Polyhexamethylene biguanide and its antimicrobial role in wound healing: a narrative review

Abstract: A wound offers an ideal environment for the growth and proliferation of a variety of microorganisms which, in some cases, may lead to localised or even systemic infections that can be catastrophic for the patient; the development of biofilms exacerbates these infections. Over the past few decades, there has been a progressive development of antimicrobial resistance (AMR) in microorganisms across the board in healthcare sectors. Such resistant microorganisms have arisen primarily due to the misuse and overuse of antimicrobial treatments, and the subsequent ability of microorganisms to rapidly change and mutate as a defence mechanism against treatment (e.g., antibiotics). These resistant microorganisms are now at such a level that they are of grave concern to the World Health Organization (WHO), and are one of the leading causes of illness and mortality in the 21st century. Treatment of such infections becomes imperative but presents a significant challenge for the clinician in that treatment must be effective but not add to the development of new microbes with AMR. The strategy of antimicrobial stewardship (AMS) has stemmed from the need to counteract these resistant microorganisms and requires that current antimicrobial treatments be used wisely to prevent amplification of AMR. It also requires new, improved or alternative methods of treatment that will not worsen the situation. Thus, any antimicrobial treatment should be effective while not causing further development of resistance. Some antiseptics fall into this category and, in particular, polyhexamethylene hydrochloride biguanide (PHMB) has certain characteristics that make it an ideal solution to this problem of AMR, specifically within wound care applications. PHMB is a broad-spectrum antimicrobial that kills bacteria, fungi, parasites and certain viruses with a high therapeutic index, and is widely used in clinics, homes and industry. It has been used for many years and has not been shown to cause development of resistance; it is safe (non-cytotoxic), not causing damage to newly growing wound tissue. Importantly there is substantial evidence for its effective use in wound care applications, providing a sound basis for evidence-based practice. This review presents the evidence for the use of PHMB treatments in wound care and its alignment with AMS for the prevention and treatment of wound infection.

Declaration of interest: This work was funded by Advanced Medical Solutions, UK. There are no other conflicts of interest. Advanced Medical Solutions did not have any input to manuscript preparation.

antimicrobial resistance • biofilm • infection • PHMB • polyhexamethylene biguanide • wound • wound care • wound dressing • wound healing

Various levels of microorganism can be present in wounds. These levels range from wound colonisation, which is characterised by the presence of replicating bacteria in the wound but without causing any detrimental effects on the wound or tissue,[1] to wound infection, which is typified by the presence of high levels of proliferating bacteria that cause local tissue damage and delayed healing.[2] Wound infection involves the presence of more than one species of microorganism and, for wounds, *Staphylococcus* and *Pseudomonas* spp. are the most common.[3,4]

However, wound infection can be exacerbated by the development of a biofilm—a community of microbial cells organised within a slimy extracellular matrix that is adherent to a surface (e.g., a wound surface).[5] The presence of antimicrobial-resistant microorganisms and the increased resistance to antimicrobial agents offered by a biofilm[6] means that the removal of antimicrobial-resistant microbes and biofilm are key to promoting wound healing.[7] For infected wounds, the inclusion of antimicrobials is a requirement of the treatment regimen, and the use of topical antimicrobial agents is an important component for infection control in wound care.[8]

Topical antimicrobials can be divided into three main groups:

- Disinfectants: chemical substances or compounds used to inactivate or destroy microorganisms on inert surfaces (e.g., sodium hypochlorite)
- Antiseptics: substances that destroy or inhibit the growth or action of microorganisms (such as bacteria), especially in or on living tissue (e.g., polyhexamethylene biguanide (polyhexanide, PHMB), chlorhexidine, iodine, silver, hydrogen peroxide)
- Antibiotics: substances that can inhibit or kill microorganisms (e.g., bacitracin, mupirocin, neomycin).

Mark G Rippon,[1,2] PhD, Visiting Clinical Research Associate; Consultant;
Alan A Rogers,[3] BSc (hons), Independent Wound Care Consultant*;
Karen Ousey,[4,5,6] PhD, FRSB, RGN, FHEA, CMgr MCMI, Professor of Skin Integrity, Director for the Institute of Skin Integrity and Infection Prevention; Adjunct Professor; Visiting Professor; Chair (IWII); President Elect (ISTAP)
***Corresponding author email:** alan@woundcaresol.co.uk
1 Huddersfield University, Huddersfield, UK. **2** Dane River Consultancy Ltd, Cheshire, UK. **3** Flintshire, North Wales, UK. **4** University of Huddersfield Department of Nursing and Midwifery, Huddersfield, UK. **5** School of Nursing, Faculty of Health at the Queensland University of Technology, Australia. **6** RCSI, Dublin, Eire.

Fig 1. Subunit structure of polyhexamethylene biguanide (PHMB). Schematic structure of mono-protonated PHMB with chloride as counter-ion **(a)** and monomers: hexamethylenediamine **(b)** and sodium dicyanamide **(c)**

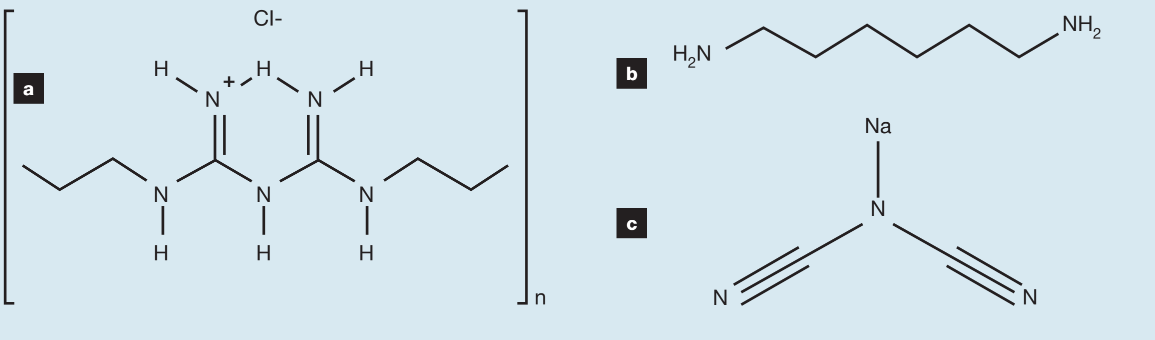


Fig 2. Membrane disruption mechanism of action for polyhexamethylene biguanide (PHMB)

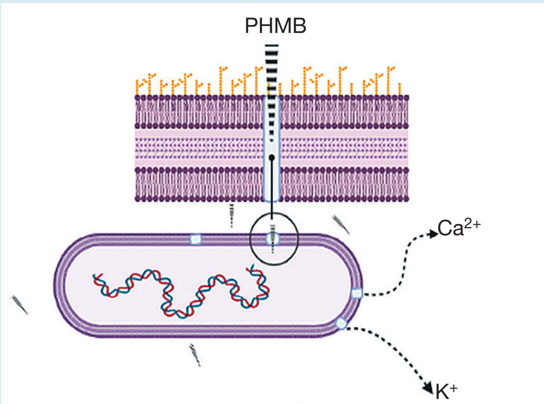
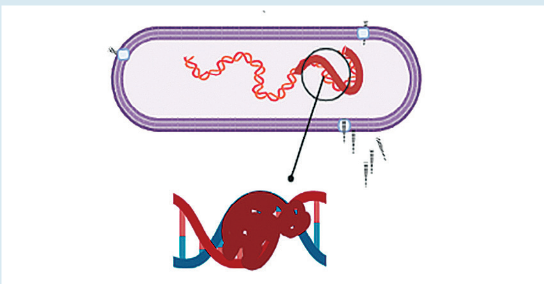


Fig 3. DNA binding/condensation mechanism of action for polyhexamethylene biguanide (PHMB)



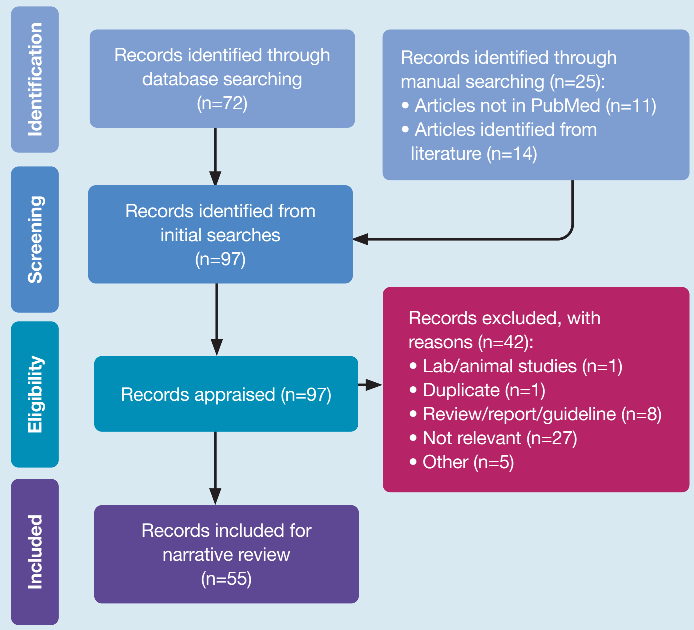
Disinfectants in the healthcare setting are applied to inanimate objects and materials, such as instruments and surfaces, to control and prevent infection. Disinfectants are not used on wounds but are used to reduce microbial numbers on objects such as hospital trolleys and surgical instruments.[9] Antiseptics and antibiotics are used to treat wound infections; however, there are advantages and disadvantages. For example, in contrast to antibiotics that specifically target a particular pathogen, antiseptics can target multiple microorganisms and therefore have a broader spectrum of activity. Antiseptic solutions are applied topically and help to reduce wound bioburden, which is critical in promoting wound healing.[8,10] Previously, antiseptics were not recommended for routine use in wound care;[11] their rise in popularity has been driven in part by the current effort to reduce the prescribing of antibiotics due to concerns about drug resistance.[8,12]

