Using PHMB antimicrobial to prevent wound infection

Post-operative wound infections may result in delayed healing, extended hospital stay and increased costs. The increase in antibiotic-resistant bacteria mitigates against the prophylactic use of antibiotics. An effective alternative is the use of antiseptics that are less likely to generate resistance. AMD™ wound dressings use polyhexamethylene biguanide (PHMB) which has a low toxicity for wound cells and is effective in killing antibiotic-resistant bacteria. This paper reviews the evidence for the efficacy and cost-effectiveness of AMD dressings in the prevention of surgical site infections when routinely used in standard wound care protocols.

KEY WORDS
AMD™ wound dressings
Cost-effectiveness
MRSA
Polyhexamethylene biguanide (PHMB)
Wound infection

It has been estimated that 15% of patients who have elective surgery and 30% of patients whose surgery was classified as ‘contaminated’ suffer from surgical site infections (SSIs) (Bruce et al, 2001). Patients with SSIs will have extended hospital stays, they will have a greater risk of morbidity and mortality, and treatment costs will be increased (Kirklan et al, 1999). Wound management programmes that reduce the incidence of SSIs will improve patient outcomes and reduce the cost of treatment.

It is almost inevitable that both surgical wounds and chronic wounds will become contaminated to some extent with bacteria (Kingsley, 2001). If allowed to proliferate, increasing numbers of bacteria will develop into critical wound colonisation or infection. If inappropriately managed, the consequences for the surgical wound may be delayed healing, wound breakdown and transfer of bacteria to the environment. However for many chronic wounds where bacterial numbers can maintained at low levels healing can be achieved without infection developing (Bowler, 2001).

Against a background of increasing bacterial resistance to antibiotics and the fact that wound bacteria can delay healing, it is necessary to prevent the proliferation of bacteria in wounds while at the same time constraining the prophylactic use of antibiotics. Antiseptics provide an alternative antibacterial strategy and because they affect multiple targets are less likely to generate resistance (Gilbert, 2006) when used prophylactically over a prolonged period. The antiseptic polyhexamethylene biguanide (PHMB) has been in general use for about 60 years with no evidence of the development of resistance. It exerts little toxicity and has found applications as diverse as treatment of eye infections (Larkin et al, 1992) and sanitising swimming pools.

PHMB has now been introduced into wound management in a range of dressings containing 0.2% of the antibacterial agent. The dressings protect against the development of wound infection by decreasing the bacterial load in the dressing and bacterial penetration through the dressing. In this way they may help to prevent critical colonisation and infection and may allow healing to progress towards wound closure. They have been designed as a low-cost prophylactic antibacterial measure that simply replaces existing products without changing the existing clinical protocols.

This article reviews the interaction of bacteria in the healing process, the challenges of antibiotic resistance in relation to antibacterial prophylaxis and how PHMB dressings can be used to provide a cost-effective, simple, prophylactic measure to decrease the impact of infection on wound healing.

The impact of bacteria on healing
The majority of dermal wounds progress through a well-defined process of healing to achieve wound closure. Bacterial infection is one among a number of factors that may delay healing or result in the development of a chronic non-healing wound. For surgical wounds a relationship can be demonstrated between the development of wound infection and prolonged healing times. By comparing initial wound size and time to heal a direct relationship can be demonstrated and expected healing time can be calculated (Marks et al, 1983). If wound infection occurs this relationship does not hold and a reduction in the rate of wound closure is found. Wounds exhibiting the highest bacterialcounts take longer than predicted to heal.

Bacteria influence the healing process by producing toxins and proteases that...
may interact directly with the cells in the wound bed or indirectly by releasing endotoxins to stimulate an excessive inflammation that interferes with the healing process. The sum total of these activities is described as bacterial virulence with some organisms being more virulent than others. The potential impact on healing can also be contributed to by the number of organisms present and, for the majority of organisms, it is considered that >10⁵ organisms per gram of tissue will impede healing (Robson, 1997).

The flora of open wounds healing by secondary intention is polymicrobial and the outcome of healing may be considered to be a balance between the negative factors exerted by increasing numbers of organisms as they proliferate and the ability of the host’s immune response to prevent proliferation. Even a superficially clean environment will be contaminated with a range of bacteria and wound tissue provides such a good medium for bacterial growth it is highly likely that all wounds are contaminated to some extent with bacteria. This has led to the concept of a bacterial continuum (Kingsley, 2001) (Figure 1) that describes the effect of increasing bacterial numbers in wound tissue. After surgery a sterile wound rapidly becomes contaminated with bacteria leading to colonisation of the wound tissue. At this level of bacterial numbers the host immune response can keep the bacteria in check. However, should the host response fail to prevent bacterial proliferation, colonisation will progress to critical colonisation and possible outright infection resulting in delayed healing and potential wound deterioration.

