Using the principle of hydrophobic interaction to bind and remove wound bacteria

Reducing the microbial load in an infected wound may help to promote healing. A hydrophobic dressing, which binds microbes whose surface contains water-repellent molecules, may reduce the use of antibiotics. This paper explains how

wound infection; hydrophobic; cell surface hydrophobicity

Skin, soft-tissue and wound infections are usually caused by wound pathogens such as *Staphylococcus aureus* and group A Streptococci (GAS),[1] *Pseudomonas aeruginosa*, members of the Enterobacteriaceae, Enterococci, and other Streptococci families and anaerobic microbes such as *Fusobacterium necrophorum* and *Bacteroides fragilis*.[1,2]

Chronic infections are often of polymicrobial origin.[3] In these, Trichophyton, *Candida albicans* and other fungi are commonly isolated, while the role of anaerobic species is often underestimated.[4,5]

Infection may lead to local tissue degradation and, subsequently, necrotising fasciitis, osteitis[4,6,7] and septicaemia. Clinicians should be aware that:

- Surgical-site infection can be dependent on the procedure and the anatomical location[3]
- Burns have a high potential to become infected[8,9]
- Patients with diabetes can develop lower extremity wound infections associated with vascular insufficiency and/or minor trauma[10]
- Exacerbation of atopic dermatitis or psoriasis is associated with colonisation by superantigen-producing *Staphylococcus aureus*[4,11,12]
- Animal-bite wounds may become infected with *Pasteurella multocida* or Capnocytophaga spp.[13]
- Wounds exposed to sea water may become infected with Aeromonas and Vibrio spp.[14]

The initial event of a skin or wound infection is the adhesion of the pathogenic microbe to damaged skin.[15] This can be mediated by receptor-specific hydrophobic or electrostatic interactions between the microbe and human tissue structures.

- Hydrophobic (lacking an affinity for water molecules) interactions take place when molecules expressing cell-surface hydrophobicity (CSH) come into contact with each other
- Electrostatic interactions occur when a microbe, generally expressing a negative net surface charge, comes into contact with a tissue molecule expressing a positive charge.

Microbes

Microbial cell surface proteins mediate binding to extracellular matrix (ECM) proteins — fibronectin, collagen, vitronectin, laminin — and plasma proteins, such as fibrinogen, by receptor-specific interaction.[16] This binding leads to adhesion to host tissue, which may lead to infection. Elgalai and Foster showed that over 85% of *Staphylococcus aureus* isolated from wound infections expressed binding of fibrinogen.[17] Although isolates differed in their ability to bind plasma and ECM proteins, a significant correlation was found between expression of binding and infection of burns.

Several microbial cell surface structures have been reported to express hydrophobic properties, and are therefore likely to mediate adhesion to tissues by hydrophobic interaction.

Examples of hydrophobic tissue adhesions include:

- Fimbriae of Gram-negative bacteria[18]
- Cell surface proteins of fungi[19-21]
- S-layer proteins (capsule-like polysaccharide surface coatings)[22]
- Lipoteichoic acid of Gram-positive bacteria.[23]

Production of a carbohydrate polymer capsule — for example, by GAS and *Staphylococcus aureus* — renders the cell surface more hydrophilic (attracting water molecules),[1,23] and therefore less prone to adhere to hydrophobic structures in human tissue or to hydrophobic dressings. This means that hydrophobic dressings are unlikely to be able to remove such bacteria.

Similarly, teichoic acid, a main constituent of the *Staphylococcus aureus* cell wall, confers a less negative charge on the bacterial cell surface, and mediates adhesion to various polymer surfaces.[24] Thus, teichoic acid is less prone to mediate binding to tissue, other microbes or charged dressings by electrostatic interaction. Since they express lower cell surface hydrophobicity these microbes will also bind less avidly to hydrophobic dressings.