PHMB is a molecule composed of repeating basic biguanidine units connected by hexamethylene hydrocarbon chains leading to a cationic and amphipathic structure (Fig 1).[13–15] PHMB is a mixture of polymers and is a synthetic compound structurally similar to naturally occurring antimicrobial peptides (AMPs). The basic molecular chain of PHMB can be repeated from 2–30 times, with increasing polymer chain length correlating with increasing antiseptic/antimicrobial efficacy.[16] PHMB was first synthesised in the 1950s.[17] It has been reviewed by the US Environmental Protection Agency (EPA) and noted, with the exception of occupational users, as having a very low aggregate risk of adverse health effects to the public or environment.[17–19] It has been shown to have a limited effect on mammalian cells.[18] There is evidence that there is a wide safety margin when used in cosmetic[20] and clinical applications,[21] including wound care treatments.[22] It has low absorption via the epidermis and therefore is associated with a low probability of occurrence of allergic reactions.[17]

Several mechanisms of action (MoA) have been proposed. Previous studies on the MoA of PHMB have focused on its ability to interact with microbial membranes in preference to mammalian membranes.[23–25] As previously stated, PHMB is structurally similar to AMPs, and these AMPs have a broad spectrum of activity against bacteria, viruses and fungi.[26] They are positively charged molecules that bind to bacterial cell membranes and induce cell lysis by destroying membrane integrity (Fig 2). PHMB binds to the negatively charged phosphate head groups of phospholipids at the bacterial cell wall, causing increased rigidity, sinking non-polar segments into hydrophobic domains, disrupting the membrane with subsequent cytoplasmic shedding culminating in cell death.[27,28] The destabilisation of the bacterial membranes causes leakage of a number of important ions, resulting in cell death.[29] At high concentrations of PHMB—concentrations used under antiseptic conditions—the bactericidal effect is very rapid, but even at low concentrations the release of cellular constituents occurs. Other studies have suggested an alternative mechanism of action for PHMB. PHMB is able to enter bacterial cells, arrest cell division and condense chromosomes.[18] PHMB initiates the formation of a complex between PHMB and bacterial nucleic acid, which results in the precipitation of DNA and its inactivation.[30–32] The binding of PHMB to DNA potentially blocks DNA replication or DNA repair pathways, with subsequent cell division arrest and chromosome condensation (Fig 3).[15,18]

PHMB is a broad-spectrum antimicrobial that kills bacteria, fungi, parasites and certain viruses with a high therapeutic index that is widely used in clinics, homes and industry.[33] It is a chemical antiseptic that is used as an active ingredient in a variety of personal care wet wipes and wound management products, wound irrigation solutions, sterile dressings and disinfectants.[27] A systematic review of the effectiveness of PHMB for the treatment of hard-to-heal wounds supports its use in these wounds.[34] PHMB wound solutions have demonstrated experimentally anti-biofilm efficacy against wound pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and the multispecies biofilm,[35] biofilms[35–37] and antimicrobial-resistant microorganisms.[38] There are numerous types of dressings, both commercially available and under development, that contain PHMB as an antimicrobial component used to reduce or eradicate bacterial infections. PHMB gauze and foam dressings do not release the PHMB into the wound; the bacteria are killed in the dressing above the wound.[39]

Fig 4. Narrative review search strategy results flow diagram



The bactericidal properties of PHMB have been demonstrated against a wide range of species[14] with the killing activity being shown to be rapid (within one hour of application).[18] Also, the comparatively lower level of killing activity against mammalian cells (e.g., human cells) compared with microorganisms contributes to its high therapeutic index.[40]

Table 1. Search strategy summary

Items	Specification
Date of search	4 October 2022 to 5 October 2022
Databases and other sources searched	PubMed database
Search terms used (including any MeSH and free text search terms and filters)	(phmb OR 'polyhexamethylene biguanide' OR polyhexanide); antimicrobial; (wound OR ulcer); paper type: case report, clinical study, clinical trial, controlled clinical trial, observational study, randomised control study; language: English; publication date: from 1 January 1995 to 30 September 2022
Timeframe	January 1995 to September 2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Papers written in English related to the antimicrobial action of polyhexamethylene biguanide (PHMB) in wounds were included. Any papers not written in English were excluded. Using PubMed database filters specific study types were included: case report, clinical study, clinical trial, controlled clinical trial, observational study, randomised controlled trial. Non-clinical studies were excluded: review, commentary, protocol and guideline papers were excluded. Papers with no abstract available were also excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.	The selection process was performed independently by authors MGR and AAR
Any additional considerations, if applicable	No additional considerations

Table 2. Selection of experimental evidence for antimicrobial activity of polyhexamethylene biguanide (PHMB)

Microorganism	Example	Reference
Gram-positive bacteria	*Actinomyces*	120, 121
	Staphylococcus	35, 122
	Streptococcus	123, 124
	Enterococcus	125, 126
Gram-negative bacteria	*Acinetobacter*	127, 128
	Proteus	126, 129
	Enterobacter	104, 130
	Klebsiella	131, 132
Bacterial biofilm	*Staphylococcus*	104, 122
	Multi-species	35, 103
Fungi	*Candida*	125, 133
Protozoa	*Acanthamoeba*	134, 135
Virus	Adenovirus	136
	Human immunodeficiency virus (HIV)	13

Aim

The aim of this review is to provide an overview of the clinical evidence exploring the antimicrobial role of polyhexamethylene biguanide (PHMB) on wound healing.

Methods

In this narrative review, we searched the PubMed database using the following keywords and keyword search strings: (phmb OR 'polyhexamethylene biguanide' OR polyhexanide), antimicrobial, and (wound OR ulcer). Published papers from January 1995 to September 2022 were included (Table 1).

In addition, a manual search for papers in wound care journals not indexed in PubMed (e.g., *Wounds UK*, *Wounds International*) and related to the use of clinical use of PHMB in wounds was also carried out. Papers identified as relevant from reference lists, but which were not identified in the other searches carried out, were also included in this narrative review.

Results

From the search of the PubMed database, 72 records were identified using the search strategy summarised in the Methods and Table 1. A further 11 papers were identified from wound care journals not indexed in the PubMed database, and an additional 14 papers were included as relevant and identified from reviews and paper reference lists. A total of 97 papers were identified for appraisal.

After an initial appraisal of the titles and abstracts, 41 papers were excluded using the exclusion criteria detailed in Table 1. Papers assessed as not being relevant to the aim of the narrative review were also excluded. At this stage, one paper was excluded as a duplicate reference. Once concluded, 55 papers were included as the basis for this narrative review (Fig 4).

Discussion

The experimental evidence demonstrates antimicrobial activity for PHMB against a wide variety of microorganisms, including both Gram-negative and Gram-positive bacteria, pathogenic fungi, viruses and unicellular protozoa (Table 2).

The antimicrobial activity of PHMB in clinical wound healing

PHMB and the treatment of wound infection

There is a significant body of evidence for the use of PHMB (as a solution or having been incorporated into a dressing matrix) against a variety of microorganisms (Table 3).

PHMB solutions

Clinically, as part of routine wound treatment, fluid irrigation is used to dislodge foreign debris, loosely attached bacteria and devitalised tissue from the wound surface.[41] The goal of wound irrigation is to remove foreign material, decrease bacterial contamination of the wound, and to remove cellular debris or exudate from the surface of the wound.[42] Normal saline or Ringer's solution are most frequently used to irrigate both acute and hard-to-heal wounds.[43] These solutions are isotonic, minimally toxic to exposed tissue and do not impede healing progression, while being relatively cost-effective.[42] In addition, there are specialised wound cleansers that contain antimicrobials that are effective in the treatment of wounds where a reduction of wound bioburden to host-manageable levels is required.[44] These antimicrobials include sodium hypochlorite,[35,45] hypochlorous acid,[46–48] povidone-iodine[49] and PHMB/polyhexanide.[50–52]

There are several clinical studies documenting the effect of PHMB solutions on wound bioburden in a variety of wound types (Table 4). Hard-to-heal wounds, such as venous leg ulcers (VLUs),[50,51,53–55] diabetic foot ulcers (DFUs),[53,56,57] pressure ulcers (PUs)[53,58] and malignant wounds,[59] have all benefitted from treatment including the use of PHMB solutions. Burn wounds[60] and acute wounds, such as surgical wounds,[61–63] skin graft donor site wounds[64] and traumatic wounds,[65] have also shown positive results for PHMB solution irrigation in terms of reducing wound bioburden. Irrigation of wounds with PHMB solution as part of negative pressure wound therapy (NPWT) is an example of PHMB solutions being used as an adjunct with medical devices to treat contaminated and/or infected wounds[57,66] including orthopaedic patients with problematic wounds.[67,68]

Several studies indicated that treatment with PHMB solutions led to an improvement in wound condition[69] and improved healing response.[26,51,58,60,70] In the studies where the level of bioburden or risk of infection was a wound parameter under study, several indicated reductions in levels of microorganisms[50,53,61,62] and a decrease in the likelihood of infection developing.[61,63,65,67,68] A few studies indicated that the use of PHMB solutions had no effect on bacterial loads in wounds,[57,64] and one study indicated that biofilm

