

PHMB: a well-tolerated antiseptic with no reported toxic effects

The increase in antibiotic resistance has led to renewed interest in alternative antimicrobials, including antiseptics. Polyhexanide (PHMB) has a proven efficacy against pathogens commonly found in wounds, and has been recommended as a first-choice treatment for locally infected and critically colonised wounds. This article reviews the in vitro and in vivo evidence on its safety, tolerability and efficacy. It also describes its potential to achieve cost savings in clinical practice

Keywords: bacterial resistance; safety and tolerability; mechanism of action

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Originally popularised as a swimming pool sanitiser, the antiseptic agent polyhexamethylene biguanide (PHMB, polyhexanide) is now commonly used as a preservative in cosmetics and personal hygiene products, as a multi-purpose disinfectant and as a deodoriser. However, it is as a promoter of wound healing that it has generated particular excitement.

In 2004, a consensus meeting named PHMB as the first choice for the treatment of locally infected and critically colonised wounds, and recommended its use on refractory wounds, such as second-degree burns, and for lavage.¹ A second expert meeting, held in 2008, reaffirmed this position, praising PHMB for its ease of use and extended duration of action.² The market for PHMB-containing products, which now includes liquids, gels and antimicrobial dressings, is expanding rapidly. This article outlines the evidence on the antimicrobial properties of PHMB.

Biocidal activity

Laboratory studies have demonstrated that PHMB is effective against several bacterial species known to colonise wounds, including *Staphylococcus epidermidis* and *Staphylococcus aureus* (both meticillin-susceptible and resistant strains).³⁻⁵ In further tests, PHMB was bactericidal against *Escherichia coli* at concentrations of >10mg/l,⁶ while Suprasorb X + PHMB (Activa Healthcare), a HydroBalanced biocellulose wound dressing containing 0.3% PHMB, rapidly halted the growth of *S. aureus*.⁷

Absence of bacterial resistance

There have been no reported instances of bacteria acquiring resistance to PHMB.

Prolonged (50-day) exposure of *S. aureus* to PHMB (0.2µg/ml) had no effect on its IC₅₀ (Fig 1). By comparison, silver nitrate's IC₅₀ increased markedly over time.⁷ The IC₅₀ is the dose required to deliver a half-maximal inhibitory effect.

Furthermore, 70 rounds of resistance provocation undertaken over 10 weeks increased the antiseptic effects of the PHMB-containing wound cleansing solution Prontosan, as well as of the preservative Cosmocil, a 20% aqueous solution of PHMB, as assessed in zone-of-inhibition tests involving *S. aureus*.⁸ Resistance provocation tests repeatedly expose bacteria to an antibacterial in order to determine whether resistance mechanisms develop.

Reported bacterial resistance to silver⁹ makes the use of alternative antimicrobials for which no such problems have been reported, such as PHMB, all the more appealing.

Mechanism of action

PHMB's precise mechanism of action is still not fully known. However, the failure of bacteria to develop resistance mechanisms to it suggests it may effect their killing through multiple means.

The primary targets for PHMB's antibacterial action 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,¹⁰⁻¹³ which results in cell death.

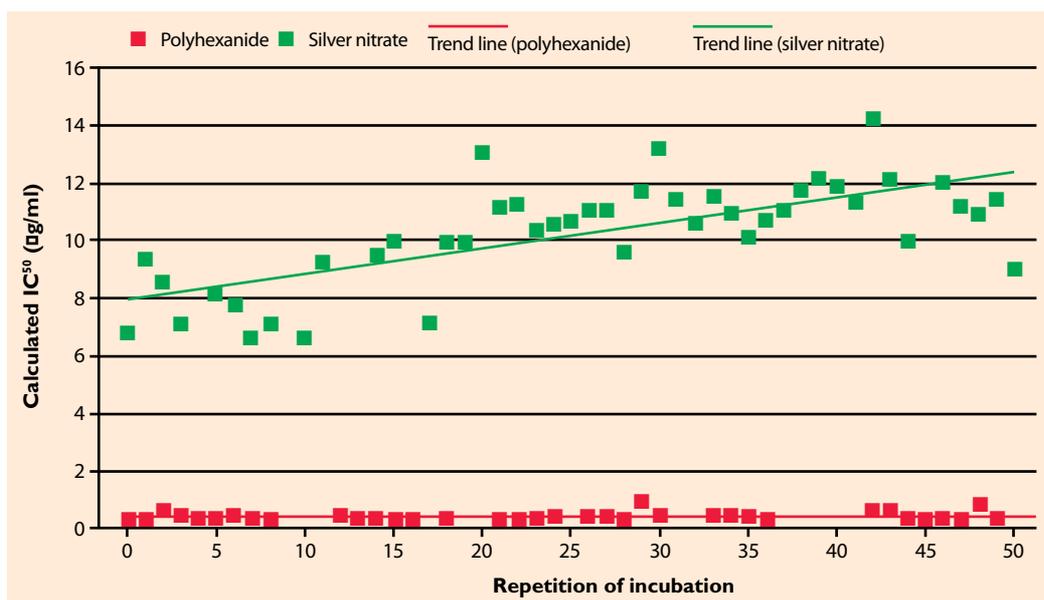


Fig 1. Trend of the IC₅₀ during repeated incubation of *Staphylococcus aureus* with polyhexanide or silver nitrate for 100 days