Chronic wounds — diabetic foot ulcers, venous leg ulcers and pressure ulcers — are also subject to the concept of an infection continuum. However, by definition, they last longer than most surgical wounds and with a longer standing exposure to bacterial flora in the skin and the general environment, have a greater chance of being colonised or critically colonised. A treatment strategy can be devised for wound infection on the basis of microbiological analysis and the observed clinical signs of infection (Cutting and Harding, 1994). A critically colonised wound will not exhibit the classic symptoms of infection, and bacteriology may be of little help because of the complex interactions that may occur between the numbers and variety of bacteria that can be isolated from chronic wounds (Bowler et al, 2001). Bacteriology alone will not therefore assist in defining the bacterial status of a chronic wound and needs to be considered in the context of an overall assessment of the patient and their wound status (Cooper, 2005). Identifying where a wound lies on the infection continuum is difficult but important to the progression towards healing as reducing the bacterial numbers within chronic wound tissue is considered an essential step towards preparing the wound for healing (Schultz et al, 2003).

For healing to proceed it is important to prevent the establishment of critical colonisation and infection. For both acute and chronic wounds this may involve prevention of progression to colonisation or the management of an established critical colonisation. For surgical wounds in particular the former is desirable as prevention, if achievable, will be easier than treatment. Prevention of wound bacterial contamination, is desirable but probably unachievable. Increasing awareness of the impact of colonisation on healing and the difficulties of defining the microbiological status of a wound will therefore lead to an increasing prophylactic use of antimicrobial agents. The increasing incidence of antibiotic resistance directs the clinician to use topical antimicrobial agents where resistance has not so far proved to be an issue. A number of such agents are available and are of particular value where they can be incorporated into wound dressings for localised delivery to wound tissue.

**Antibacterial strategies**

The evolution of antibiotic resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and the clinical challenge they pose to wound management has been well publicised (Guyot and Layer, 2006). Resistance is an inevitable consequence of the
widespread use of an antibiotic as selective evolutionary pressures are placed on those organisms that are resistant to its action. MRSA is most prevalent in surgical wards and long-term care facilities where indwelling devices are used (Coia et al, 2006). Guidelines for the management of MRSA include the avoidance of the inappropriate or unnecessary use of antibiotics to reduce the likelihood of emergence and spread of resistant strains (Coia et al, 2006). Thus the use of antibiotics to prevent wound colonisation is undesirable.

Antibiotics were originally defined as naturally occurring antibacterial compounds produced by microorganisms such as fungi although some are now chemically synthesised. An alternative is the use of purely synthetic antimicrobial agents that differ in mode of action from antibiotics and do not appear to generate resistance. A number of agents such as silver (Thomas and Mc Gabbin, 2003) and iodine (Selvaggi et al, 2003) have been incorporated into wound dressings and other devices such as urinary catheters (Davenport and Keeley, 2005) for prophylaxis against urinary tract infection. Both iodine and silver have a long history as antibacterial agents with silver dollars reputedly being used to maintain the freshness of drinking water by early American settlers in the 1800s.

Silver and iodine both exert antimicrobial activity by chemically denaturing proteins such as enzymes and membrane proteins leading to cellular death. They are thus biocides or antiseptics rather than antibiotics, whose mode of action differs in that they lethally interfere with bacterial metabolism rather than denaturing proteins. Silver is often used in the care of burns yet little evidence has been found of emerging resistance (Percival et al, 2005). An undesirable consequence of biocidal activity is that it is not restricted to bacteria, and silver can be toxic for cells that are essential to the healing process such as fibroblasts (McCaulley et al, 1989) and keratinocytes (Ziegler et al, 2006). The toxicity of these agents has to be balanced against their antibacterial properties when formulating wound treatments.

**Antimicrobial peptides**

Naturally occurring antimicrobial peptides (AMPs) were discovered about 25 years ago and have been found to be produced by the majority of living organisms. About 600 different AMPs have been identified. They have a broad spectrum of activity against bacteria, viruses and fungi and have been suggested as therapeutic alternatives to antibiotics (Hancock and Sahl, 2006). AMPs are positively-charged molecules that bind to bacterial cell membranes and induce cell lysis by destroying membrane integrity. This mechanism of cell killing is similar to that found with antibiotics such as the penicillins and cephalosporins, which interfere with cell wall synthesis to cause cell fragility and lysis. They can be produced by many cells at the wound site, such as keratinocytes and inflammatory neutrophils, where they are considered to play a role in protection against infection (Sorensen et al, 2003).