Table 3. Summary of papers identified for review as part of the narrative review (n=55)

First author	Clinical setting	Patients, n	Main results
Alblas et al. (2013)[90]	Necrotising fasciitis	1	Significant debridement and wound improvement with therapy including biocellulose + PHMB dressing
Andriessen et al. (2008)[51]	Venous leg ulcers	59	Patients treated with polyhexanide (versus Ringer's solution or saline) healed faster and in more cases (97% versus 89%, respectively)
Assadian et al. (2018)[53]	Hard-to-heal wounds	260	Highest reduction in bacterial bioburden achieved with aqueous solution containing betaine, zinc and PHMB
Becerro de Bengoa Vallejo et al. (2011)[61]	Nail avulsion surgery	71	0.1% polyhexanide irrigation solution more effective at reducing bacterial load versus saline or 0.2% nitrofurazone. No patient from PHMB group developed postoperative infection
Bellingeri et al. (2016)[58]	Vascular leg ulcers, pressure ulcers	289	Higher efficacy of propyl-betaine-polyhexanide solution versus saline solution in reducing inflammation and accelerating healing
Borges et al. (2018)[50]	Venous leg ulcers	44	PHMB and saline solutions effective in reducing bacterial load. However, biofilm was present after cleansing
Brantley et al. (2016)[86]	Hard-to-heal wounds	5	Collagen matrix + PHMB dressing manages wound bioburden
Çeviker et al. (2015)[72]	Hard-to-heal wounds	31	Overall, 17/31 (66.7% PHMB, 43.8% Ringer's; p=0.181) were treated successfully and healed; wound cultures were negative in 19/31 (47.4% PHMB, 52.6% Ringer's) patients
Chai et al. (2020)[56]	Diabetic foot ulcer	1	A multidrug *Pseudomonas* infection treated with polyhexanide solution/gel and systemic antibiotic resulted in healing of ulcer 40 days after clearing the bone displacement and fracture
Daeschlein et al. (2007)[60]	Second-degree burns	4	Clinically and histologically the mesh grafts treated with polyhexanide showed by far the best re-epithelialisation compared with the deep tissue necrosis and marked fibrin discharge observed for application of povidone-iodine and silver nitrate
Dettmers et al. (2016)[67]	Orthopaedic implant wounds	4	The use of a negative pressure wound therapy with instillation (NPWT-i) and dwell time was developed for treatment for postoperative wound infection on patients at high risk of surgical complications including infection found that there was no recurrence of infection
Durante et al. (2014)[77]	Hard-to-heal wounds	124	Treatment with a polyhexanide and propyl betaine-based gel resulted in improvement in wound appearance and reduction in wound area. There was also a decrease in the percentage of patients with wounds with devitalised tissue and/or with biofilm
Eberlein et al. (2012)[91]	Infected wounds of various aetiology	38	Compared with silver dressings, in the polyhexanide-containing biocellulose wound dressing group critical colonisation and local wound infection had been reduced significantly faster and better (p<0.001) over the 28-day study period
Elzinga et al. (2011)[92]	Paediatric heel lacerations	20	The use of a PHMB-impregnated biocellulose dressing on paediatric lacerations achieved good healing outcomes. No cases of local infection were noted over the assessment period
Fabry et al. (2006)[62]	Contaminated acute wounds	50	Treatment with moist dressings of fractionated PHMB and macrogolum 4000, when compared with wounds treated with Ringer's solution, led to a faster and significant reduction in microorganisms on the wound surface
Fumarola et al. (2010)[93]	Various wounds	10	Reduction in infection of wounds treated with a biocellulose dressing impregnated with PHMB
Goertz et al. (2010)[78]	Skin graft donor sites	44	A polyhexanide-preserved wound gel was superior to Flamazine with respect to a number of parameters important for patient and healthcare practitioner satisfaction
Hagelstein et al. (2013)[102]	Venous leg ulcers	5	Use of a moist wound dressing impregnated with PHMB led to a reduction in signs of infection in some patients. Several patients remained infection-free in wounds that were at high risk of reinfection
Horrocks (2006)[69]	Hard-to-heal wounds	10	Use of propyl-betaine-polyhexanide wound irrigation and gel is appropriate for cleaning, moistening and decontaminating encrusted, contaminated and hard-to-heal skin wounds
Hunt (2016)[79]	Diabetic foot ulcer	1	Treatment of ulcer with propyl-betaine-polyhexanide wound solution and gel showed some improvement but required oral antibiotics to resolve a recurrent local infection. Clinician switched to surfactant-based solution which leads to wound progression
Johnson and Leak (2011)[83]	Various wounds	25	Using a foam dressing impregnated with PHMB all wounds showed improved healing outcomes. In two patients with MRSA present, repeat swabs were subsequently negative. No new infections were recorded
Kiefer et al. (2018)[80]	Burns requiring skin graft	51	Wounds treated with propyl-betaine-polyhexanide gel were assessed for tolerability and safety as well as graft take and healing of the skin graft. The gel was shown to be efficacious, safe and well tolerated. No wound infection occurred
Kim et al. (2015)[66]	Infected wounds	100	Comparing 0.9% normal saline versus 0.1% polyhexanide plus 0.1% betaine as part of negative pressure wound therapy with instillation (NPWT-i) for the adjunctive treatment of infected wounds, results suggest that saline is as effective as an antiseptic for NPWT-i
Koullias (2021)[87]	Various wounds	16	Patients treated with weekly debridement, application of a purified native collagen with PHMB followed by placental allografts resulted in good wound closure rates

Table 3. Summary of papers identified for review as part of the narrative review (n=55) (continued)

First author	Clinical setting	Patients, n	Main results
Lavery et al. (2020)[57]	Diabetic foot ulcers	150	Comparing the efficacy of negative pressure wound therapy (NPWT) with and without irrigation with 0.1% propyl-betaine-polyhexanide found that there was no change to clinical outcomes with the addition of irrigation. Parameters included incidence of reinfection
Lehner et al. (2011)[137]	Infected orthopaedic implant wounds	32	Acute and chronically infected implants were treated with negative pressure wound therapy with instillation (NPWT-i). More than 80% of patients with both infections retained their implants 4–6 months after treatment
Lenselink and Andriessen (2011)[94]	Hard-to-heal wounds	28	Treatment of hard-to-heal locally infected and/or critically colonised wounds with a biocellulose dressing impregnated with PHMB led to significant improvement in wound area reduction. 63% of patients showed good reduction in biofilm and 32% scored a moderate reduction
Lintzeris et al. (2018)[88]	Various wounds	8	Of the wounds treated with a purified native collagen with PHMB, 6/9 (one patient had two wounds) healed and the remaining three demonstrated improvement in wound appearance
Mancini et al. (2018)[98]	Hard-to-heal wounds	25	Wound cleansing and control of wound bioburden using a hydro-active dressing impregnated with PHMB was assessed in a variety of hard-to-heal wounds. As well as a decrease in wound surface fibrin levels and an increase in appearance of granulation tissue, bacterial bioburden remained constant over the 7-day assessment period in 50% of cases, decreased in 15%, and increased in 35% of cases
Monteiro Vasconcelos et al. (2022)[138]	Pressure wounds	14	PHMB had an immediate antimicrobial effect on *Serratia marcescens* with no wound swabs showing this microorganism by the second week. All other microorganisms assessed were present in wound swab samples suggesting concern for the effectiveness of PHMB in managing microorganisms
Moore et al. (2016)[70]	Hard-to-heal wounds	49	Wounds treated with propyl-betaine-polyhexanide gel improved and the clinicians concluded that the gel provides a moist wound healing environment facilitating wound closure. Only five of 49 patients required additional antimicrobial therapy. The use of this gel inhibited bacterial colonisation and reduced the need for further antimicrobial therapy
Motta and Trigilia (2004)[73]	Various wounds requiring packing	21	There were more prominent changes in polymicrobial bioburden in a gauze dressing containing PHMB compared with a gauze dressing without PHMB. With PHMB, bioburden was reduced, whereas without PHMB bioburden increased to 60% above baseline
Motta and Trigilia (2005)[84]	Tracheostomy wound sites	10	Culture results showed an absence of pathogens and presence of normal skin flora for 11 study days in patients randomised to the PHMB dressing group and an absence of pathogens and presence of normal skin flora for six study days in patients in the control group
Muangman et al. (2011)[74]	Skin graft donor sites	32	Treatment with either a chlorhexidine-coated paraffin tulle dressing or a cotton dressing impregnated with PHMB resulted in no infections in the PHMB group and only one infection in the tulle dressing. The PHMB-impregnated dressing provided a shorter re-epithelialisation time and generated lower pain levels compared with the tulle dressing
Mueller and Krebsbach (2008)[75]	Surgical site infections	19,574	Before the introduction of a gauze dressing with 0.2% PHMB, 101 SSIs occurred after 9372 surgical procedures (1.08%), 20 of which were identified as MRSA (0.21%). After introduction of AMD, 84 SSIs occurred after 10,202 surgical procedures (0.82%), representing a rate reduction of 24.07% (p=0.035), with 11 identified as MRSA (0.11%), representing a reduction of 47.62% (p=0.047)
Napavichayanun et al. (2018)[95]	Skin graft donor sites	21	Half each of STSG donor site wounds were randomly assigned to cover with (a) a bacterial cellulose wound dressing containing silk sericin and PHMB (BCSP) or (b) a chlorhexidine-containing tulle gras dressing. There was no significant difference in wound healing time between the two dressings, but in (a) wound quality was better (p<0.05). There were no signs of infection with either dressing
Nielsen and Andriessen (2012)[96]	Surgical wounds	60	Pain levels were significantly lower, and the dressing adhered significantly less in the group which received a biocellulose dressing with polyhexanide, compared with a group receiving a hydrophobic dressing with dialkylcarbamoyl chloride
Nunes et al. (2019)[54]	Venous leg ulcers	28	Two bundles in venous leg ulcer treatment assessed, with both bundles receiving propyl-betaine-polyhexanide solution. Both bundles were assessed as being effective in the treatment of venous leg ulcers
Oropallo (2019)[89]	Hard-to-heal wounds	41	No wounds showed any signs of infection at 12 weeks of treatment with a collagen matrix/PHMB wound dressing. 73% of wounds demonstrated a reduction in wound area at 12 weeks, and 37% achieved complete wound closure
Payne et al. (2018)[139]	Acute traumatic wounds	61	The polyhexanide 0.04% group showed a significant decrease in $\log_{10}$ colony-forming units (CFU) (p<0.001) in acute traumatic wounds after 60 minutes' treatment in comparison to baseline CFU, whereas the Ringer's solution group did not show a significant change in cfu during 60 minutes' treatment
Piatkowski et al. (2011)[97]	Burn wounds	60	The group treated with the biocellulose + polyhexanide dressing demonstrated a better and faster pain reduction in the treated partial-thickness burns, compared with patients treated with a silver-sulfadiazine cream. The results indicate the polyhexanide containing biocellulose dressing to be safe for partial-thickness burns
Romanelli et al. (2010)[55]	Venous leg ulcers	40	The treatment with the propyl-betaine-polyhexanide solution was well tolerated by the patients and was found useful in the absorption of wound odours

