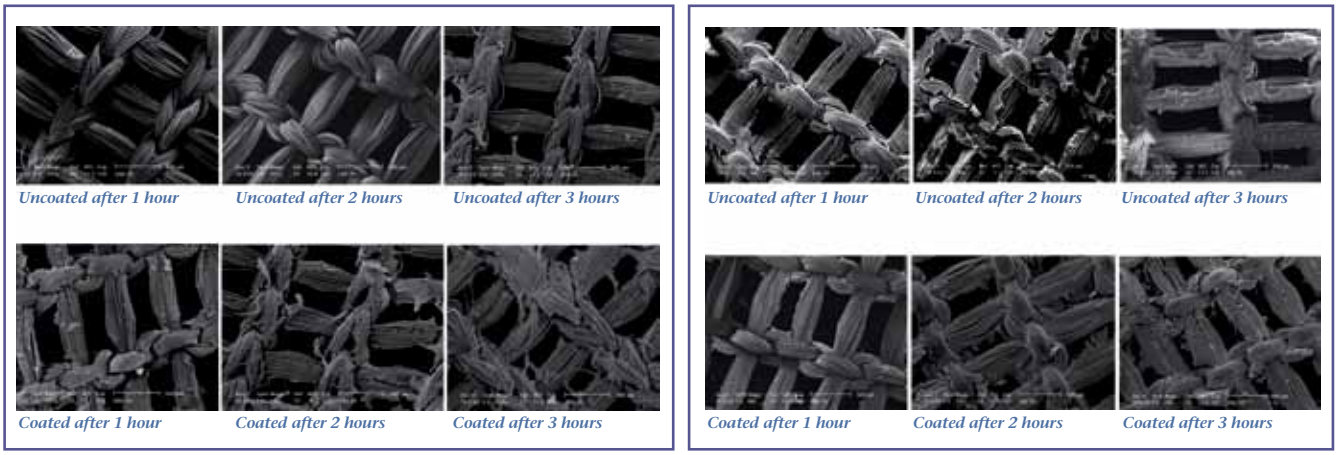
Fig 4: Binding action of Cutimed Sorbact: Staphylococcus aureus (yellow), Pseudomonas aeruginosa (purple), Enterococcus faecalis (blue), Klebsiella spp (green) bound to the dressing at 4,000 times magnification

Effects of CSH on binding

There is evidence that the efficiency of binding depends on the CSH of the bacterium and the duration of exposure to DACC. In a conference presentation, Hastings reported on an *in vitro* experiment in which cultures of *C. difficile* and *S. aureus* were grown in the laboratory under conditions that produced cells with high and low CSH.[89] Cells were suspended in a pseudo-extracellular fluid and exposed to DACC-coated dressings. The length of exposure time was varied and noted, and bacterial cells and *C. difficile* spores were visualised by staining and direct microscopy visualisation. The results clearly demonstrated the ability of bacteria and *C. difficile* spores to adhere to the dressing material. Sixteen per cent of cells in samples of *S. aureus* with a high CSH bound to the dressing within 10 minutes' exposure. This figure rose steadily to nearly 60% after 180 minutes' exposure. Cultures of *C. difficile* with a high CSH achieved 10% cell binding to the dressing at 10 minutes, rising to 35% after 180 minutes. Hastings suggests that the binding of *C. difficile* spores and of *C. difficile* and *S. aureus* bacteria in the wound environment could reduce the potential sources of infection.[89]

Bowler et al., in a study investigating the efficacy of bacterial sequestration in different dressing materials, reported a correlation between a high CSH and efficacy of binding. It compared Hydrofiber and alginate dressings, which absorb and retain bacteria within the dressing matrix by mechanical action, with the hydrophobic dressing material, Sorbact (name correct at time of publication).[18] The test was only carried out over a 4-hour period, but Sorbact bound significantly more *S. aureus* and *P. aeruginosa* than both the alginate comparators ($p<0.05$). In particular, it was highly effective in binding *P. aeruginosa* (78.6%); this is thought to be related to the chemical nature of Gram-positive and Gram-negative bacteria and their relative CSH. The investigators concluded that the differential sequestration between *S. aureus* and *P. aeruginosa* strain observed was probably attributable to the fact that the CSH of *P. aeruginosa* is three times that of *S. aureus*,[18] and so the binding of *P. aeruginosa* to the hydrophobic wound contact layer is likely to be more aggressive.