A number of synthetic compounds with the antimicrobial activity of AMPs have been produced as alternatives to conventional antibiotics. One of these — polyhexamethylene biguanide (PHMB) — is structurally similar to AMPs. This allows it to insert into bacterial cell membranes and kill bacteria in the same way as AMPs. PHMB has been demonstrated to block *Pseudomonas aeruginosa*-induced infection and prevent its degradation of wound fluid and skin proteins in vitro (Werthen et al, 2004).

**Resistance and infection control**

PHMB can be considered an antiseptic rather than an antibiotic. Antiseptics have been in use much longer than antibiotics yet resistance to antiseptics is less of a problem. They have multiple targets of action which render bacteria less likely to generate resistance mechanisms (Gilbert, 2006). However, bacteria can protect themselves by pumping some antiseptic agents out of the cell using ‘efflux pumps’. PHMB acts to kill bacteria by integrating into the cell membrane and reorganising the membrane structure (Gilbert, 2006). This structural change prevents the cell from pumping PHMB out of the membrane and bactercidal concentrations are maintained in cell.

**PHMB in wound management**

PHMB has been incorporated into a new range of wound management products that are designed to be integrated into standard wound care protocols by simply replacing existing products. The AMD™ range of infection control dressings (Tyco Healthcare, Basingstoke) is impregnated with 0.2% PHMB. The product range includes Telfa™ AMD non-adherent wound dressings, Kerlix™ AMD gauze dressings and Excilon™ AMD drain and intravenous sponges.

**Antibacterial activity of AMD™ dressings**

The PHMB component of AMD dressings can kill a diverse range of bacteria and the fungus *Candida albicans* in a zone of inhibition assay (Shah, 2000). In this study, assay discs cut from the dressing were overlaid onto bacteria growing on agar in petri dishes. Antibacterial agents in the dressing can diffuse out into the agar and bacterial killing can be seen in clear zones around the dressing (Table 1).

The larger the zone of inhibition the more effective the PHMB is in preventing growth of a particular organism. Control dressings without PHMB did not show any bacterial killing (zone of 0mm). The dressing containing 0.2% PHMB was effective against all the organisms tested. A second study (Lee et al, 2004) using a

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone of inhibition (mm)</th>
<th>Kerlix™</th>
<th>Kerlix™</th>
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</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>2.01</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>0.43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>2.10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>0.83</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>S. coagulase</em></td>
<td>1.55</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>0.62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>S. marcescens</em></td>
<td>1.37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>1.62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>1.97</td>
<td>0</td>
<td>0</td>
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* Containing 0.2% PHMB
** Control – no PHMB (Shah, 2000)
slightly different methodology to assess growth inhibition confirmed these initial results and showed it to be able to kill an extended range of bacteria. This study also demonstrated that AMD dressings retained residual antimicrobial activity for four days when re-challenged with fresh bacteria on a daily basis.

PHMB is effective in standard in-vitro tests against antibiotic resistant organisms often found in wounds such as MRSA (Case, 2000a) and also against other organisms such as vancomycin resistant Enterococcus faecalis (Case, 2000b). Kerlix AMD gauze dressings were inoculated with the test organism and sampled at 24 and 48 hours of incubation. No growth of either organism could be detected in the dressing containing PHMB.

While killing bacteria in wound tissue beneath the dressing is important for healing, it is vital for infection control to prevent the transfer of bacteria from the wound to the clinical environment. As wound fluid is absorbed, bacteria will migrate into a dressing. Here the bacteria potentially may evade the host immune system allowing them to proliferate. The ability of AMD dressings containing PHMB to prevent bacterial contamination has been demonstrated in a human volunteer study (Reitsma and Rodeheaver, 2000). A standard gauze dressing was taped to the skin of the volunteer; inoculated with a culture of penicillin-resistant S. epidermidis and the gauze covered with an occlusive film dressing. After 24 hours the gauze was removed and bacteria contaminating the skin beneath the dressing and surviving within the dressing assessed. No bacteria could be cultured from the skin beneath the dressing containing PHMB or within the dressing itself. In contrast, the control gauze allowed bacteria to be transferred to the skin and to survive within the gauze.