Table 3. Summary of papers identified for review as part of the narrative review (n=55) (continued)

First author	Clinical setting	Patients, n	Main results
Roth et al. (2017)[65]	Traumatic wounds	7104	The prophylactic application of wound irrigation using 0.04% PHMB, 1% povidone-iodine (PVP-I), 4% hydrogen peroxide or undiluted Ringer's solution indicated that PHMB showed the highest efficacy in preventing infection in traumatic soft tissue wounds ($p<0.001$)
Saleh et al. (2016)[64]	Skin graft donor sites	40	Soaking tie-over dressings with PHMB solution in full-thickness skin grafting had no effect on postoperative bacterial loads and increased the risk of SSI development
Sams-Dodd and Sams-Dodd (2020)[81]	Complex wound	1	Treatment of patient with infected complex wound included clearance of devitalised tissue and removal of soft tissue infection. When treatment changed to include PHMB gel tissue degeneration was observed and there was disruption of structure of exposed bone
Sibbald et al. (2011)[85]	Hard-to-heal wounds	40	The use of PHMB foam dressing was a significant predictor of reduced wound superficial bacterial burden ($p=0.016$) at week 4 as compared with the foam alone. Polymicrobial organisms were recovered at week 4 in 5.3% in the PHMB foam dressing group versus 33% in the control group ($p=0.04$)
Strobel et al. (2020)[63]	Surgical wounds	393	Significantly fewer SSIs occurred in the group irrigated with 0.04% polyhexanide: n=70 (34.7%) versus n=41 (21.5%); $p=0.004$. Wound irrigation with polyhexanide was associated with a lower risk of SSI
Timmers et al. (2009)[68]	Post-traumatic osteomyelitis	124	Treated with negative pressure wound therapy with irrigation (NPWT-i) with polyhexanide compared with patients treated with standard care (including debridement, and intravenous antibiotics). In the instillation group the rate of recurrence of infection was 10% compared with 58.5% in the control group ($p<0.0001$). For the instillation group the total duration of hospital stay was shorter and the number of surgical procedures smaller
Tuncel et al. (2013)[100]	Hard-to-heal wounds	50	A saline-soaked antibacterial gauze-based negative pressure wound therapy (NPWT) treatment compared with conventional dressing therapy which included the use of polyhexanide solution. The patients treated with antibacterial gauze-based NPWT had a significantly reduced recurrence (two wounds versus 14 wounds; p=0·001) and increased number of culture-negative cases (22 wounds versus 16 wounds; p<0·047) in a follow-up period of 12 months
Vallejo et al. (2022)[140]	Hard-to-heal wounds	50	An assessment of combination effect of PHMB and low-frequency contact ultrasonic debridement (LFCUD) indicated that there was a reduced bacterial load after 12 weeks in the PHMB/LFCUD group compared with the control group (non-antimicrobial products and irrigation cleansing)
Villela-Castro et al. (2018)[59]	Malodorous malignant wounds	24	Comparison between treatment with 0.8% metronidazole solution (control) and 0.2% PHMB found that 100% of patients in both groups were classed as having 'no wound odour' by day 8
Wandhoff et al. (2020)[99]	Surgical wounds (joint arthroplasty)	13,315	'Universal decolonisation' with polyhexanide did not reduce overall SSIs, but was effective in reducing *Staphylococcus aureus*
Wattanaploy et al. (2017)[82]	Burn wounds	46	There was no significant difference between most parameters including infection rates and bacterial colonisation rates when burn wounds treated with propyl-betaine-polyhexanide gel or silver sulfadiazine cream were compared
Wibbenmeyer et al. (2012)[76]	Burn wounds	108	Use of a PHMB-impregnated gauze dressing assessed in treatment of burn wounds. There were significantly fewer infections in the study group (18.52% of cases had infections) compared with the historic control group (28.70% of cases had infections) ($p=0.047$)
Wild et al. (2012)[101]	Pressure ulcers	30	Comparison between cleansing with polyhexanide swabs (control group) and receiving a polyhexanide-containing cellulose dressing (study group) in patients with pressure ulcers containing MRSA. Wound disinfection was found to be effective in both groups with superior results for the study group

AMD—antimicrobial dressing; BCSP—bacterial cellulose wound dressing; MRSA—meticillin-resistant *Staphylococcus aureus*; PHMB—polyhexamethylene biguanide; SSI—surgical site infection; STSG—split-thickness skin graft

remained after treatment with PHMB solution application.[50]

PHMB wound dressings

A Cochrane Review concluded that there was little evidence to suggest that one wound dressing (advanced (e.g., films, hydrocolloid) or otherwise) was any better at reducing the risk of surgical site infections (SSIs), or that covering a wound with any dressing reduced the risk of infection.[71] Most evidence presented is of relatively low quality.[71] Table 5 summarises the clinical evidence available (including randomised controlled trials) for the use of PHMB-incorporated dressings in the treatment of acute and hard-to-heal wounds.

PHMB has been incorporated into a number of different dressing types including gauze,[72–76] gel,[56,69,70,77–82] foam dressings,[83–85] collagen matrix dressings,[86–89] biocellulose dressings[90–97] and hydro-active dressings.[98] PHMB-incorporated wound dressings have been used to treat a variety of acute wounds,[84] including surgical wounds,[75,96,99] skin graft donor sites,[74,78,95] paediatric heel lacerations[92] and burn wounds,[76,80,82,97] as well as a number of different hard-to-heal wounds,[70,72,77,85,86,89,94,98,100] including VLUs,[69] DFUs,[56,79] PUs[101] and other complex wounds.[81]

Several studies indicated that treatment with PHMB-impregnated dressings led to an improvement in wound condition[69,77,88,90,95,98] and improved healing

Table 4. Clinical evidence to support the use of polyhexamethylene biguanide (PHMB) solution for the treatment and prevention of wound infection