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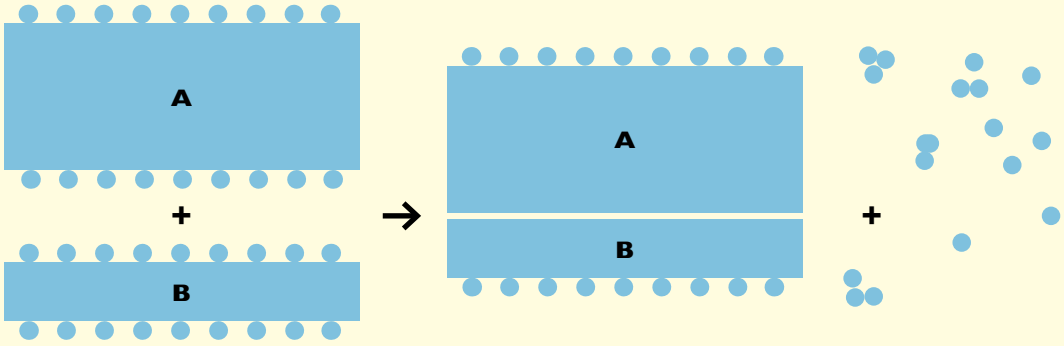
Fig 1. The hydrophobic principle: two hydrophobic molecules associate with each other and expel water



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Protease production by microorganisms enhances the local spread of infection and tissue destruction.[6] Matrix metalloproteases (MMPs) interact with ECM proteins and enhance tissue invasion.[25] MMP-13, a collagenase-3, impairs wound healing.[26] MMP-19 regulates cellular growth factor response and inflammatory response by cleavage of cytokines and chemokines.[27] MMP-19 is present in dermal fibroblasts and endothelial cells during wound repair, and it is postulated that it plays a role in angiogenesis.

Some extracellular toxins, like haemolysin, toxic shock syndrome toxin-1 (TSST-1), exfoliatin and superantigens of *Staphylococcus aureus* and GAS, contribute to tissue destruction and interfere with the immune defence system. Of these, the staphylococcal exfoliatin targets desmosomes, causing scalding of the epidermis, which may clinically correspond to second or third degree burns.[28]

In experimental porcine wounds, *Staphylococcus aureus* and *Pseudomonas aeruginosa* form biofilms[29,30] which act as a barrier to antibiotic penetration and hamper signalling to the host immune system. This may be one cause of chronicity of wounds, and may be overlooked by wound-care strategies.

Hydrophobic principle in bacteria removal

When two water-repellent (hydrophobic) molecules collide with each other they increase the entropy (disorder of molecules).[31] Although there is no force of attraction between the hydrophobic molecules, they will associate with each other by hydrophobic interaction and expel water molecules[31,32] (Fig 1).

Microbes that express CSH during *in vitro* conditions that mimic a human wound are highly likely to bind to a hydrophobic dressing. Hydrophobic molecules may affect cell signalling and initiate innate immune responses.[33] In *Staphylococcus aureus*, a conserved hydrophobic domain of the auto-inducing peptide binds to a hydrophobic pocket of the AgrC receptor, leading to activation of agr, which controls major virulence factors as well as quorum sensing.[34] In this way the presence of CSH-expressing microbes in a wound may stimulate or antagonise wound healing.

This is an interesting area that so far has not been much explored.

Expression of cell surface hydrophobicity by microbes

Expression of CSH is an important mechanism of adhesion by microorganisms[23] and is often a reaction to stress conditions such as starvation. CSH is mediated by cell surface proteins (hydrophobins).[35] Bacteria such as Peptostreptococci and other anaerobes express high CSH.[23,36-38] However, strains of the same species may vary in their CSH. In *Staphylococcus aureus*, for example, staphylococcal delta-toxin, exfoliatin, TSST-1 and enterotoxin A are quite hydrophobic, whereas alpha-toxin and gamma-toxin are moderately hydrophobic, and the other staphylococcal enterotoxins have been shown to express low CSH.[39] The expression of different toxins may thus influence the overall expression of CSH by an individual strain.

The expression of CSH is influenced by the availability of nutrients and the environmental atmosphere. In a previous study we grew microorganisms in a simulated wound environment comprising rich agar medium (haematin agar) covered by 1mm human serum. Cultures were incubated in 5% CO_2 at 37°C. This resulted in expression of increased CSH compared with growth on poorer media incubated in air (Table 1).[40]

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 vegetative cells,[41] and it is likely that this can be a more general property of bacterial spores.