Fig 5: Binding of MRSA (left) and P. aeruginosa biofilms (right): DACC-coated dressings versus a control



Quantitative data to support binding

In 2006, Ljungh et al. conducted a study designed to demonstrate microbial binding to DACC-coated dressings.[32] Bioluminescence was used to quantify adherent microbes.[90] Binding of *S. aureus* Newman and *P. aeruginosa* BD510 was measured over time periods ranging from 0.5 minutes to 20 hours. Results showed that:

- Binding increased after 10 minutes
- Binding rate reached a maximum at 120 minutes when 10^7 out of 10^9 added *P. aeruginosa* had bound to the hydrophobic dressing
- Bacterial counts remained stable at 20 hours for *P. aeruginosa*, and increased only from 10^6 to $10^{6.5}$ after 20 hours for *S. aureus*, demonstrating that bacterial proliferation is significantly curtailed after binding to the hydrophobic dressing.

Adding increasing numbers of bacterial or fungal cells (10^8 – $10^{9.5}$ bacterial cells, $10^{6.2}$ – $10^{7.5}$ fungal cells) showed that 10^8 cells of *S. aureus* Newman and $10^{4.8}$ cells of *Candida albicans* bound, but satisfaction (the term used to describe the point where no more organisms could bind to the dressing) was only shown for *C. albicans*. When $10^{10.3}$ cells of *Enterococcus faecalis* were added, $10^{6.7}$ cells bound, again showing no satisfaction. This shows the hydrophobic dressing is likely to be able to bind more than 10^8 *S. aureus* and more than $10^{6.7}$ *E. faecalis*. For *Bacteroides fragilis*, more than 10^6 cells bound out of the 10^8 added, and for *Fusobacterium nucleatum,* $10^{7.5}$ cells bound out of the $10^{8.5}$ cells added. Binding of a mixed culture containing *S. aureus*, *P. aeruginosa* and *C. albicans* to the hydrophobic dressing showed that, on the dressing, microbes co-aggregate and bind to each other as well as to the dressing. Ljungh et al. concluded that coated Cutimed Sorbact can be used on clinical infections because its binding action reduces the microbial load in a wound without the need for antibiotics (Fig 4).[32] This indicates that the dressing has the capacity to prevent colonised wounds from becoming infected.

Efficacy against biofilms

Biofilms have decreased sensitivity to antimicrobial agents and antibiotic therapy, making them particularly difficult to manage and control.[91,92] In a poster presentation, Cooper and Jenkins described tests undertaken to determine whether DACC has a potential role to play in biofilm management.[93] Samples of MRSA and *Pseudomonas* biofilms were tested with Cutimed Sorbact dressing material. Samples of the DACC-coated product were compared with uncoated dressings. These were examined under an electron microscope after 1, 2 and 3 hours of exposure. The images gave clear evidence that biofilms of MRSA and *P. aeruginosa* bound more extensively to DACC-coated dressings than uncoated product (Fig 5). These images were then assessed by blinded volunteers to ensure reliability. This test demonstrated that, *in vitro*, DACC enhances biofilm binding.

In vivo studies

Laboratory conditions are very different to the uncontrolled environments found in the clinical environment. Since its introduction, DACC-coated Cutimed Sorbact dressings have been successfully used in the management of patients with wound bioburden. The findings of a variety of published comparative and non-comparative clinical trials, along with multiple case-study series, have supported the findings of *in vitro* studies.

An early non-comparator study by Friman trialled Cutimed Sorbact on 32 infected wounds (31 patients).[94] Determination of infection was based on the presence of pus in the wound. All wounds were assessed at least twice weekly; treatment continued until the wound no longer showed signs of infection or until the treatment was deemed unsuccessful (wound showed no change in presentation or exhibited increased debris or necrotic tissue).

Of those tested, 69% (n=22) showed improvement, with the greatest improvement being noted within the first week of treatment (median treatment period 9 days). At initiation, wound cultures demonstrated that seven wounds grew only *S. aureus*. In six of these cases, this bacterium was still present on the final culture, but the wounds no longer showed clinical signs of infection. On wounds displaying a mixed bacterial flora at initiation, the *Staphylococci* were completely eradicated. This effect was found to be statistically significant ($p<0.05$).