Studies have sought to identify PHMB's specific membrane targets. While it forms no association with the neutral phospholipids that populate animal cell membranes, it does strongly interact with a key component of bacterial membranes, the acidic phosphatidylglycerol (PG).^{14,15}

The importance of this interaction is illustrated by the fact that artificial depletion of phosphorus in *E. coli* cultures reduces membrane PG content and confers resistance to PHMB.¹⁶

There is evidence that some of PHMB's antibacterial effects follow its penetration into target cells. In 1984, Broxton et al. reported that maximal bactericidal activity occurs under conditions that promote rapid transportation of PHMB to the cytoplasm and cytoplasmic membrane.¹⁶

It has since been demonstrated that PHMB binds to DNA and other nucleic acids and precipitates them from aqueous solution.¹⁷ This suggests it may damage or inactivate bacterial DNA.

Safety and tolerability

PHMB is well tolerated when used topically on skin, eyes, the ciliated epithelium of the nose, and wounds.^{1,2,18}

In 1998 and 2005, the responses of a combined total of 3,529 patients to PHMB were measured in standard patch tests. Reported sensitisation rates were low (approximately 0.5%), even though the tested drug concentrations (2.5 and 5%) far exceeded typical treatment doses.^{19,20}

Suprasorb X + PHMB was also found to be well tolerated, causing no discernible damage to the peri-wound skin.²¹

Biocompatibility index

The biocompatibility index (BI) measures an antiseptic agent's antimicrobial activity in relation to its cytotoxicity. A BI greater than 1 is indicative of an effective antimicrobial with a relatively low cytotoxicity.

PHMB was tested for its relative effects on *E. coli*, *S. aureus* and mouse-derived fibroblasts.²² Its BI values were 1.51 for *E. coli* and 1.36 for *S. aureus*, placing it second among the 11 antiseptic agents screened, above chlorhexidine, povidone-iodine, triclosan, silver nitrate, mild silver protein and silver (I) sulfadiazine. BI values for mild silver protein ranged from 0.1 to 0.25; silver nitrate and silver (I) sulphadiazine's values were in calculably low. The listing is given in Table 1.

PHMB as a wound antimicrobial

PHMB is incorporated into a wide range of wound-healing products, including cleansing solutions, hydrogels and dressings.

While the primary role of PHMB-impregnated dressings is to reduce wound bioburden, other important benefits include reduction of pain, malodour²³ and fibrin slough.²⁴ Moreover, by preventing the build-up of necrotic tissue in chronic wounds, PHMB may promote

Rank	<i>E. coli</i> versus murine fibroblasts	<i>S. aureus</i> versus murine fibroblasts
1	Octenisept (octenidine dihydrochloride)	Octenisept (octenidine dihydrochloride)
2	PHMB	PHMB
3	Chlorhexidine digluconate	Chlorhexidine digluconate
4	Betaisodona ointment (povidone-iodine)	Cetylpyridinium chloride
5	Betaisodona solution (povidone-iodine)	Betaisodona ointment (povidone-iodine)
6	Benzalkonium chloride	Benzalkonium chloride
7	Cetylpyridinium chloride	Betaisodona solution (povidone-iodine)
8	Triclosan	Triclosan
9	Mild silver protein	Mild silver protein
-	Silver nitrate*	Silver nitrate*
-	Silver (I) sulfadiazine*	Silver (I) sulfadiazine*

* Incalculably low (due to failure to sufficiently reduce viable bacteria counts)

Table 1. Commonly used antiseptics ranked according to biocompatibility index²²

connective tissue regeneration and re-epithelialisation; indeed, it is more effective than povidone-iodine and silver nitrate in this regard.²⁴

The prophylactic potential of PHMB has been discussed² and tested, with promising results.²⁵⁻²⁷ It has also been trialled as a perioperative cleansing agent.²⁸

Controlled trials

The few studies published on PHMB indicate that it promotes healing of problem wounds.