Table 1. Influence of culture conditions on expression of cell surface hydrophobicity

Culture conditions	*Staphylococcus aureus**	*Staphylococcus haemolyticus*	*Escherichia coli***	*Enterobacter cloacae*	*Pseudomonas aeruginosa*
Blood agar, air	>2	0.25	>2	>2	<2
Blood agar, 5% CO_2	2	0.1	2	2	>2
Blood plus serum, air	2	0.1	1	2	2
Blood plus serum, 5% CO_2	1	0.01	0.5	1	1
Blood plus inactivated serum, 5% CO_2	1	0.01	0.5	1	1
Haematin agar, air	>2	0.1	2	>2	>2
Haematin agar, 5% CO_2	2	0.1	2	2	2
Haematin plus serum, air	1	0.01	0.5	1	1
Haematin plus serum, 5% CO_2	0.5	0.01	0.25	0.5	1
Haematin plus inactivated serum, 5% CO_2	0.5	0.01	0.25	0.5	1

* Cell surface hydrophobicity was analysed by salt aggregation test (SAT). Results given are the lowest concentration of NH_4SO_3 giving visible aggregation. Two methicillin-resistant *Staphylococcus aureus* (MRSA) strains and four methicillin-sensitive *Staphylococcus aureus* strains were tested, giving the same results

** Two *Escherichia coli* strains were tested, giving the same results

In summary, the wound environment enhances expression of CSH by colonising microbes.[40]

Methods used to determine CSH include:[23]

- Water contact angle
- Binding of aliphatic acids
- Adhesion to hydrocarbons
- Two-phase partitioning
- Hydrophobic interaction chromatography (HIC).

In vitro measuring of CSH by microbes provides information on whether or not they are likely to bind to a hydrophobic dressing *in vivo*.

Binding of microorganisms

Cutisorb Sorbact (Abigo Medical AB, Askim, Sweden) is a hydrophobic coated dressing that uses the basic physicochemical principle of hydrophobic interaction to bind and subsequently remove microbes expressing CSH from wounds. In other words, only microbial cells expressing profound to moderate CSH, according to *in vitro* testing, will bind to the dressing; microbes expressing a hydrophilic cell surface will be left behind.

To study binding of microorganisms to a solid surface such as a wound dressing, we use bioluminescence to quantify the microbial ATP by referring to a species-specific standard curve. Unlike conventional culture techniques, this method also quantifies adherent microbes.[42]

Using this method, binding of *Staphylococcus aureus* Newman and *Pseudomonas aeruginosa* BD510 was measured from 0.5 minutes to 20 hours:

- Binding increased after 10 minutes
- Binding reached a maximum at 120 minutes when 10^7 out of 10^9 added *Pseudomonas aeruginosa* had bound to the hydrophobic dressing
- Bacterial counts remained stable during 20 hours for *Pseudomonas aeruginosa*, and increased only from 10^6 to $10^{6.5}$ after 20 hours for *Staphylococcus aureus*, showing that microbes multiply to a very low extent after binding to the hydrophobic dressing (data not shown).

Adding increasing numbers of bacterial or fungal cells (10^8 to $10^{9.5}$ bacterial cells and $10^{6.2}$ to $10^{7.5}$ fungal cells) showed that 10^8 cells of *Staphylococcus aureus* Newman bound and $10^{4.8}$ cells of *Candida albicans* bound, but satisfaction (when more microbial cells could not bind to the dressing) was only shown for *Candida albicans*, where the curve tends to level off. When $10^{10.3}$ cells of *Enterococcus faecalis* were added, $10^{6.7}$ cells bound, again showing no satisfaction — in other words, still more bacteria could bind (data not shown). This means that the hydrophobic dressing is likely to be able to bind more than 10^8 *Staphylococcus aureus* and more than $10^{6.7}$ *Enterococcus 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.

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Binding of a mixed culture containing *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* to the hydrophobic dressing is shown in Fig 2. This figure also shows that, on the dressing, microbes coaggregate and bind to each other as well as to the dressing.