Retrospective review

Von Hallern and Lang undertook a retrospective review of 418 patients with contaminated, colonised and infected wounds treated with the Cutisorb (now known as Cutimed) Sorbact dressing over a 22-month period.[95] The review aimed to determine whether a dressing with a purely physical mechanism of action can reduce the microbial count, especially in colonised and infected

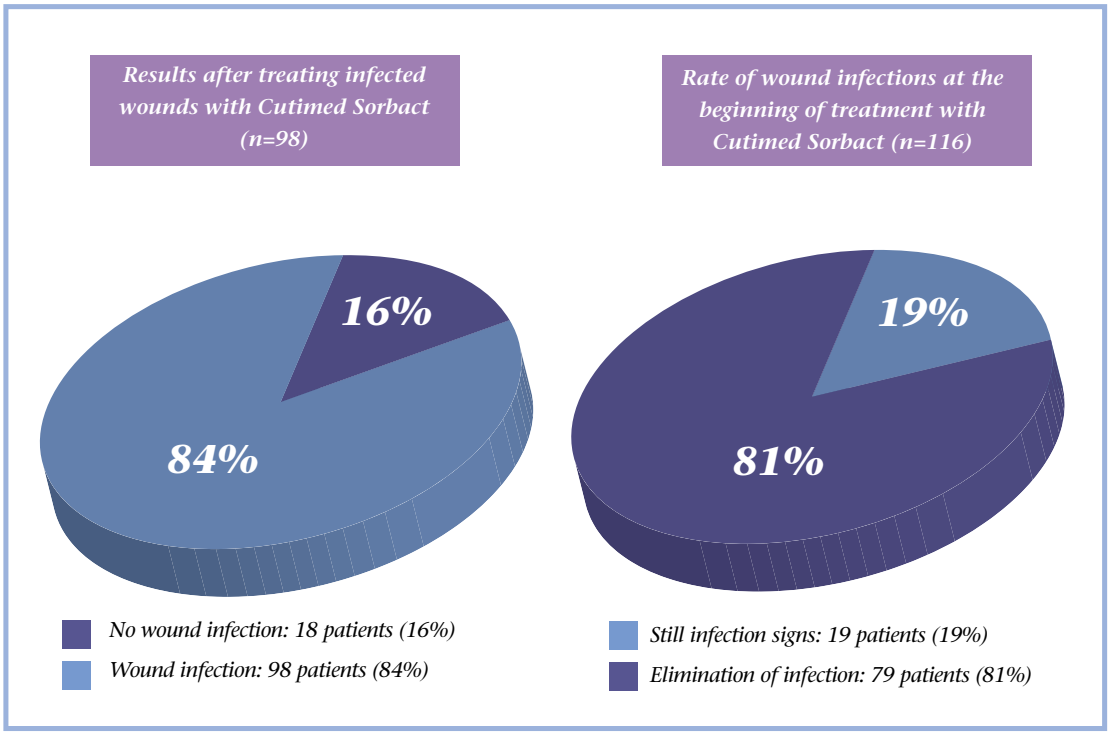
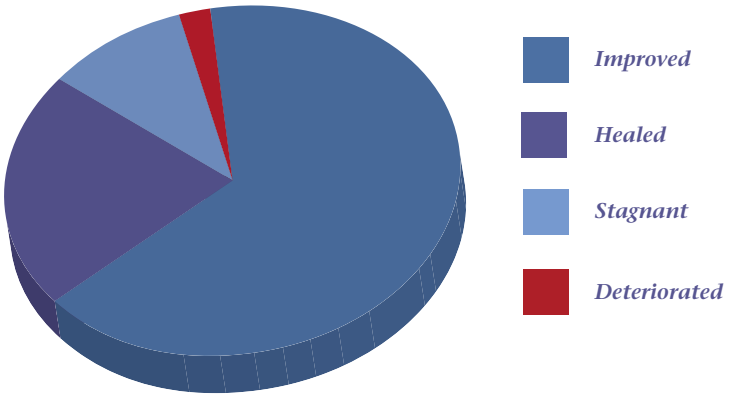


Fig 6: Infection rates before and after treatment with the DACC-coated dressing

wounds, without adversely affecting the wound healing process and can be removed atraumatically and painlessly. The breakdown of wound aetiologies treated was:

- Contaminated, colonised, infected traumatic wounds: 112 patients
- Abscesses: 85 patients
- Colonised and infected post-operative wounds: 72 patients
- Colonised and infected pressure ulcers: 72 patients
- Colonised and infected leg ulcers: 55 patients
- Infected diabetic gangrene – pre-operative: 22 patients.