In a randomised controlled trial (RCT), 30 patients with pressure ulcers contaminated with MRSA were evenly divided into two groups:

- Group 1, which was treated with Prontosan. This was applied when the cotton gauze dressing was changed (once daily), thus providing short-term decontamination only
- Group 2, which was treated continuously with Suprasorb X + PHMB.

In group 1, swab results indicated that methicillin-resistant *S. aureus* (MRSA) was eliminated in 6/15 patients in one week and in 10/15 patients in two weeks. In contrast, in group 2 MRSA was eliminated in 13/15 patients after one week ($p < 0.05$ versus group 1) and in all patients after two weeks ($p < 0.05$ versus group 1).²⁹

A randomised, open-label study involving 21 patients with different types of wounds that required packing, including diabetic foot ulcers and pressure ulcers, revealed trends toward reduced levels of local infection (assessed by counting bacterial populations) in wounds treated with a PHMB-impregnated gauze, when compared with a control gauze.³⁰

In a randomised, controlled, double-blind study involving 50 patients with acute, contaminated, soft-tissue wounds, cotton dressings moistened with the PHMB-containing antiseptic Lavasept more rapidly eradicated the contaminating bacteria than others moistened with Ringer's solution.³¹

Eight days following instigation of treatment, the number of bacterial isolates collected from wounds fell from 27 to eight in the Lavasept group, and from 19 to 15 in the control group. Moreover, Lavasept significantly reduced bacterial counts (colony forming units) and markedly improved wound inflammation profiles.

A randomised, controlled, descriptive case series (n=10) compared the effects of a PHMB-impregnated drain sponge dressing and a control sponge on bacterial colonisation of tracheostomy sites.³² Culture results showed that PHMB accelerated the clearance of *S. aureus* and *Pseudomonas aeruginosa*.

In separate series, Suprasorb X + PHMB was found to greatly enhance the healing of unresponsive, mixed-aetiology lower extremity wounds⁵ and venous/mixed aetiology leg ulcers.^{21,33} Associated benefits included significant pain reduction and decreased wound bioburden. These results were reported in both in- and outpatients.^{21,33}

Case studies

A PHMB-impregnated gauze was used to treat a purulent, MRSA-infected surgical wound in a patient following a coronary artery bypass graft.³⁴ Treatment removed the need for analgesia during dressing changes, and within five days the percentage of granulation tissue had increased from approximately 50% to 100%, while the wound

Reference	Period	No. of SSIs	Estimated cost per SSI (US\$)	Cost of treating all SSIs (US\$)*	Savings associated with PHMB (US\$)
45	2000 [†]	18	15,646 [‡]	281,628	
	2001	12		187,752	93,876
	2002	9		140,814	140,814
	2003	6		93,876	187,752
	2004	3		46,938	234,690
	2005	4		62,584	219,044
	Total[§]				876,176
27	2003 [†]	23	15,646 [‡]	359,858	
	2004	11		172,106	187,752
	Total[¶]				171,537
25	2004 to [†] ^{**}	81 ^{††}	19,036 ^{‡‡}	1,541,916	
	2005	20 [#]		858,500	
	2005 to	73 ^{††}		1,389,628	152,288
	2006 ^{**}	11 [#]		472,175	386,325
	Total[§] Total[¶]				538,613 508,605

^{*} Based on estimated cost per SSI
[†] PHMB-impregnated gauze not used
[‡] Not inflation-adjusted
[§] Gross
^{||} First two quarters
[¶] Net (adjusted for additional cost of PHMB-impregnated gauze)
^{**} July 1 to May 31
^{††} Non-MRSA SSI
^{‡‡} Inflation-adjusted to 2007 costs
[#] MRSA SSI
 SSI = surgical site infection

Table 2. Cost savings associated with the use of PHMB-impregnated gauze

size decreased by more than half (from 20 x 10 x 11cm to 17 x 7 x 8cm).

A similar result was achieved when a PHMB-impregnated gauze was applied to 16 patients with pressure ulcers.³⁵ The mean reduction in size was 23% after 14.7 days (actual sizes were not specified) and the appearance of the wound improved in 11 patients. 'Infection indicators' decreased in all wounds.

PHMB has shown potential to promote healing in burn injuries, according to a small pilot study.²⁴ Second-degree burns covered with dressings soaked in 0.04% PHMB (diluted Lavasept) healed painlessly and efficiently in all 14 subjects. PHMB also proved superior to silver nitrate in terms of its effects on fibrin accumulation.