This dressing can be used on clinical infections because it reduces the microbial load in a wound without the use of antibiotics. *In vitro* testing and our studies in a simulated wound environment show that most wound pathogens are likely to express a higher CSH in wounds than in conventional *in vitro* culture. Reduction but not elimination of microbes in a wound may stimulate wound healing.[43]

The dressing should be used on wounds with high and medium exudate levels as hydrophobic interaction is most effective in a moist environment. Furthermore, there is no risk of allergic reactions, and limited risk of spreading antibiotic-resistant microorganisms to the environment (Box 1).

The hydrophobic dressing is available in the UK, and recently has been included on the Drug Tariff.

Fig 2. Cutisorb Sorbact incubated with a mixture of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*. Microorganisms bind both to each other and to the dressing. (Raster electron microscopy)

Influence on the efficacy of the hydrophobic dressing *in vitro*

Wounds are commonly washed with disinfectants or antiseptics before dressing application.[44,45] This may reduce expression of CSH by the microbes,[44] and therefore affect the action of wound dressings. Additionally, during wound debridement, pain relief is often necessary.

If substances used in wound treatment decrease or abolish CSH, hydrophobic dressings become less effective. We therefore explored the influence of disinfectants, antiseptics and a cutaneous pain-relieving cream, lidocaine (Emla), on CSH expression. The substances used were:

- Octenidine dihydrochloride with phenoxyethanol (Octenisept, Schülke & Mayr, Norderstedt, Germany); there is no UK equivalent
- 2-propanol, 1-propanol, 2-biphenylol (Kodan, Schülke & Mayr, Norderstedt, Germany); UK equivalents are Hibisol, Manusept, Mediswab, Sterets H
- Ethacridine lactate (Rivanol, Chinosol, Seelze, Germany); the UK equivalent, Burn Aid, is no longer available
- Povidone-iodine (Betaisodona, Mundipharma GmbH, Limburg, Germany); UK equivalent is Betadine
- Hexamethylen biguanide (Lavasept, Fresenius Kabi, Bad Homburg, Germany); no UK equivalent
- Modified starch polymer with glycerol (Askina hydrogel, B. Braun Hospicare, Collooney, Ireland)
- Sodium chloride (Hypergel, Mölnlycke Health Care AB, Sweden); UK equivalents are Flowfusor, Irriclens, Irripod, Miniversol, Normasol, Stericlens, Steripod, Verso
- Lidocaine (Emla, AstraZeneca, London, UK).

Washed bacterial suspensions (10^9 cells) were incubated with the substance for 15 minutes at room temperature. CSH was measured before and after using the salt aggregation test. Of the substances studied, only Emla abolished expression of CSH. However, as expected, treatment with Askina Hydrogel decreased expression of CSH (Table 2), and so should not be used before treatment with a hydrophobic dressing.

Clinical studies

Few studies investigating the hydrophobic dressing have been published. An open study involving 31 patients with 32 infected wounds[46] (diabetic, arteriosclerotic, postoperative or post-traumatic leg

Box 1. Properties of Cutisorb Sorbact

Binds microorganisms expressing cell surface hydrophobicity
Binds bacterial toxins
Leaves non-hydrophobic microorganisms in the wound to stimulate healing
Low likelihood of spreading bacteria during a dressing change
Non-allergenic
Optimal binding capacity in a moist environment
No development of antibiotic resistance

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Table 2. Influence of wound treatments on cell surface hydrophobicity

Microbe SAT*	Octenisept	Kodan	Rivanol	Betaisodona	Lavasept	Askina hydrogel	Hypergel	Emla
Staphylococcus aureus	0.12	0.25	0.5	0.5	0.5	1	0.1	≥2
Pseudomonas aeruginosa	0.12	0.12	0.25	1	1	2	0.25	≥2
Candida albicans	0.25	0.12	0.5	1	0.1	0.5	0.1	2