Fig 7: Clinical efficacy of the DACC-coated dressing



The DACC-coated dressings were applied between a few hours to 48 months post-injury and the product was used for 2–53 days. Subjective parameters such as pain at dressing change, comfort and patient and nursing staff satisfaction were elicited at every dressing change. Bacteriological analyses were performed on deep brush biopsy wound swab specimens from 38 patients with chronic (venous leg ulcer, pressure ulcer) and secondary healing wounds (postoperatively after open forefoot amputation, fistula excisions and infected haematomas).

Quantitative decreases in bacterial strains such as *S. aureus*, MRSA, *Pseudomonas*, *Streptococci* and *Escherichia coli* were observed. In some cases, organisms were identified from the removed dressing materials that were no longer found in the direct deep wound swabs. The investigators concluded that the use of a DACC-coated dressing resulted in microbial elimination. This was supported by clinical observations, which noted that,

Pain score (VAS)	Baseline	End of study
0 (no pain)	52.2%	83.5%
1–3 (mild pain)	33%	14.8%
4–6 (moderate pain)	4.3%	0.9%
7–10 (severe pain)	10.4%	0.9%

Table 2. Pain scores before and after treatment

after 2 to 8 days, there was often a marked decrease in signs of infection. In such cases, the Cutisorb Sorbact (correct at publication, now known as Cutimed Sorbact) dressing was replaced by simple wound dressings. Cutimed Sorbact was discontinued after an average 10 to 12 days in all but patients with forefoot amputation due to diabetic gangrene or arterial occlusive disease. In these cases, Cutimed Sorbact was used as a prophylactic in combination with a hydrogel and an absorbent dressing pad, often up to the end of treatment.

DACC therapy was found to be an effective bioburden control method and did not prolong the total duration of healing compared with hydroactive dressings.[95]

Multicentre study

The efficacy of DACC in managing bacterial burden was supported in a study published 3 years later. Kammerlander et al.[33] presented the findings of a 116-patient multicentre study undertaken between 2003 and 2006 in four centres in Europe. In order to test the efficacy of Cutimed Sorbact, the study questioned whether it could:

- Reduce signs of peri-focal inflammation
- Reduce or eliminate local infection
- Improve the course of wound healing
- Demonstrate subjective tolerability by patients
- Demonstrate broad compatibility with other wound management products
- Provide easy product handling during dressing changes.

A wide variety of wounds healing by secondary intention were treated using the accepted wound management protocols of the participating clinics. A standardised evaluation form was used to monitor and record the wound's progression towards healing. Peri-wound skin condition was also observed. Patients enrolled in the study with a systemic infection (an infection in addition to the local wound infection) were treated with antibiotics. Tolerability was determined using pain assessment (documented at every dressing change [n=1150] using a 0–10 visual analogue pain scale). Subjects (n=115) were asked about their subjective impression of the feel of the dressing, grading it as 'neutral', 'unpleasant, 'pleasant', or 'very pleasant'.

Clinicians determined the secondary dressing used (e.g hydrogels, alginates, hydrocolloids) depending on the wound. They were also asked to comment on the handling and application of the trial product at each dressing change. These could be rated as 'very good', 'good', 'satisfactory' or 'unsatisfactory'. Additional comments were also encouraged.

The profile of the patients enrolled was as follows:

- Mean treatment period: 37 days (range 4–134 days)
- Mean age: 63 years (range 27–95 years)
- Mean baseline wound duration: six months (range 1 day to 54 months)
- Gender distribution: 54 women, 62 men
- Recorded number of dressing changes: 1,150
- Mean frequency of dressing change: 2.5 per week

Concomitant diseases included diabetes (39%), peripheral arterial occlusive disease (PAOD) (39%), chronic venous insufficiency (CVI) (9%), hemiplegia (7%), paraplegia (2%), renal insufficiency (3%) and cardiac failure (2%).

Wound infection was diagnosed at baseline in 98 of the 116 documented wounds (84%). One patient developed a wound infection during the course of treatment. There were no incidents of a recurrence of a successfully treated wound infection. Less than 10% of the patients with a wound infection received additional antibiotic treatment. Of the 98 infected wounds at baseline, 79 (81%) were successfully treated at the study end (Fig 6).

The clinical efficacy of Cutimed Sorbact in bioburden management was assessed during and following wound treatment. In seven cases (6%) the wounds remained stagnant, one case (1%) deteriorated, 84 cases (72%) improved and 24 cases (21%) were healed (Fig 7).

