

# PHMB: an effective antimicrobial in wound bioburden management

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## Abstract

The effective management of bacterial bioburden is an essential element of wound care. Recent years have seen the increased use of topical antimicrobial dressings to control colonisation and infection, yet there is concern that some may inhibit wound healing and may have systemic sequelae (World Union of Wound Healing Societies (WUWHS), 2008). This article focuses on the safety and effectiveness of PHMB, an antimicrobial compound that is relatively underused in the UK, and argues that it is an effective option for the management of bacterial colonisation and infection.

**Key words:** PHMB ■ Polihexanide ■ Wound infection ■ Bioburden ■ Antimicrobial dressing

Wound infection results from the complex interaction between an individual's immune system, the condition of the wound and the number and virulence of bacteria present (Thomson and Smith, 1994; Dow, 2001; Dowsett et al, 2004; Stotts, 2004; Best Practice Statement, 2011). Underlying medical problems such as poor blood supply, hypoxia and metabolic disorders are also contributing factors (Hunt and Hopf, 1997). If bacterial species are allowed to flourish, the states of colonisation, critical colonisation, or wound infection, as outlined in the wound infection continuum (Kingsley, 2001; White et al, 2001), will occur. This is not only costly to the patient, but also has serious financial and legal implications for healthcare providers. Reducing the risk of infection through effective management of wound bioburden is thus an essential aspect of wound care (Shultz et al, 2003; World Union of Wound Healing Societies (WUWHS), 2008).

## Effects of bioburden

Although there are no clinical studies on the impact of specific microorganisms on the healing process, clinicians agree that infection causes serious delays in healing as a result of the expression of bacterial virulence factors (Schlüter and König, 1990; Thomson, 2000). These factors are believed to damage the wound bed in a variety of ways:

- Microorganisms consume nutrients and oxygen required for wound repair

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- Protease virulence determinants (e.g. elastase) damage the extracellular matrix
- White cell function is impaired by the release of short-chain fatty acids produced by anaerobes. Endotoxins stimulate production of interleukins: tumor necrosis factor and matrix metalloproteinases (MMPs)
- Free oxygen radical production increases
- Imbalances occur between MMPs and tissue inhibitors of metalloproteinases (TIMPs)
- Fibroblast production is decreased or delayed, collagen disorganised and scar strength decreased.

Additional consequences for the patient may include increased pain and discomfort, inconvenience, and life-threatening illness. Adverse consequences for the healthcare system may be extended hospital stay, heightened risk of litigation and increased treatment costs incurred by extra antibiotic and dressing usage, as well as extra staff costs.

## Approaches to bioburden control

Spreading infection in an individual has serious implications for patient wellbeing and acts as a pathogenic reservoir, increasing the risk of cross-contamination. Accurate differential diagnosis and treatment with appropriate systemic antibiotics is essential (European Wound Management Association (EWMA), 2006; WUWHS, 2008). Topical antibiotics, which are linked to bacterial resistance, should be avoided (WUWHS, 2008). Adjuvant topical antimicrobial dressings may be used to help reduce the wound bioburden (EWMA, 2006; WUWHS, 2008).

However, critical colonisation and localised, subclinical infection remain an issue, and are significant contributors to prolonged wound healing (Edwards and Harding, 2004; Warriner and Burrell, 2005). In recent years, topical antimicrobial agents have become the first line of treatment in managing bacterial burden, particularly in chronic wounds (White et al, 2001; Cooper, 2004). Their prophylactic use remains controversial, but can be justified in immunocompromised individuals or where there is a high risk of infection. Current opinion suggests that the ideal antimicrobial is:

- Associated with minimal systemic absorption
- Effective against likely contaminants and pathogens
- Fast-acting, with prolonged residual activity after a single dose
- Inexpensive
- Incapable of promoting bacterial resistance
- Non-carcinogenic and non-teratogenic (i.e. does not cause DNA damage, which could result in carcinoma or foetal abnormality) to host cells
- Non-toxic
- Widely available (Drosou et al, 2003).

Antimicrobial dressings should be capable of bactericidal activity against both planktonic bacteria and those in biofilm colonies. In addition, the active substances must be contained in a delivery system that would normally, although not exclusively, be a contact dressing, which can be left in contact with the wound for 12 hours or more and remain active for the duration of wear time (Best Practice Statement (BPS), 2011).

Until relatively recently, the main antimicrobial compounds used by clinicians in the UK contained silver, iodine, chlorhexidine, and honey. The rapid rise in the availability of antimicrobial products is testament to the growing significance placed on clinical bioburden-control. These are now commercially available in a number of dressing formats. But, despite their widespread use, there is concern regarding their indiscriminate and prolonged application (BPS, 2011). In some cases, there are specific issues relating to their use, and these will be covered throughout the following sections of this article.