Repetition of this experiment in an animal wound model demonstrated that the AMD gauze dressing performed equally well when acting as a barrier to prevent wound invasion by P. aeruginosa (Cazzaniga et al, 2000). By comparison to the control dressing AMD gauze reduced the number of bacteria that gained access to the wound bed by 10,000 to 100,000 fold and also inhibited bacterial proliferation within the dressing over a 72-hour period of wear time.

Clinical efficacy of AMD dressings

As mentioned earlier the toxicity of some antiseptics for cells within the wound has to be balanced against the beneficial effects of their antimicrobial activity. Treatment of split-thickness dermal wounds demonstrates that toxicity is not an issue for dressings containing 0.2% PHMB. No difference in the rate of healing could be detected between wounds dressed with saline-moistened gauze containing 0.2% PHMB and control wounds treated with saline-moistened plain gauze (Davis et al, 2002). Both groups of wounds exhibited accelerated healing rates compared with wounds exposed to dry air:

The experimental data available indicate that AMD dressings exert antibacterial activity with no deleterious effect on healing. The long-term use of PHMB for other applications (Gilbert, 2006) with no observed resistance suggests that this is unlikely to happen when its usage is extended to wound management. These combined properties indicate that the AMD dressings would be ideal for reducing the risk of wound infection while reducing the need for antibiotic use. Examination of the bacterial flora in wounds treated with these dressings indicates that they can have a marked impact on contaminating bacteria.

Infections are frequently found at tracheostomy sites following prolonged intubation (Brook, 1987). Such wounds managed with Excilon AMD drain sponge containing PHMB demonstrated a marked reduction in frequency of isolation of organisms most commonly found in these wounds (Motta and Triglia, 2005). In this study the wounds of five subjects were treated with five daily changes of the PHMB dressing and a control group of five was treated with a non-PHMB dressing. Wounds were swabbed daily and the presence or absence of four specific wound pathogens were determined. The results (Table 2) indicated a marked decrease in frequency of isolation of MRSA and P. aeruginosa when treated with the drain sponge containing PHMB.

A further study of 24 patients with wounds that required packing, delayed surgical closures, pressure ulcers and diabetic foot ulcers investigated the effect of Kerlix AMD on bacteria found in the wound (Motta et al, 2004). The results demonstrated that PHMB produced a larger reduction in the total number of bacteria and a reduction in the number of species present compared with the control dressing, which contained no antibacterial agent. The decrease in bacterial bioburden was accompanied by a marked improvement in healing in the group treated with the PHMB dressing.

A number of case studies have demonstrated the value of PHMB in treating infected wounds. Seven days of treatment of an infected surgical site following coronary artery bypass with Kerlix AMD and no antibiotics converted a wound that was 100% yellow with a purulent discharge to one with 100% red granulation tissue within five days (Hutton, 2005). Within seven days wound area decreased from 5.5 cm² to 1 cm² and the patient was discharged from hospital within a further seven days. In the treatment of 16 patients with pressure ulcers for a mean 14.7

Table 2.
Frequency of isolation of wound pathogens: PHMB compare with non-PHMB dressing

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of days pathogen present</th>
<th>PHMB dressing</th>
<th>Control – no PHMB</th>
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<tbody>
<tr>
<td>MRSA</td>
<td>3</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>E. cloacae</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Maximum number of days possible for each organism = 25 (5 patients tested 5 times) From: Motta and Triglia, 2005
days, the same product induced a mean 23% decrease in wound size with wound appearance improving in 69% of ulcers (McCullin, 2005).

Surgical site infections and the cost-effectiveness of using AMD dressings

Patients who develop surgical site infections (SSI) remain inpatients longer than those who do not develop an infection and this results in an increase to the cost of treatment (Kirkland et al, 1999). They are more likely to spend time in intensive care units and twice as likely to die. Thus wound management programmes that reduce the incidence of SSIs will improve patient outcomes and reduce the cost of treatment.

Although vascular surgical sites have a high-risk of infection, the substitution of AMD dressings for non-medicated dressings in the treatment of these wounds over five years helped to produce a year-on-year decrease in SSIs in a study carried out in the US (Penn et al, 2006). Their incidence fell from 4.6% before introduction of the PHMB

![Graph showing percentage of infected surgical sites over years](image)

**Figure 2:** Penn et al (2006) studied patients with vascular surgical incisional wounds at risk of infection. Regular non-medicated gauze dressings were replaced with 0.2% PHMB dressings. Postoperatively PHMB dressings were used until the surgeon discontinued dressings or the patient was discharged.

**AMD Gauze Case Study**

**Case A**

This elderly gentleman developed a grade 4 sacral pressure ulcer three months before the first image was taken. The wound had been debrided and granulation had developed. However, a sudden deterioration was noted in both the wound and the patient’s general condition.