Patients identified the dressing as pleasant or very pleasant with no pain, burning, skin irritation or negative sensations in 71% of cases and in only 2% of cases was the dressing identified as 'unpleasant'. Pain scores reported at baseline and at the study end are given in Table 2. Patients did not report any undesirable side effects of the vari-

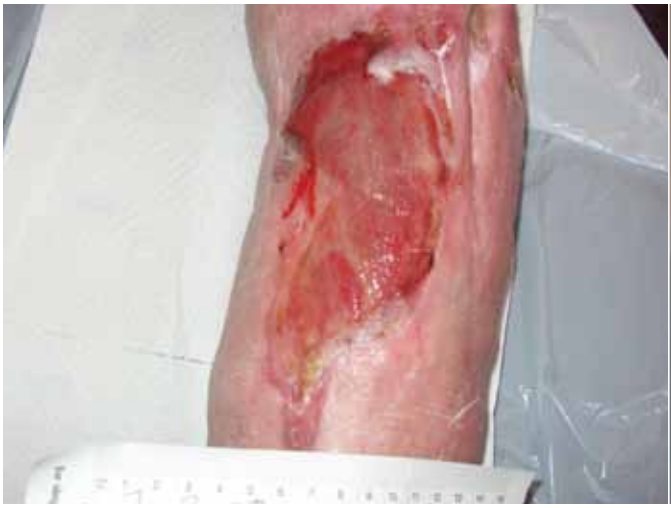


Fig 8: In this patient, maldour and exudate were a problem prior to using the DACC-containing dressing

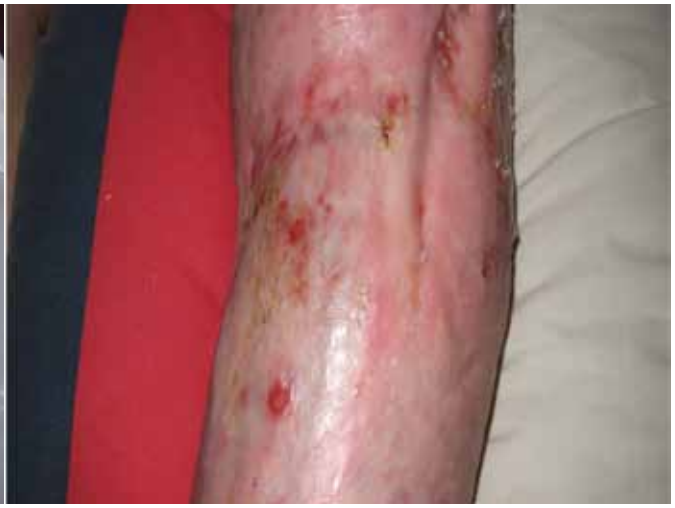


Fig 9: After 8 months, the wounds had almost healed

ous dressing combinations. Furthermore, Cutimed Sorbact did not cause discolouration in any of the wounds and no product-specific odour was reported.

Different presentations of Cutimed Sorbact were selected by clinicians according to individual wound presentation (location, depth, topography, area). In 97% of cases, the dressing change was rated as 'good' or 'very good'. Clinicians were extremely satisfied with the handling characteristics of the dressings.

In this study, Cutimed Sorbact was tested under the conditions normally found in the participating clinics. It achieved a good level of efficacy in bioburden management within a phased programme of wound care. Using Cutimed Sorbact in this study, 81% of wounds showing signs of infection at the start of treatment healed and in 93% of cases there was an improvement in wound healing or complete closure. The study demonstrated that Cutimed Sorbact can reduce signs of peri-focal inflammation, reduce or eliminate local infection, achieve subjective tolerability by patients, has a broad compatibility with other wound management products and provides easy product handling during dressing changes. In particular, the consistently easy handling convinced health-care professionals of the versatility and value of this alternative to current antimicrobial dressings.

Johansson et al. undertook a non-comparative, open study of the ability of DACC to manage the bioburden of interdigital infections in 20 diabetic subjects with fungal foot infections.[96] All the subjects had confirmed fungal infections and received 10 daily treatments with Cutimed Sorbact ribbon. Following treatment, 75% of the subjects improved or healed by day 10, 20% remained unchanged and one patient had deteriorated (the fungal skin reaction improved but the ulceration on the fourth phalanx worsened, possibly due to the use of inappropriate footwear). A total of 83% of patients found the treatment easy or very easy to apply. Mycology findings revealed a broad variety of fungi present prior to commencement of Cutimed Sorbact. In 55% of subjects no fungi were cultured on day 10.[96] This study is particularly relevant to clinical practice as diabetic patients are particularly prone to fungal infections.[97,98] Traditional management of this condition has relied on systemic or topical administration of pharmaceutical antifungal agents. This has had varying success and can cause potential adverse reactions (toxicity or allergy) plus the risk of the resistance development.[99]

Case series

A number of authors have presented a series of case studies to demonstrate the outcomes of using DACC-coated Cutimed Sorbact dressings in the clinical environment. Although these reports lack the rigour of formalised trials, they do give a good impression of the product's effectiveness in clinical practice in treating wounds of differing aetiologies.