First author	Clinical setting	Patients, n	Main results
Andriessen and Eberlein (2008)[51]	Venous leg ulcers	59	Patients treated with polyhexanide (versus Ringer's solution or saline) healed faster and in more cases (97% versus 89%, respectively)
Assadian et al. (2018)[53]	Hard-to-heal wounds	260	Highest reduction in bacterial bioburden achieved with aqueous solution containing betaine, zinc and PHMB
Becerro de Bengoa Vallejo et al. (2011)[61]	Nail avulsion surgery	71	0.1% polyhexanide irrigation solution more effective at reducing bacterial load versus saline or 0.2% nitrofurazone. No patient from PHMB group developed postoperative infection
Bellingeri et al. (2016)[58]	Vascular leg ulcers, pressure ulcers	289	Higher efficacy of propyl-betaine-polyhexanide solution versus saline solution in reducing inflammation and accelerating healing
Borges et al. (2018)[50]	Venous leg ulcers	44	PHMB and saline solutions are effective in reducing bacterial load. However, biofilm was present after cleansing
Chai et al. (2020)[56]	Diabetic foot ulcer	1	A multidrug *Pseudomonas* infection treated with polyhexanide solution/gel and systemic antibiotic resulted in healing of ulcer 40 days after clearing the bone displacement and fracture
Daeschlein et al. (2007)[60]	Second-degree burns	4	Clinically and histologically the mesh grafts treated with polyhexanide showed by far the best re-epithelialisation compared with the deep tissue necrosis and marked fibrin discharge observed for application of povidone-iodine and silver nitrate
Dettmers et al. (2016)[67]	Orthopaedic implant wounds	4	The use of a negative pressure wound therapy with instillation (NPWT-i) and dwell time was developed for treatment for postoperative wound infection on patients at high risk of surgical complications, including infection, found that there was no recurrence of infection
Fabry et al. (2006)[62]	Contaminated acute wounds	50	Treatment with moist dressings of fractionated PHMB and macrogolum 4000, when compared with wounds treated with Ringer's solution, led to a faster and significant reduction in microorganisms on the wound surface
Horrocks (2006)[69]	Hard-to-heal wounds	10	Use of propyl-betaine-polyhexanide wound irrigation and gel is appropriate for cleaning, moistening and decontaminating encrusted, contaminated and hard-to-heal skin wounds
Hunt (2016)[79]	Diabetic foot ulcer	1	Treatment of ulcer with propyl-betaine-polyhexanide wound solution and gel showed some improvement but required oral antibiotics to resolve a recurrent local infection. Clinician switched to surfactant-based solution which leads to wound progression
Kim et al. (2015)[66]	Infected wounds	100	Comparing 0.9% normal saline versus 0.1% polyhexanide plus 0.1% betaine as part of negative pressure wound therapy with instillation (NPWT-i) for the adjunctive treatment of infected wounds, results suggest that saline is as effective as an antiseptic for NPWT-i
Lavery et al. (2020)[57]	Diabetic foot ulcers	150	Comparing the efficacy of negative pressure wound therapy (NPWT) with and without irrigation with 0.1% propyl-betaine-polyhexanide found that there was no change to clinical outcomes with the addition of irrigation. Parameters included incidence of reinfection
Moore et al. (2016)[70]	Hard-to-heal wounds	49	Wounds treated with propyl-betaine-polyhexanide gel improved and the clinicians concluded that the gel provides a moist wound healing environment facilitating wound closure. Only five of 49 patients required additional antimicrobial therapy. The use of this gel inhibited bacterial colonisation and reduced the need for further antimicrobial therapy
Nunes et al. (2019)[54]	Venous leg ulcers	28	Two bundles in venous leg ulcer treatment assessed, with both bundles receiving propyl-betaine-polyhexanide solution. Both bundles were assessed as being effective in the treatment of venous leg ulcers
Romanelli et al. (2010)[55]	Venous leg ulcers	40	The treatment with the propyl-betaine-polyhexanide solution was well tolerated by the patients and was found useful in the absorption of wound odours
Roth et al. (2017)[65]	Traumatic wounds	7,104	The prophylactic application of wound irrigation using 0.04% PHMB, 1% povidone-iodine (PVP-I), 4% hydrogen peroxide or undiluted Ringer's solution indicated that PHMB showed the highest efficacy in preventing infection in traumatic soft tissue wounds (p<0.001)
Saleh et al. (2016)[64]	Skin graft donor sites	40	Soaking tie-over dressings with PHMB solution in full-thickness skin grafting had no effect on postoperative bacterial loads and increased the risk of SSI development
Strobel et al. (2020)[63]	Surgical wounds	393	Significantly fewer SSIs occurred in the group irrigated with 0.04% polyhexanide: n=70 (34.7%) versus n=41 (21.5%); p=0.004. Wound irrigation with polyhexanide was associated with a lower risk of SSI
Timmers et al. (2009)[68]	Post-traumatic osteomyelitis	124	Treated with negative pressure wound therapy with irrigation (NPWT-i) with polyhexanide compared with patients treated with standard care (including debridement, and intravenous antibiotics). In the instillation group the rate of recurrence of infection was 10% compared with 58.5% in the control group (p<0.0001). For the instillation group the total duration of hospital stay was shorter and the number of surgical procedures smaller
Villela-Castro et al. (2018)[59]	Malodorous malignant wounds	24	Comparison between treatment with 0.8% metronidazole solution (control) and 0.2% PHMB found that 100% of patients in both groups were classed as having 'no wound odour' by day 8

SSI—surgical site infection

Table 5. Clinical evidence on the use of polyhexamethylene biguanide (PHMB)-containing dressings for the treatment and prevention of wound infection

First author	Clinical setting	Dressing	Patients, n	Main results
Alblas et al. (2013)[90]	Necrotising fasciitis	Biocellulose	1	Significant debridement and wound improvement with therapy including biocellulose + PHMB dressing
Brantley et al. (2016)[86]	Hard-to-heal wounds	Collagen	5	Collagen matrix + PHMB dressing manages wound bioburden
Çeviker et al. (2015)[72]	Hard-to-heal wounds	Gauze	31	Overall, 17/31 (66.7% PHMB, 43.8% Ringer's; p=0.181) were treated and successfully healed with wound cultures being negative in 19/31 (47.4% PHMB, 52.6% Ringer's) patients
Chai et al. (2020)[56]	Diabetic foot ulcer	Gel	1	A multidrug *Pseudomonas* infection treated with polyhexanide solution/gel and systemic antibiotic resulted in healing of ulcer 40 days after clearing the bone displacement and fracture
Durante et al. (2014)[77]	Hard-to-heal wounds	Gel	124	Treatment with a polyhexanide and propyl betaine-based gel resulted in improvement in wound appearance and reduction in wound area. There was also a decrease in the percentage of patients with wounds with devitalised tissue and/or with biofilm
Eberlein et al. (2012)[91]	Infected wounds of various aetiology	Biocellulose	38	Compared with silver dressings, in the polyhexanide-containing biocellulose wound dressing group critical colonisation and local wound infection had been reduced significantly faster and better (p<0.001) over the 28-day study period
Elzinga et al. (2011)[92]	Paediatric heel lacerations	Biocellulose	20	The use of a PHMB-impregnated biocellulose dressing on paediatric lacerations achieved good healing outcomes. No cases of local infection were noted over the assessment period
Fumarola et al. (2010)[93]	Various wounds	Biocellulose	10	Reduction in infection of wounds treated with a biocellulose dressing impregnated with PHMB
Goertz et al. (2010)[78]	Skin graft donor sites	Gel	44	A polyhexanide-preserved wound gel was superior to Flamazine with respect to a number of parameters important for patient and health care practitioner satisfaction
Hagelstein and Ivins (2013)[102]	Venous leg ulcers	Dressing	5	Use of a moist wound dressing impregnated with PHMB led to a reduction in signs of infection in some patients. Several patients remained infection-free in wounds that were at high risk of reinfection
Horrocks (2006)[69]	Hard-to-heal wounds	Propyl-betaine gel	10	Use of propyl-betaine-polyhexanide wound irrigation and gel is appropriate for cleaning, moistening and decontaminating encrusted, contaminated and hard-to-heal skin wounds
Hunt (2016)[79]	Diabetic foot ulcer	Propyl-betaine gel	1	Treatment of ulcer with propyl-betaine-polyhexanide wound solution and gel showed some improvement but required oral antibiotics to resolve a recurrent local infection. Clinician switched to surfactant-based solution which leads to wound progression
Johnson and Leak (2011)[83]	Various wounds	Foam	25	Using a foam dressing impregnated with PHMB all wounds showed improved healing outcomes. In two patients with MRSA present, repeat swabs were subsequently negative. No new infections were recorded
Kiefer et al. (2018)[80]	Burns requiring skin graft	Propyl-betaine gel	51	Wounds treated with propyl-betaine-polyhexanide gel were assessed for tolerability and safety as well as graft take and healing of the skin graft. The gel was shown to be efficacious, safe and well tolerated. No wound infection occurred
Koullias (2021)[87]	Various wounds	Collagen	16	Patients treated with weekly debridement, application of a purified native collagen with PHMB followed by placental allografts resulted in good wound closure rates
Lenselink and Andriessen (2011)[94]	Hard-to-heal wounds	Biocellulose	28	Treatment of hard-to-heal locally infected and/or critically colonised wounds with a biocellulose dressing impregnated with PHMB led to significant improvement in wound area reduction. 63% of patients showed good reduction in biofilm and 32% scored a moderate reduction
Lintzeris et al. (2018)[88]	Various wounds	Collagen	8	Of the wounds treated with a purified native collagen with PHMB, 6/9 (one patient had two wounds) healed and the remaining three demonstrated improvement in wound appearance
Mancini et al. (2018)[98]	Hard-to-heal wounds	Hydro-active	25	Wound cleansing and control of wound bioburden using a hydro-active dressing impregnated with PHMB was assessed in a variety of hard-to-heal wounds. As well as a decrease in wound surface fibrin levels and an increase in appearance of granulation tissue, bacterial bioburden remained constant over the 7-day assessment period in 50% of cases, decreased in 15%, and increased in 35% of cases
Moore et al. (2016)[70]	Hard-to-heal wounds	Propyl-betaine gel	49	Wounds treated with propyl-betaine-polyhexanide gel improved and the clinicians concluded that the gel provides a moist wound healing environment facilitating wound closure. Only five of 49 patients required additional antimicrobial therapy. The use of this gel inhibited bacterial colonisation and reduced the need for further antimicrobial therapy

Table 5. Clinical evidence of the use of polyhexamethylene biguanide (PHMB)-containing dressings for the treatment and prevention of wound infection (continued)