### Silver

Silver-based products are extensively used in wound care (Klasen 2000a, 2000b; Demling and De Santi, 2001; Clarke, 2003), with skin discolouration (argyria) and irritation being the only visible side effects (White, 2002). It is thought that silver has a number of antimicrobial modes of action (Thurman and Gerba, 1989; Russell and Hugo, 1994). However, questions have been raised over the long-term use of these dressings, especially in infants (Denyer, 2009a; 2009b). Recently, there have been concerns about silver toxicity (Parsons et al, 2005; Burd et al, 2007), and the systemic uptake and deposition of silver in organs have been noted in a number of studies (Wan et al, 1991; Denyer, 2009a; Wang et al, 2009). To date, the pathological consequences of this are unknown. Added to this, there are fears about the emergence of silver resistance (Percival et al, 2005; Loh et al, 2009). It would seem that, in academic circles at least, questions exist over its continued widespread clinical use. This has been further enhanced by questions about its cost-effectiveness (Bergin and Wraight, 2006; Chaby et al, 2007; Michaels et al, 2009), which in some areas has led to product restrictions.

### Iodine

Iodine-based products have been used in wound care for many years. Like all antiseptics, iodine simultaneously affects multiple sites in microbial cells, resulting in cell disruption and death (Cooper, 2007). However, not only have its antimicrobial efficacy and chemical stability been debated, but also its toxicity to host tissues and the ensuing effect on patient comfort (Kramer, 1999; Wilson et al, 2005). It has been found that providone-iodine is not as effective as some other biocides in eradicating *Staphylococcus epidermis* within in vitro biofilms (Presterl et al, 2007). Cadexomer iodine provides sufficient iodine for biofilm suppression without causing significant damage to the host (Akiyama et al, 2004; Rhoads et al, 2008) but pain has been reported as a side effect of its use (Hansson, 1998).

### Honey

In recent years, there has been resurgence in interest in honey-based products for bioburden management (White, 2002). The

exact mode of action of honey is not yet fully understood. However, it is hyperosmolar and, thus, restricts the availability of environmental water to bacteria and other organisms (Molan, 2001), leading to cell disruption and death. However, this effect is lessened as the honey becomes more diluted by wound exudate (Molan, 1999). A secondary action is the release of hydrogen peroxide as the honey is diluted by exudate (Molan and Betts, 2004). However, some honeys, particularly *Leptospermum* or manuka varieties, have been found to retain their bactericidal properties even without the presence of hydrogen peroxide (Cooper et al, 2002a; 2002b), which is thought to be associated with a phytochemical component (Karayil et al, 1998; Molan, 2002). The antibacterial properties of honey, therefore, vary according to its source.

### Chlorhexidine

Chlorhexidine has been used clinically for about 50 years (Russell, 2002). It is active against gram-negative organisms such as *Pseudomonas aeruginosa* and gram-positive organisms such as *Staphylococcus aureus* and *Escherichia coli*, although methicillin-resistant *Staphylococcus aureus* (MRSA) resistance has been recorded (Cookson, 2000). Chlorhexidine appears to be relatively safe, with little effect on the healing process. However, results from studies are insufficient to draw conclusions about its use on open wounds. In addition, there are concerns about the safety of additives frequently used in chlorhexidine-based preparations to modify their handling properties. More human trials need to be performed to assess its efficacy and long-term safety (White et al, 2001; Main, 2008).

### The dilemma

Careful and objective review of the literature suggests that the use of many antiseptics in wound management must be subject to a risk-benefit assessment of possible local toxicity and beneficial antibacterial action (Brennan and Leaper, 1985). In short, it is advised that, before use, the beneficial antimicrobial effects and bioavailability should be weighed against any possible cellular toxicity (Wilson et al, 2005).

Given the widespread availability of antimicrobial products, factors likely to influence selection include:

- Clinician familiarity
- Availability, cost and reimbursement issues
- Ease of use and implications for pattern of care
- Efficacy and safety (WUWHS, 2008).

As there appears to be concern about the safety and efficacy of commonly used and familiar antimicrobial products, clinicians need to cast the net wider and search for alternative safe, effective and efficient products.

### PHMB

The antiseptic agent polyhexamethylene biguanide (also known as polihexanide or PHMB) has been used for over 60 years in a wide range of applications from swimming pool sanitisers to preservatives in cosmetics and contact lens solutions. In Europe, it has been available as a wound irrigation fluid for some time.

PHMB is a fast-acting biguanide compound composed of a synthetic mixture of polymers. The compound is structurally similar to the antimicrobial peptides (AMPs) produced by

many cells within the wound, such as keratinocytes and inflammatory neutrophils, where they are thought to help protect against infection (Sorensen et al, 2003; Ousey and McIntosh, 2009). AMPs have a broad spectrum of activity against bacteria, viruses and fungi, inducing cell death by disrupting cell membrane integrity (Ikeda et al, 1983; Ikeda et al, 1984; Moore and Gray, 2007;).