Hampton reports a case series of 21 patients treated with DACC-coated dressings.[100] These patients, with a mean age of 83 years (range 67–96

years), had chronic non-responding wounds of at least 3 months duration with a variety of underlying aetiologies. All the patients were treated for at least 4 weeks; those healing but not yet closed were treated for up to 10 weeks. Dressings were renewed as frequently as clinically indicated.

After 4 weeks treatment, six wounds had healed and 14 were progressing towards healing (as determined by an improved status on a wound healing continuum[101] assessment). Malodour was identified in 56% of the wounds on day 1, with 28% of wounds being recorded as extremely malodorous and 28% as having some malodour. A reduction in odour from 56% to 0% at the end of the 4-week evaluation was reported.[100]

During the evaluation, improvements in the patients' peri-wound skin condition was observed with 38% of patients having healthy skin on day 1, increasing to 68% on day 28. The Cutimed Sorbact absorbent pads absorbed exudate well with no peri-wound maceration or excoriation and in all patients exudate levels reduced with product use. Consequently, dressing changes were also reduced from three dressing changes per week (on average) to one or two per week (on average), making the dressing increasingly cost-effective. Pain scale scores, which were assessed weekly throughout the study, were significantly reduced during the evaluation. This decrease in perceived pain may relate to a reduction in wound bioburden and reduced inflammation. Clinicians reported that the product was easy to use, the dressings stayed in place between changes and were easy to remove without inducing wound bed trauma.

Powell reported on a series of case studies using DACC-coated dressings to manage bacterial burden and so facilitate wound healing.[102] Three patients with indolent, highly exuding, chronic leg ulcers were treated with DACC in combination with compression therapy and absorbent dressings. In each case odour, exudate and pain reduced significantly shortly after the introduction of the product. In one of these cases, the DACC-coated dressing was safely used for approximately four months, and kick started healing in a previously recalcitrant wound. Two patients were treated with Cutimed Sorbact following the breakdown of wide excision and surgical closure wounds to correct pilonidal sinus. These wounds are notoriously painful[103] and due to the anatomical position rapidly become heavily colonised with bacteria. In both cases, the application of Cutimed Sorbact ribbon brought about a rapid improvement in wound healing with rapid closure by secondary intention (Figs 8 and 9). Finally, Powell reported on the treatment of a patient with multiple fungating lesions to the breast and abdomen. Prior to treatment, these wounds were heavily exuding, sloughy and extremely malodorous. A palliative regimen was implemented using daily DACC-coated ribbon and absorbent dressing pads. This was highly successful and within 3 days the offensive odour was no longer a problem. Two weeks of treatment witnessed marked reduction in exudate and an improvement in the peri-wound skin condition. By this time, the dressing only needed to be changed twice a week. Powell concluded that DACC-coated Cutimed Sorbact dressings are effective treatment when critical colonisation and signs of infection are observed and should be considered for wounds at risk of infection due to location and aetiology.[102] The product is now included within the trusts' wound care formulary.[104]

Case reports

Riley adopted a case study approach to the treatment of two patients with diabetes and foot wounds. Both patients had serious arterial occlusion and exposed bone in their wounds.[105] Patient 1 was advised that amputation of his lower limb was required and patient 2 had already undergone a forefoot amputation. DACC-coated dressings were introduced to manage the bacterial burden in both patients. Despite the poor vascularisation and extent of the two wounds (patient 1 measured 4.5 x 3.5cm at presentation, and patient 2 was 13.5 cm in length) both healed following 20 weeks of treatment with Cutimed Sorbact. During therapy no other form of antimicrobial was required.

Haycocks and Chadwick reported the use of Cutimed Sorbact on a diabetic patient with a foot wound and a previous history of recurrent foot ulceration and osteomyelitis.[106] He had developed further ulceration with underlying osteomyelitis in the head and distal three quarters of the first metatarsal. This had been resistant to therapy, so he was taken to theatre for resection of the infected bone. He was home treated with intravenous antibiotics and had gentamicin beads inserted into the wound bed.