First author	Clinical setting	Dressing	Patients, n	Main results
Motta et al. (2004)[73]	Various wounds requiring packing	Gauze	21	There were more prominent changes in polymicrobial bioburden in a gauze dressing containing PHMB compared with a gauze dressing without PHMB. With PHMB bioburden was reduced whereas without PHMB bioburden increased to 60% above baseline
Motta and Trigilia (2005)[84]	Tracheostomy wound sites	Foam	10	Culture results showed an absence of pathogens and presence of normal skin flora for 11 study days in patients randomised to the PHMB dressing group and an absence of pathogens and presence of normal skin flora for six study days in patients in the control group
Muangman et al. (2011)[74]	Skin graft donor sites	Gauze	32	Treatment with either a chlorhexidine-coated paraffin tulle dressing or a cotton dressing impregnated with PHMB resulted in no infections in the PHMB group and only one infection in the tulle dressing. The PHMB-impregnated dressing provided a shorter re-epithelialisation time and generated lower pain levels compared with the tulle dressing
Mueller and Krebsbach (2008)[75]	Surgical site infections	Gauze	19,574	Before the introduction of a gauze dressing with 0.2% PHMB, 101 SSIs occurred after 9372 surgical procedures (1.08%), 20 of which were identified as MRSA (0.21%). After introduction of AMD, 84 SSIs occurred after 10,202 surgical procedures (0.82%), representing a rate reduction of 24.07% (p=0.035), with 11 identified as MRSA (0.11%), representing a reduction of 47.62% (p=0.047)
Napavichayanun et al. (2018)[95]	Skin graft donor sites	Biocellulose	21	Half each of STSG donor site wounds were randomly assigned to cover with (a) a bacterial cellulose wound dressing containing silk sericin and PHMB (BCSP) or (b) a chlorhexidine-containing tulle gras dressing. There was no significant difference in wound healing time between the two dressings, but in (a) wound quality was better (p<0.05). There were no signs of infection with either dressing
Nielsen and Andriessen (2012)[96]	Surgical wounds	Biocellulose	60	Pain levels were significantly lower, and the dressing adhered significantly less in the group which received a biocellulose dressing with polyhexanide, compared with a group receiving a hydrophobic dressing with dialkylcarbamoyl chloride
Oropallo (2019)[89]	Hard-to-heal wounds	Collagen	41	No wounds showed any signs of infection at 12 weeks of treatment with a collagen matrix/PHMB wound dressing. 73% of wounds demonstrated a reduction in wound area at 12 weeks, and 37% achieved complete wound closure
Piatkowski et al. (2011)[97]	Burn wounds	Biocellulose	60	The group treated with the biocellulose + polyhexanide dressing demonstrated a better and faster pain reduction in the treated partial-thickness burns, compared to patients treated with a silver-sulfadiazine cream. The results indicate the polyhexanide-containing biocellulose dressing to be safe for partial-thickness burns
Sams-Dodd et al. (2020)[81]	Complex wound	Gel	1	Treatment of patient with infected complex wound included clearance of devitalised tissue and removal of soft tissue infection. When treatment changed to include PHMB gel tissue degeneration was observed and there was disruption of structure of exposed bone
Sibbald et al. (2011)[85]	Hard-to-heal wounds	Foam	40	The use of PHMB foam dressing was a significant predictor of reduced wound superficial bacterial burden (p=0.016) at week 4 as compared with the foam alone. Polymicrobial organisms were recovered at week 4 in 5.3% in the PHMB foam dressing group versus 33% in the control group (p=0.04)
Tuncel et al. (2013)[100]	Hard-to-heal wounds	Gauze	50	A saline-soaked antibacterial gauze-based negative pressure wound therapy (NPWT) treatment compared with conventional dressing therapy which included the use of polyhexanide solution. The patients treated with antibacterial gauze-based NPWT had a significantly reduced recurrence (two wounds versus 14 wounds; p=0·001), and increased number of the culture-negative cases (22 wounds versus 16 wounds; p<0·047) in a follow-up period of 12 months
Wandhoff et al. (2020)[99]	Surgical wounds (joint arthroplasty)	Wipes	13,315	'Universal decolonisation' with polyhexanide did not reduce overall SSIs, but was effective in reducing *Staphylococcus aureus*
Wattanaploy et al. (2017)[82]	Burn wounds	Propyl-betaine gel	46	There was no significant difference between most parameters including infection rates and bacterial colonisation rates when burn wounds treated with propyl-betaine-polyhexanide gel or silver sulfadiazine cream were compared
Wibbenmeyer et al. (2012)[76]	Burn wounds	Gauze	108	Use of a PHMB-impregnated gauze dressing assessed in treatment of burn wounds. There were significantly fewer infections in the study group (18.52% of cases had infections) compared with the historic control group (28.70% of cases had infections) (p=0.047)
Wild et al. (2012)[101]	Pressure ulcers	Biocellulose	30	Comparison between cleansing with polyhexanide swabs (control group) and receiving a polyhexanide-containing cellulose dressing (study group) in patients with pressure ulcers containing meticillin-resistant *Staphylococcus aureus* (MRSA). Wound disinfection was found to be effective in both groups with superior results for the study group

AMD—antimicrobial dressing; BCSP—bacterial cellulose wound dressing; MRSA—meticillin-resistant *Staphylococcus aureus*; SSI—surgical site infection

JoWC_2023_32_1_Rogers_REPRINT 16pp Lic.indd 10 18/01/2023 14:5

response.[56,70,72,74,83,87–90,92,94,97] In the studies where the level of bioburden or risk of infection was a wound parameter under study, several indicated reductions in levels of microorganisms[72,73,83–86,91,93,94,98,100–102] and a decrease in the likelihood of infection developing.[70,74–76,84,99,100,102]

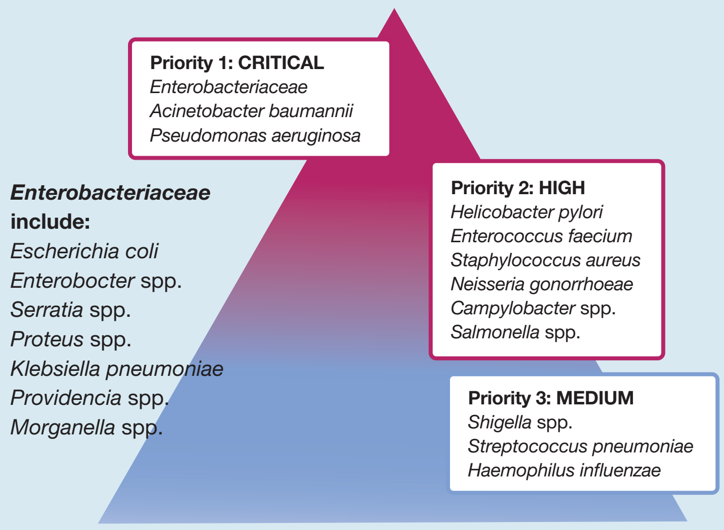
PHMB and the prevention of wound infection
Several studies identified in this review provide an insight into the potential use of PHMB in the prevention of wound infection. For some wounds, treatment with PHMB resulted in no wound infections developing over the course of the studies—a finding true for both studies with acute[61,63,65,75,76,84] and hard-to-heal wounds.[70,100,102] For example, in one study several patients with VLUs remained infection-free in wounds that were at high risk of reinfection,[102] and in a group of patients with non-healing wounds the use of PHMB reduced the requirement for further antimicrobial treatment.[70] However, in one study, soaking of tie-over dressings with PHMB solution (where sutures are placed around the skin graft and which are then tied over a bolster made of PHMB-soaked gauze) in full-thickness skin grafting had no effect on postoperative bacterial loads and increased the risk of SSI development.[64]

Anti-biofilm activity of PHMB
Biofilms are ubiquitous in wounds and are a major cause of delayed healing.[35,103] Their management presents a significant challenge to clinicians treating infected wounds, and a variety of antimicrobials (e.g., iodine, silver, polyhexamethylene biguanide, octenidine, hypochlorous acid, benzalkonium chloride, and a surfactant-based topical gel containing poloxamer 188) have been used and tested for effectiveness.[104] The effectiveness of PHMB against biofilms has been demonstrated in a number of experimental studies.[35,38]

Several studies have demonstrated a reduction in the presence of biofilm in hard-to-heal wounds when these wounds are treated with PHMB-impregnated dressings.[88,94] In one study, treatment with a polyhexanide and propyl betaine-based gel resulted in improvement in wound appearance and reduction in wound area. There was also a decrease in the percentage of patients with wounds with devitalised tissue and/or with biofilm.[77] The precise contribution of PHMB to this anti-biofilm activity is unclear as betaine is a surfactant able to disrupt biofilm.[105] In a further study, although a PHMB solution was effective at reducing bacterial load in VLUs, the authors reported that wound biofilm was still present after wound cleansing with PHMB solutions.[50]

PHMB and its effect on antimicrobial-resistant microorganisms
The effectiveness of PHMB's antiseptic activity against microorganisms extends to a number of antimicrobial-resistant bacteria in laboratory studies,[106]

Fig 5. World Health Organization priority pathogens list[116]



including bacteria identified by the WHO as 'priority resistant pathogens'.[37,107] Clinical evidence for a significant antimicrobial effect of PHMB is currently sparse, with no specific clinical studies investigating this important subject having been carried out to our knowledge. However, there are some studies that give an insight into the potential impact of PHMB on antibiotic-resistant bacteria. Several studies report reductions in the level of meticillin-resistant *Staphylococcus aureus* (MRSA) in wounds as a result of treatment with PHMB.[75,83,101] Chai et al.[56] report the healing of a DFU with a multidrug-resistant *Pseudomonas* infection after treatment with PHMB.