Washed microbial cells (10^9 cells) were incubated with the substance for 15 minutes at room temperature.
* Salt aggregation test (SAT) values are presented as a numerical value of the lowest concentration of ammonium chloride in which visible aggregation occurs; therefore, the lower the value, the more pronounced the cell surface hydrophobicity. This was measured before and after incubation. The original SAT value was 0.5

ulcers, and ulcerated leukaemic infiltrates) and another study[47] comprising 12 patients with infected wounds (pressure ulcers, burns and diabetic wounds) that did not heal during conventional treatment (cleansing, compression bandaging of venous leg ulcers, systemic antibiotic treatment and mobilisation) have been published. Results of the former show that signs of infection disappeared during treatment with the hydrophobic dressing in 69% of patients and remained unchanged or deteriorated in 31%.[46] In the latter study the chronic wounds healed following part-skin transplantation and use of the hydrophobic dressing over a six- to seven-week period.[47]

In 1990 we undertook a study on three patients with chronic leg ulcers treated with the hydrophobic dressing and compression therapy for four weeks.[48] The dressing reduced the bacterial load and pus secretion in all three patients. Quantitative bacterial cultures were taken twice weekly, nurses performed a clinical estimation of wound healing five times a week and computerised image analysis was undertaken three times a week. Visual estimation by a trained nurse was a satisfactory method of estimating cleansing rate and wound healing. However, computerised image analysis may be a more objective and faster method of estimating healing.

Box 2. Summary of the main findings

Microbes that express cell surface hydrophobicity (CSH) — that is, are water repellent — are likely to bind to a hydrophobic dressing

Cutisorb Sorbact, a dressing with a hydrophobic coating, binds and removes from wounds microbes expressing CSH

Use of the dressing may reduce the microbial load in a wound

The hydrophobic dressing should be used in wounds with high and medium exudate levels as hydrophobic interaction is most effective in a moist wound environment

In a prospective randomised study comparing the hydrophobic dressing with daily cleansing using 0.5% chlorhexidine in 70% ethanol on umbilical cords, the hydrophobic dressing slowed down the bacterial digestion of the umbilical cord leading to later separation, although no other differences were found between the two regimens.[49]

In a recent study[50] involving 33 patients with infected pressure ulcers, those treated with the hydrophobic dressing (19 patients) showed a significant improvement in the colour of the ulcer bed (94.7% versus 71.4%, p=0.034), increased cell debris solution (52.6% versus 42.8%, p=0.048), a reduction of perilesional erythema and oedema (78.9% versus 57.1%, p=0.028) and a reduction in the number of treatment days (9 ± 2 versus 11 ± 2, p=0.041).

The control group (14 patients) was treated with mobilisation, appropriate nutrition, broad-spectrum antibiotics, topical iodine solution, collagenase and medicated plaster (an unspecified hydrocolloid). In the study group the hydrophobic dressing was used instead of the medicated plaster.

An important finding was that, in five patients who could not be given systemic antibiotic treatment because of renal impairment, treatment with the hydrophobic dressing achieved comparable results to those for systemic broad-spectrum antibiotics plus the hydrophobic dressing.

Conclusion

The pathogenesis of acute and chronic skin and wound infections is multifactorial and influenced by the immune and nutritional status of the patient, the underlying vascular disease, diabetes, smoking status and the virulence properties and load of colonising microbes.[3,10,45,51] Reducing the microbial load is therefore a hallmark of treatment. However, due to the complications associated with antibiotics, particularly those with a broader spectrum, there is a need to develop non-antibiotic management strategies as an alternative or even adjunct to a decreased antibiotic treatment.

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A hydrophobic dressing is a non-allergic, non-toxic alternative for reducing the microbial load in open wounds without enhancing nosocomial spread, and can reduce the use of antibiotics. Hydrophobic microorganisms bind to the dressing, preferably in a humid environment, and are removed with it. They multiply to quite a low extent when absorbed in the dressing, and may not produce extracellular toxins and enzymes. Mechanisms of resistance to hydrophobic interaction have not been described.

We are currently comparing adhesion on the hydrophobic dressing of microbes grown in wound-like conditions with that for alginates and different dressings. Clinical studies are also under way comparing the hydrophobic dressing with different dressings. A silver-containing dressing may initially be superior, but it is only a matter of time before we see the emergence of resistance to silver among Gram-positive bacteria. Indeed, *Staphylococcus aureus* commonly express resistance to other metals, such as mercury. ■

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