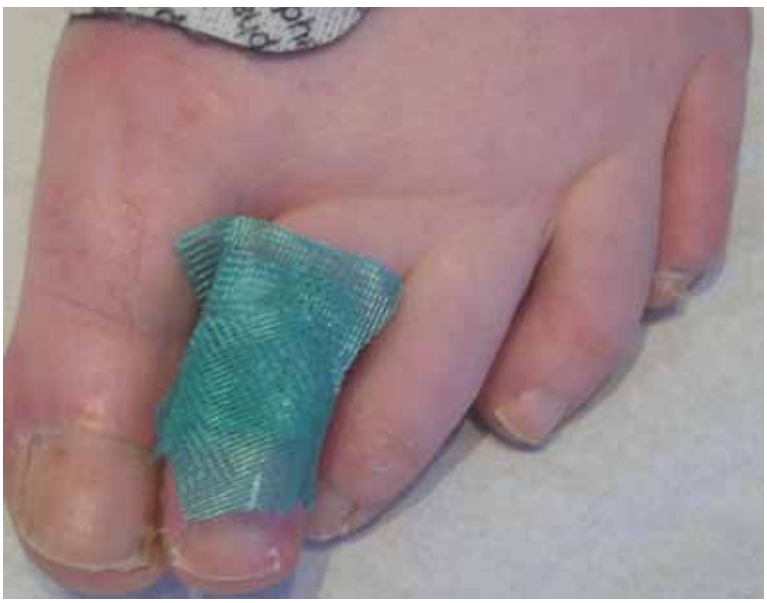
DACC-coated dressings were initiated 2 weeks postoperatively when the gentamicin beads were removed. The dressing was changed three times a week and he was reviewed at the podiatry clinic

weekly. The dressing was found to be easy to use and was said to be comfortable by the patient. Throughout treatment, the wound remained clean and infection free, with complete closure being achieved in 15 weeks. Haycocks and Chadwick reported that bioburden management is a vitally important consideration in high-risk patients. There were no side effects and no risks of cytotoxic or irritative reactions. The ability of DACC in Cutimed Sorbact to bind effectively to the hydrophobic, pathogenic bacteria and fungi found in many diabetic wounds makes Cutimed Sorbact 'an important, safe and innovative newcomer to the antimicrobial dressing toolkit'.[106]

Skinner and Hampton presented a series of four diabetic patients treated with Cutimed Sorbact.[107] All the wounds were colonised, three of which displayed signs of local infection. All the clinicians and patients involved found the product easy to use, even on digits which can be difficult to dress (Fig 10). All the patients improved with the treatment, with three out of the four healing completely; the one exception had poor blood glucose control and arterial insufficiency. However, even in this case bacterial bioburden was well managed.

Hardy reported on the use of DACC-coated Cutimed Sorbact dressings in the management of patients with lymphoedema, chronic oedema and lymphorrhoea at the Kendal Lymphology Centre.[108] In the article, the author argues that skin hygiene and bioburden control are essential elements in the management of these conditions. Lymphorrhoea is a particular problem with wet, sodden dressings acting as a portal for bacterial and fungal infections and a cause of peri-wound maceration. The author describes the treatment of two patients with chronic oedema and leg ulceration who had previously experienced recurrent infections. The implementation of a therapy regimen incorporating DACC-coated Cutimed Sorbact products to achieve bioburden management has resulted in significant wound improvement, improvement in the patients' quality of life and significant reduction in the cost of care.

Fig 10: Application of Cutimed Sorbact to a digit



Key benefits of DACC-coated dressings

- No development of resistance
- No endotoxin release
- No upper binding capacity
- Can bind all common wound pathogens plus toxins
- No systemic absorption so suitable for use of all patients regardless of their age or underlying illnesses
- No cell debris

Derbyshire reported on a series of three case studies.[109,110] Two of these involved highly exuding and painful leg ulcers, which had been present for a number of years and one involved a gentleman with extensive solar skin damage to his scalp. All the patients' wounds had been resistant to conventional therapies and had involved considerable nursing intervention and years of dressing prescriptions. In all cases, the use of DACC-coated dressings resulted in reduced bacterial bioburden with resultant reductions in pain, exudation and maceration (Figs 11 and 12). Due to the chronic nature of these wounds healing is slow but ongoing; however, the author has identified substantial cost savings in the use of Cutimed Sorbact as well as improved wound healing outcomes.