Animal studies

Pig skin closely resembles human skin, both morphologically and functionally. In one pig study, a PHMB-impregnated gauze massively reduced (by 4–5 logs) the colonisation by *P. aeruginosa* of partial-thickness wounds.³⁶ A follow-up study showed that it achieved this without interfering with normal wound re-epithelialisation.³⁷

Another study compared a PHMB-impregnated cotton gauze with a silver-coated dressing (SCD)

in a pig model in which excisions were artificially contaminated with *P. aeruginosa* and *Staphylococcus* spp. before being dressed.³⁸ The SCD comfortably outperformed the gauze in measures of re-epithelialisation and inflammation. However, this may be because, unlike the gauze, the SCD did not adhere to the wound. The PHMB-impregnated gauze was also less effective than the SCD in reducing the bacterial growth in *in vitro* zone-of-inhibition tests.³⁸ This suggests that the gauze did not release PHMB under the test conditions. In contrast, Suprasorb X + PHMB has been shown to readily release PHMB in laboratory tests.^{5,39}

In a randomised, double-blind study, daily application of 0.04% PHMB in the form of a spray more effectively accelerated closure of superficial wounds in piglets when compared with Octenisept (0.1% octenidine dihydrochloride, 2% phenoxyethanol).¹

In vitro studies

Laboratory test data complement those from clinical studies. For example, the demonstration that PHMB reduces *P. aeruginosa* biofilms *in vitro*⁸ suggests it may combat wound biofilms in clinical practice, while the observation that mucins (glycosylated proteins found in mucus) abolish the

antimicrobial activity of Lavasept⁴⁰ raises questions about PHMB's likely effectiveness against mucous membrane infections. Elsewhere, a recent report that PHMB and Suprasorb X + PHMB eliminate artificial plaques of fibrin *in vitro*⁴¹ substantiates previous clinical observations.²⁴

In vitro tests have also provided welcome mechanistic insights. PHMB's ability to inhibit the formation of reactive oxygen species *in vitro*⁴² may underscore its anti-inflammatory effects *in vivo*.³¹ Moreover, clinically relevant concentrations of PHMB enhanced the *in vitro* proliferation of normal human keratinocytes,⁴³ while both PHMB and Suprasorb X + PHMB protected HaCaT keratinocytes from the damaging and antiproliferative effects of *S. aureus*.⁴⁴ This may help explain PHMB's ability to promote re-epithelialisation *in vivo*.²⁴

Infection rates and cost savings

The use of antimicrobial dressings has repeatedly been reported to reduce surgical site infection (SSI) rates, thereby yielding substantial cost savings (Table 2).

In one such case, investigators from Nebraska, USA, found that replacing plain gauze dressings with PHMB-impregnated gauze reduced the overall SSI rate by 24% and the MRSA SSI rate by 47%.²⁵ Based on estimates of SSI treatment costs, this delivered a \$508,605 net saving during the one-year evaluation period.

Key points

1. Two expert meetings have recommended that the antiseptic PHMB should be the first choice of treatment for critically colonised and locally infected wounds.
2. There are no reported instances of bacteria acquiring resistance to PHMB. In contrast, bacterial resistance has been reported for silver.
3. PHMB targets the bacterial cell membrane and possibly damages or inactivates the bacterial DNA. It does not harm human tissue.
4. PHMB is safe and well tolerated.
5. Controlled trials indicate that PHMB promotes healing of chronic wounds.

Another US study found that replacing conventional gauze with PHMB-impregnated gauze in the treatment of patients undergoing vascular surgery resulted in a progressive year-on-year fall in infection rates from 4.6% in 2000 to 0.4% in 2005, with an overall estimated saving of \$876,176.⁴⁵

In a third US trial, the hospital-wide introduction of the same PHMB-impregnated gauze resulted in a reduction in the incidence of infections from 23 to 11 (both reported in separate six-month observation periods).²⁷ Calculated net savings were \$171,537.

A trial conducted in the University of California San Diego Medical Center, USA, concluded that Suprasorb X + PHMB was more cost-effective than other treatment regimens for recalcitrant wounds.⁵ Calculations were based on material costs, which averaged \$5.99–9.01 per patient per day and were as low as \$2.14 per day in one patient, and dressing change frequency.

Conclusion

PHMB has recently emerged as a credible alternative to silver for preventing and combating wound infections. Based on what is a rapidly expanding body of evidence, it appears to be a highly effective antiseptic for chronic wounds.

Given that it is well tolerated with no notable toxic effects, PHMB's efficacy has been probed in RCTs and case studies. These have shown that it eradicates bacterial pathogens, including MRSA. It has also been found to reduce wound pain, both persistent and at dressing change.

The prophylactic use of PHMB-impregnated dressings has reduced the incidence of SSIs, which can be expensive to treat. Indeed, preliminary trials suggest it may be highly cost-effective in this regard.

Future studies are needed to more thoroughly compare the effectiveness of PHMB with other bactericidal agents, so that their relative efficacies in different contexts may be fully evaluated.

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