Aligning the use of PHMB wound treatments with antimicrobial stewardship
Biofilm plays a significant role in the development of antimicrobial-resistant bacteria by encouraging the transfer of antibiotic-resistant genes between bacterial species.[108] The WHO has declared that 'Antimicrobial resistance is one of the top 10 global public health threats facing humanity'.[109] It is noteworthy that PHMB is effective against antimicrobial-resistant bacteria and, in particular, some of those microorganisms identified by the WHO as priority resistant pathogens (Fig 5). Additionally, with the resistance of microbes specifically to antibiotics, there is the emergence of multidrug-resistant nosocomial infections.[110] The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.) are the leading cause of nosocomial infections across the world, with many ESKAPE bacteria becoming drug resistant.[111] Several studies have investigated the effectiveness of PHMB against such antimicrobial-resistant microorganisms, and results suggest that PHMB is effective against all ESKAPE pathogens.[50,112]

In an age of increasing resistance, antiseptics are emerging as an alternative (to antibiotics) for infection control because of their much lower risk (or absence) of bacterial resistance.[113] This is particularly important as resistance to PHMB has not been reported, despite its having been used for decades.[15,114] One study has reported a reduced susceptibility to PHMB of MRSA with prolonged exposure to low levels of this antimicrobial agent in in vitro tests, but this reduced susceptibility was not observed in an in vivo decolonisation treatment using PHMB.[115]

The development of antimicrobial resistance (AMR) has diminished the effectiveness of many antimicrobials used to prevent/treat wound infections. AMR is a growing global public health challenge that has been identified as one of the top 10 threats to global health by the WHO.[116] To help address AMR, antimicrobial stewardship (AMS) programmes have been developed, designed to educate healthcare workers, and control the prescribing and targeting of antibiotics, and hence reduce the likelihood of AMR. The topical use of antiseptics for wound care has a role in AMS strategies.[117–119] The inclusion of PHMB in wound treatments supports AMS in that it is an effective antimicrobial treatment while not causing microbial resistance.

Conclusion

The aim of this narrative review was to provide an overview of clinical evidence exploring the antimicrobial role of polyhexamethylene biguanide (PHMB) on wound healing. This was achieved by searching the PubMed database and undertaking a manual search for appropriate papers based on identified key words relevant to the primary research question. The resulting papers identified were interrogated for those that aligned with the primary research question. Analysis of these papers showed that the experimental evidence demonstrated significant antimicrobial activity for PHMB against a wide variety of microorganisms, including both Gram-negative and Gram-positive bacteria, as well as biofilms and antimicrobial-resistant bacteria. Additionally, PHMB was demonstrated to be effective against pathogenic fungi, viruses and unicellular protozoa.

The mechanism of action of PHMB as an antimicrobial was defined in terms of a two-stage process:

1. Attachment and integration into the bacterial cell wall, inducing pores in this structure and resulting in leakage of bacterial intracellular components.
2. Transit of PHMB through the bacterial cell wall and then interaction of PHMB with nuclear components, resulting in condensation of proteins and inactivation of the bacteria.

The review identified evidence that supports a key role for PHMB in the prevention and treatment of wound infection against many different microorganisms and across a wide variety of different wound types. Included papers highlighted alignment with the use of PHMB in supporting an AMS role in that it is not only a highly effective antimicrobial, specifically against biofilms and resistant microorganisms, but that importantly it does not induce such AMR. **JWC**

Reflective questions

- Against which microbials is polyhexamethylene biguanide (PHMB) effective?
- What are the two mechanisms of action (MoA) of PHMB against bacteria?
- How effective is PHMB against biofilms and/or antimicrobial-resistant organisms, e.g., meticillin-resistant *Staphylococcus aureus* (MRSA)?
- What evidence is there (if any) to show that PHMB can cause antimicrobial resistance?
- Can PHMB support antimicrobial stewardship strategy in preventing development of antimicrobial resistance (AMR), and, if so, how?

References

1 Parlet CP, Brown MM, Horswill AR. Commensal Staphylococci influence Staphylococcus aureus skin colonization and disease. Trends Microbiol 2019; 27(6):497–507. https://doi.org/10.1016/j.tim.2019.01.008

2 Wynn M. The impact of infection on the four stages of acute wound healing: an overview. Wounds UK 2021; 17(2):26–32

3 Serra R, Grande R, Butrico L et al. Chronic wound infections: the role of Pseudomonas aeruginosa and Staphylococcus aureus. Expert Rev Anti Infect Ther 2015; 13(5):605–613. https://doi.org/10.1586/14787210.2015.1023291

4 Rahim K, Saleha S, Zhu X et al. Bacterial contribution in chronicity of wounds. Microb Ecol 2017; 73(3):710–721. https://doi.org/10.1007/s00248-016-0867-9

5 Dhar Y, Han Y. Current developments in biofilm treatments: wound and implant infections. Engineered Regeneration 2020; 1:64–75. https://doi.org/10.1016/j.engreg.2020.07.003

6 Pîrvănescu H, Bălăşoiu M, Ciurea ME et al. Wound infections with multi-drug resistant bacteria. Chirurgia (Bucur) 2014;109(1):73–79

7 Sen CK, Roy S, Mathew-Steiner SS, Gordillo GM. Biofilm management in wound care. Plast Reconstr Surg 2021; 148(2):275e–288e. https://doi.org/10.1097/PRS.0000000000008142

8 Punjataewakupt A, Napavichayanun S, Aramwit P. The downside of antimicrobial agents for wound healing. Eur J Clin Microbiol Infect Dis 2019; 38(1):39–54. https://doi.org/10.1007/s10096-018-3393-5

9 Cooper R, Lawrence JC. The role of antimicrobial agents in wound care. J Wound Care 1996; 5(8):374–380. https://doi.org/10.12968/jowc.1996.5.8.374

10 Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis 2009; 49(10):1541–1549. https://doi.org/10.1086/644732

11 Wounds UK. Best practice statement. The use of topical antimicrobial agents in wound management. (3rd edition) Wounds UK, 2013

12 Cooper R, Kirketerp-Møller K. Non-antibiotic antimicrobial interventions and antimicrobial stewardship in wound care. J Wound Care 2018; 27(6):355–377. https://doi.org/10.12968/jowc.2018.27.6.355

13 Passic SR, Ferguson ML, Catalone BJ et al. Structure-activity relationships of polybiguanides with activity against human immunodeficiency virus type 1. Biomed Pharmacother 2010; 64(10):723–732. https://doi.org/10.1016/j.biopha.2010.10.001

14 Kamaruzzaman NF, Chong SQ, Edmondson-Brown KM et al. Bactericidal and anti-biofilm effects of polyhexamethylene biguanide in models of intracellular and biofilm of Staphylococcus aureus isolated from bovine mastitis. Front Microbiol 2017; 8:1518. https://doi.org/10.3389/fmicb.2017.01518

15 Sowlati-Hashjin S, Carbone P, Karttunen M. Insights into the polyhexamethylene biguanide (PHMB) mechanism of action on bacterial membrane and DNA: a molecular dynamics study. J Phys Chem B 2020; 124(22):4487–4497. https://doi.org/10.1021/acs.jpcb.0c02609