Conclusion

The effective management of wound bioburden will remain an important feature of wound care for the foreseeable future and the need to find alternative methods of pathogen control via topical antimicrobials, is likely to grow. As clinicians, we need to explore new avenues that work synergistically with the body's own defences to bring about opti-

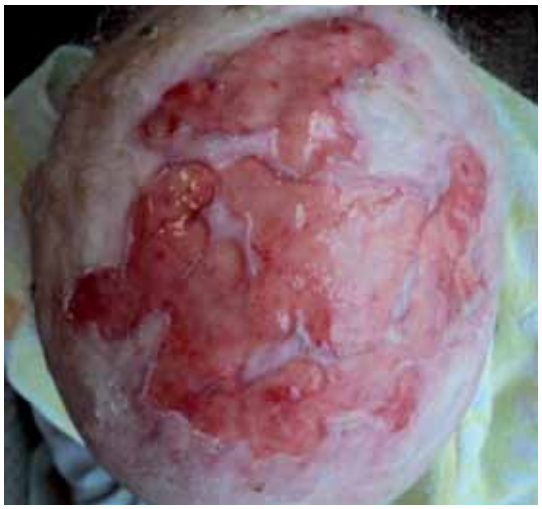


Fig 11: Head prior to application of the Sorbact-containing dressing

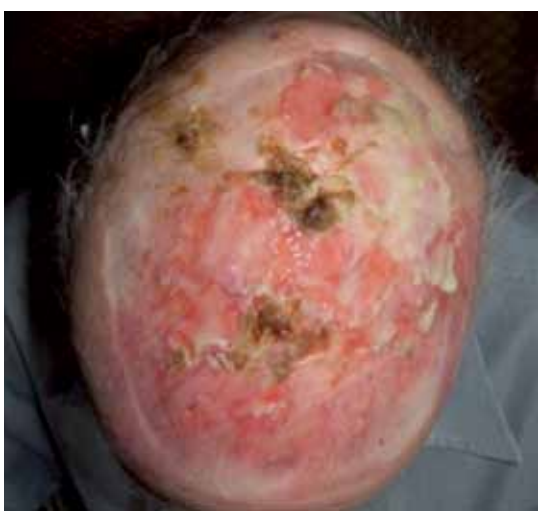


Fig 12: Formation of granulation tissue

mal wound healing outcomes.

A technology that can bind bacteria to it rather than just kill it *in situ* represents a distinct paradigm shift from previous approaches to bioburden management. As has been shown, traditional methods of control that aim to destroy microbes can be problematic as the chemical arsenal developed can turn against the environment they were designed to protect. Patient sensitisation, the development of resistant pathogens, cellular and systemic toxicity, and the promotion of extended inflammatory response are all very real issues for the wound care clinician.

Cutimed Sorbact is the first DACC-coated dressing that utilises the hydrophobic properties inherent in a wide variety of wound pathogens, including multi-resistant organisms and biofilms, to bring about control. By facilitating the irreversible binding of microbes to its DACC coating, Cutimed Sorbact is able to provide a safe and effective method for clinicians to reduce bacterial load within the wound at each and every dressing change. By providing bioburden containment and control, DACC technology offers a new treatment for wounds that are either infected or susceptible to the development of infection. This has particular relevance where such infection can be catastrophic such as in the diabetic foot wound. It enables the balance of wound bioburden to be tipped back in favour of the body's own defence systems without the risk of cytotoxic reactions or development of bacterial resistance. It should therefore always be considered, alongside other topical dressings, as a new way of providing antimicrobial care.

Key points

- Most antimicrobial dressings reduce bioburden by killing bacteria in the wound
- Effective wound management seeks to avoid eliciting a prolonged inflammatory state, but the chemicals used in most topical antimicrobial dressings can promote inflammation because of the endotoxins released by the ensuing bacterial debris in the wound
- Bacteria adhere to parts of the extracellular matrix by hydrophobic interactions. This adhesion occurs when cells expressing cell-surface hydrophobicity (CSH) come into contact with each other. Most pathogens express high to moderate CSH
- A dressing with hydrophobic properties is able to physically bind bacteria into its fibres. Such a dressing, which binds rather than kills bacteria and fungi, represents an important paradigm shift in antimicrobial thinking and management.
- Key advantages of hydrophobic dressings are that they reduce the microbial load without the need for chemically reactive dressings, and avoid the risk of cytotoxic reactions and resistance

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