**Figure 1 (day 1)**

In Figure 1 it is clear that there is exposed bone at the wound base. Following radiological examination a diagnosis of osteomyelitis was arrived at and the patient was commenced on intravenous antibiotics. As the patient’s overall condition deteriorated so the wound began to deteriorate and new necrotic tissue developed.

**Figures 2 and 3**

AMD gauze was used to pack the wound as part of a topical negative pressure therapy (Vista Pump, Talley Medical/Smith and Nephew). In Figures 2 and 3 the gauze can be seen pre- and post-application. In Figure 3 it can be seen that the gauze has remained whole.

**Figure 4 (Day 30)**

After 27 days of nutritional, antibiotic and wound therapy the wound can be seen to have stabilized and the necrotic tissue removed with the growth of granulation tissue evident across the previously exposed bone.

**Summary**

In this case AMD gauze in the form of the Tyco Magic Sponges have been used in conjunction with topical negative pressure therapy to deslough necrotic tissue, promote granulation and prevent the development of soft tissue infection. This has been achieved and the therapy continues.
dressings to 0.4% after five years routine use (Figure 2) with cost savings over this period calculated to be US$876,176. This was achieved by dressing substitution alone with no other changes to treatment protocols documented by the authors. In a 6-month period at the Yuma Regional Medical Centre, USA the use of non-antimicrobial gauze dressings was replaced by the Kerlix AMD dressing on a routine basis (Beneke and Doner, 2005). With the exception of the surgical service, all staff were blinded to the switchover. SSIs were monitored prior to the switchover and during the six-month study period. In the 12-month period before the study 42 infections complicated 9,114 surgical cases. During the study, SSIs decreased from 23 in the historical 6-month control period to 11 during the period of AMD gauze use — a reduction of 52%. Thus by simply exchanging the standard non-antimicrobial gauze for gauze containing PHMB the medical centre reduced nosocomial SSIs, improved patient outcomes and generated significant cost savings. On the basis that the attributable cost to treat an SSI was US$15,646, the authors estimated gross savings of US$187,752 by avoiding 12 SSIs. The net saving after accounting for the increased cost of the PHMB dressing was US$171,537.

Discussion

We live in an environment where every surface harbours potentially pathogenic bacteria. The skin provides an effective barrier to bacterial ingress preventing their access to subcutaneous tissue which can act as an ideal environment for their growth. Breach of the dermal barrier does not necessarily lead to infection as the host’s immune system can effectively limit bacterial proliferation. However, in situations where the bacterial load is too great or the immune response is compromised by trauma or other co-morbidities, bacteria may establish themselves within wound tissue and impact on the healing process.

It is almost inevitable therefore that wound tissue will be exposed to bacterial contamination and that some of the organisms will be resistant to antibiotics (Nixon et al, 2006). Given the economic cost and reduction to the patient’s quality of life caused by wound infections it is desirable to prevent bacterial contamination that progresses to critical colonisation or infection that will delay healing and discharge from hospital. For antibiotic resistant organisms there are other antibiotics to which the organism may be susceptible but their widespread use leads to bacteria with multiple resistance (Perwaz et al, 2007). Clearly then it is desirable to decrease wound colonisation and antibiotic usage.

Against a background of growing antibiotic resistance an alternative to antibiotic prophylaxis is required for surgical wounds. The incorporation of PHMB-containing dressings into standard post-operative treatment protocols allows for antibacterial prophylaxis without the risk of adding to the challenges of resistance. PHMB is a synthetic analogue of naturally-occurring antibacterial peptides. It has been used for 60 years with no evidence of bacterial resistance developing. Analysis of wounds treated with AMD dressings that contain PHMB shows that it decreases bacterial loading and prevents progression to critical colonisation and wound infection. The range of PHMB dressings, drain and IV sponges can be incorporated into clinical practice with no modification to standard protocols of care.

In one trial over a five-year period a 91% reduction in vascular surgical site infections has been observed (Penn, 2006). A detailed cost-effectiveness study over a six-month test period also found the reduction in SSIs created considerable cost savings (Beneke and Donor, 2005). The relatively low cost of AMD PHMB-containing dressings makes them a cost-effective option for prophylactic prevention of SSIs. The cost savings generated by avoiding even one or two wound infections are sufficient to pay for the additional cost of using AMD dressings on all patients post-operatively. In the view of one investigator (Motta et al, 2004) ‘substituting a gauze impregnated with PHMB for regular gauze is a simple solution that does not require a change in existing clinical protocols’.

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