The structural similarities to AMP mean that PHMB can infiltrate bacterial cell membranes and kill bacteria in a similar way (Moore and Gray, 2007). However, PHMB does not interfere with the proteins that make up animal cell membranes. It, therefore, has a specific antimicrobial action that does not affect animal cell integrity. It is thought that, once it has adhered to the target cell membranes, PHMB causes them to leak potassium ions and other dissolved ions from the cytoplasm (Davies et al, 1968; Davies and Field, 1969; Broxton et al, 1984a; Yasuda et al, 2003; Gilbert, 2006), resulting in cell death. PHMB has an effect on both planktonic bacteria and those in biofilms (Seipp et al, 2005; Pietsch and Kraft, 2006; Harbs and Siebert, 2007). Its action on the bacterial cell membrane also means that the efflux pump (a mechanism used by many bacterial cells to remove toxins) is unable to remove the antiseptic, so intracellular bactericidal concentrations are maintained (Kingsley et al, 2009). Once inside the cell, there is evidence that PHMB binds to DNA and other nucleic acids, suggesting it may also damage or inactivate bacterial DNA (Allen et al, 2004).

Studies have shown that PHMB is effective in vitro, while clinical studies indicate it has a broad spectrum of activity, including against human immunodeficiency virus (HIV) (Werthen et al, 2004; Krebs et al, 2005). Testing has demonstrated that exposure to PHMB causes viral cells to clump together, forming aggregates. This prevents invasion into the host cells, making PHMB a potent antiviral treatment in wound care (Pinto et al, 2009).

However, studies have shown that the product is safe in clinical use. Schnuch et al (2000; 2007) demonstrated that in trials including 3529 patients, skin sensitisation to PHMB is low (approximately 0.5%), even when the tested concentrations (2.5% and 5%) were 5–10 times that normally used in wound applications. Comparative tests of PHMB's biocompatibility (measurement of an antiseptic agent's activity in relation to its cytotoxicity) against other commonly used therapies have demonstrated its superiority to chlorhexidine, povidone-iodine, triclosan, silver and sulphadiazine (Müller and Kramer, 2008). In addition, no known resistance to PHMB has been reported, most likely owing to its rapid and non-specific bactericidal activity (Moore and Gray, 2007).

### PHMB-based wound care

Recently, PHMB has been successfully incorporated into a range of wound products with various formats. These products offer the clinician alternative methods of using PHMB in bioburden management. These products include:

- Solutions and gels (e.g. Prontosan® wound irrigation solution and wound gel (B Braun Medical Ltd), which contains 0.1% solution of PHMB)
- Non-adherent bacterial-barrier products (e.g. the AMD™ range of infection control dressings (Covidien), which

are impregnated with 0.2% PHMB. The product range includes Telfa™ AMD non-adherent wound dressings, Kerlix™ AMD gauze dressings, Excilon™ AMD drain intravenous sponges) A new addition is Kendall AMD Antimicrobial Foam, which has a higher percentage of PHMB impregnated 0.5%. These are all class IIb products

- Biocellulose PHMB-donating dressings (e.g. Suprasorb® X+PHMB (Activa Healthcare, a Lohmann & Rauscher company), which incorporates 0.3% PHMB. These are all class III products.

In current classification dressings on the market (EU classification IIb), the PHMB molecule has been chemically bound to the base material, providing it with antimicrobial properties when in contact with wound moisture. The product, therefore, protects against the development of wound infection by decreasing the bacterial load in the dressing and prevents bacterial penetration through the dressing.

In PHMB-donating products (EU classification III), the active component is not chemically bound to the dressing material, and so can be delivered into the wound and periwound tissues. Here, the dressing is a carrier for a wider antimicrobial activity as it donates the PHMB into the wound.

Wound care products incorporating PHMB have been shown to have positive effects on wound healing. In vitro and in vivo studies have shown that, in some of these products, the influence of PHMB:

- Reduces wound pain rapidly and effectively (Daeschlein et al, 2007; Galitz et al, 2009)
- Reduces wound malodour (Daeschlein et al, 2007)
- Increases formation of granulation tissue (Mueller and Krebsbach, 2008)
- Increases keratinocyte and fibroblast activity (Wiegand et al, 2008a)
- Reduces slough within the wound (Mueller and Krebsbach, 2008)
- Reduces MMP-induced periwound breakdown (Cazzaniga et al, 2002; Werthen et al, 2004)
- Helps remove non-viable tissue (Kaehn, 2009).

The success of PHMB has resulted in its recommendations as the primary antimicrobial in many European countries (Dissemond et al, 2010) and has prompted the publication of a UK consensus review (Wounds UK, 2010).

### Conclusion

PHMB appears to meet the criteria for an ideal antimicrobial agent, as described by Drosou et al (2003), and is available in presentations that provide clinicians with effective wound-care modalities for most clinical scenarios. Clinical use, both in the UK and the wider healthcare community, has shown PHMB-based wound-care products to be effective options for managing wound colonisation and infection and, so, deserve closer scrutiny. BJN

*Conflict of interest: The author has previously undertaken education grant-assisted work for a number of healthcare manufacturers including Activa Healthcare.*

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## KEY POINTS

- PHMB has proven broad antimicrobial action and anti-fungal activity
- PHMB has minimum blood/protein inactivation (reduction of effect on mucous membranes owing to presence of mucin)
- PHMB has a sustained, post-application effect
- PHMB has an established promotion of wound healing and additional anti-inflammatory properties

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