16 Wounds UK. Consensus document: PHMB and its potential contribution to wound management. Wounds UK, 2010

17 Babalska ZŁ, Korbecka-Paczkowska M, Karpiński TM. Wound antiseptics and European guidelines for antiseptic application in wound treatment. Pharmaceuticals 2021; 14(12):1253. https://doi.org/10.3390/ph14121253
18 Chindera K, Mahato M, Kumar Sharma A et al. The antimicrobial polymer PHMB enters cells and selectively condenses bacterial chromosomes. Sci Rep 2016; 6(1):23121. https://doi.org/10.1038/srep23121
19 Asiedu-Gyekye IJ, Mahmood AS, Awortwe C, Nyarko AK. Toxicological assessment of polyhexamethylene biguanide for water treatment. Interdiscip Toxicol 2015; 8(4):193–202. https://doi.org/10.1515/intox-2015-0029
20 Johnson W Jr, Boyer I, Zhu J et al. Safety assessment of polyaminopropyl biguanide (polyhexamethylene biguanide hydrochloride) as used in cosmetics. Int J Toxicol 2020; 39(3_suppl):26S–73S. https://doi.org/10.1177/1091581820958683
21 Papa V, van der Meulen I, Rottey S et al. Safety and tolerability of topical polyhexamethylene biguanide: a randomised clinical trial in healthy adult volunteers. Br J Ophthalmol 2022; 106(2):190–196. https://doi.org/10.1136/bjophthalmol-2020-317848
22 Hübner NO, Kramer A. Review on the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic. Skin Pharmacol Physiol 2010; 23(Suppl 1):17–27. https://doi.org/10.1159/000318264
23 Broxton P, Woodcock PM, Heatley F, Gilbert P. Interaction of some polyhexamethylene biguanides and membrane phospholipids in Escherichia coli. J Appl Bacteriol 1984; 57(1):115–124. https://doi.org/10.1111/j.1365-2672.1984.tb02363.x
24 Broxton P, Woodcock PM, Gilbert P. Binding of some polyhexamethylene biguanides to the cell envelope of Escherichia coli ATCC 8739. Microbios 1984; 41(163):15–22
25 Ikeda T, Ledwith A, Bamford CH, Hann RA. Interaction of a polymeric biguanide biocide with phospholipid membranes. Biochimica et Biophysica Acta (BBA) - Biomembranes 1984; 769(1):57–66. https://doi.org/10.1016/0005-2736(84)90009-9
26 Moore K, Gray D. Using PHMB antimicrobial to prevent wound infection. Wounds UK 2007; 3(2):96–102
27 Küsters M, Beyer S, Kutscher S et al. Rapid, simple and stability-indicating determination of polyhexamethylene biguanide in liquid and gel-like dosage forms by liquid chromatography with diode-array detection. J Pharm Anal 2013; 3(6):408–414. https://doi.org/10.1016/j.jpha.2013.02.007
28 Ha Y, Koo Y, Park SK et al. Liposome leakage and increased cellular permeability induced by guanidine-based oligomers: effects of liposome composition on liposome leakage and human lung epithelial barrier permeability. RSC Advances 2021; 11(51):32000–32011. https://doi.org/10.1039/D1RA05478C
29 Gilbert P, Moore LE. Cationic antiseptics: diversity of action under a common epithet. J Appl Microbiol 2005; 99(4):703–715. https://doi.org/10.1111/j.1365-2672.2005.02664.x
30 Allen MJ, Morby AP, White GF. Cooperativity in the binding of the cationic biocide polyhexamethylene biguanide to nucleic acids. Biochem Biophys Res Commun 2004; 318(2):397–404. https://doi.org/10.1016/j.bbrc.2004.04.043
31 Allen MJ, White GF, Morby AP. The response of Escherichia coli to exposure to the biocide polyhexamethylene biguanide. Microbiology 2006; 152(4):989–1000. https://doi.org/10.1099/mic.0.28643-0
32 Mashat BH. Polyhexamethylene biguanide hydrochloride: features and applications. Br J Environm Sci 2016; 4:49–55
33 Ni Y, Qian Z, Yin Y et al. Polyvinyl alcohol/chitosan/polyhexamethylene biguanide phase separation system: a potential topical antibacterial formulation with enhanced antimicrobial effect. Molecules 2020; 25(6):1334. https://doi.org/10.3390/molecules25061334
34 To E, Dyck R, Gerber S et al. The effectiveness of topical polyhexamethylene biguanide (PHMB) agents for the treatment of chronic wounds: a systematic review. Surg Technol Int 2016; 29:45–51
35 Salisbury AM, Mullin M, Chen R, Percival SL. Antibiofilm efficacy of polihexanide, octenidine and sodium hypochlorite/hypochlorous acid based wound irrigation solutions against Staphylococcus aureus, Pseudomonas aeruginosa and a multispecies biofilm. Adv Exp Med Biol 2021; 1369:53–67. https://doi.org/10.1007/5584_2021_645
36 Dydak K, Junka A, Dydak A et al. In vitro efficacy of bacterial cellulose dressings chemisorbed with antiseptics against biofilm formed by pathogens isolated from chronic wounds. Int J Mol Sci 2021; 22(8):3996. https://doi.org/10.3390/ijms22083996
37 Barrigah-Benissan K, Ory J, Dunyach-Remy C et al. Antibiofilm properties of antiseptic agents used on Pseudomonas aeruginosa isolated from diabetic foot ulcers. Int J Mol Sci 2022; 23(19):11270. https://doi.org/10.3390/ijms231911270
38 Oates A, Lindsay S, Mistry H et al. Modelling antisepsis using defined populations of facultative and anaerobic wound pathogens grown in a basally perfused biofilm model. Biofouling 2018; 34(5):507–518. https://doi.org/10.1080/08927014.2018.1466115
39 Sibbald RG, Elliott JA, Verma L et al. Update: topical antimicrobial agents for chronic wounds. Adv Skin Wound Care 2017; 30(10):438–450. https://doi.org/10.1097/01.ASW.0000524471.28441.b9
40 Kamaruzzaman NF, Firdessa R, Good L. Bactericidal effects of polyhexamethylene biguanide against intracellular Staphylococcus aureus EMRSA-15 and USA 300. J Antimicrob Chemother 2016; 71(5):1252–1259. https://doi.org/10.1093/jac/dkv474
41 Rodeheaver GT, Ratliff CR. Wound cleansing, wound irrigation, wound disinfection. In: Krasner DL, van Rijswijk L (eds). Chronic wound care: the essentials e-Book. HMP, 2018:47–62
42 Lewis K, Pay JL. Wound Irrigation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2022. https://tinyurl.com/58m6ewz6 (accessed 7 December 2022)
43 Wilkins RG, Unverdorben M. Wound cleaning and wound healing: a concise review. Adv Skin Wound Care 2013; 26(4):160–163. https://doi.org/10.1097/01.ASW.0000428861.26671.41
44 Lindfors J. A comparison of an antimicrobial wound cleanser to normal saline in reduction of bioburden and its effect on wound healing. Ostomy Wound Manage 2004; 50(8):28–41
45 Serena TE, Serena L, Al-Jalodi O et al. The efficacy of sodium hypochlorite antiseptic: a double-blind, randomised controlled pilot study. J Wound Care 2022; 31(Sup2):S32–S35. https://doi.org/10.12968/jowc.2022.31.Sup2.S32
46 Armstrong DG, Bohn G, Glat P et al. Expert recommendations for the use of hypochlorous solution: science and clinical application. Ostomy Wound Manage 2015; 61(5):S2–S19
47 Davis S, Gil J, Li J et al. Effect of mechanical debridement and irrigation with hypochlorous acid wound management solution on methicillin-resistant Staphylococcus aureus contamination and healing deep dermal wounds in a porcine model. Wound Management & Prevention 2021; 67(8):24–31. https://doi.org/10.25270/wmp.2021.8.2431
48 Burian EA, Sabah L, Kirketerp-Møller K et al. Effect of stabilized hypochlorous acid on re-epithelialization and bacterial bioburden in acute wounds: a randomized controlled trial in healthy volunteers. Acta Derm Venereol 2022; 102:adv00727. https://doi.org/10.2340/actadv.v102.1624
49 Bigliardi PL, Alsagoff SA, El-Kafrawi HY et al. Povidone iodine in wound healing: a review of current concepts and practices. Int J Surg 2017; 44:260–268. https://doi.org/10.1016/j.ijsu.2017.06.073
50 Borges EL, Frison SS, Honorato-Sampaio K et al. Effect of polyhexamethylene biguanide solution on bacterial load and biofilm in venous leg ulcers: a randomized controlled trial. J Wound Ostomy Continence Nurs 2018; 45(5):425–431. https://doi.org/10.1097/WON.0000000000000455
51 Andriessen AE, Eberlein T. Assessment of a wound cleansing solution in the treatment of problem wounds. Wounds 2008; 20(6):171–175
52 Klasinc R, Augustin LA, Below H et al. Evaluation of three experimental in vitro models for the assessment of the mechanical cleansing efficacy of wound irrigation solutions. Int Wound J 2018; 15(1):140–147. https://doi.org/10.1111/iwj.12850
53 Assadian O, Kammerlander G, Geyrhofer C et al. Use of wet-to-moist cleansing with different irrigation solutions to reduce bacterial bioburden in chronic wounds. J Wound Care 2018; 27(Sup10):S10–S16. https://doi.org/10.12968/jowc.2018.27.Sup10.S10
54 Nunes CA, Melo PG, Malaquias SG et al. Effectiveness of two bundles in venous leg ulcer healing: a randomized controlled trial. J Vasc Nurs 2019; 37(4):232–245. https://doi.org/10.1016/j.jvn.2019.09.004
55 Romanelli M, Dini V, Barbanera S, Bertone MS. Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation. Skin Pharmacol Physiol 2010; 23(Suppl 1):41–44. https://doi.org/10.1159/000318266
56 Chai W, Wang Y, Jiao F et al. A severe diabetic foot ulcer with intermediate cuneiform displacement and multidrug-resistant Pseudomonas aeruginosa infection: a rare case report. Frontiers in Medicine 2020; 7:131. https://doi.org/10.3389/fmed.2020.00131
57 Lavery LA, Davis KE, La Fontaine J et al. Does negative pressure wound therapy with irrigation improve clinical outcomes? A randomized clinical trial in patients with diabetic foot infections. Am J Surg 2020; 220(4):1076–1082. https://doi.org/10.1016/j.amjsurg.2020.02.044
58 Bellingeri A, Falciani F, Traspedini P et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. J Wound Care 2016; 25(3):160–168. https://doi.org/10.12968/jowc.2016.25.3.160
59 Villela-Castro DL, Santos VL, Woo K. Polyhexanide versus metronidazole for odor management in malignant (fungating) wounds: a double-blinded, randomized, clinical trial. J Wound Ostomy Continence Nurs 2018; 45(5):413–418. https://doi.org/10.1097/WON.0000000000000460
60 Daeschlein G, Assadian O, Bruck JC et al. Feasibility and clinical applicability of polihexanide for treatment of second-degree burn wounds. Skin Pharmacol Physiol 2007; 20(6):292–296. https://doi.

org/10.1159/000107577
61 Becerro de Bengoa Vallejo R, Losa Iglesias ME, Cervera LA et al. Efficacy of intraoperative surgical irrigation with polihexanide and nitrofurazone in reducing bacterial load after nail removal surgery. J Am Acad Dermatol 2011; 64(2):328–335. https://doi.org/10.1016/j.jaad.2010.01.011
62 Fabry W, Trampenau C, Bettag C et al. Bacterial decontamination of surgical wounds treated with Lavasept. Int J Hyg Environ Health 2006; 209(6):567–573. https://doi.org/10.1016/j.ijheh.2006.03.008
63 Strobel RM, Leonhardt M, Krochmann A et al. Reduction of postoperative wound infections by antiseptica (RECIPE)?: a randomized controlled trial. Ann Surg 2020; 272(1):55–64. https://doi.org/10.1097/SLA.0000000000003645
64 Saleh K, Sonesson A, Persson K et al. Can dressings soaked with polyhexanide reduce bacterial loads in full-thickness skin grafting? A randomized controlled trial. J Am Acad Dermatol 2016; 75(6):1221–1228.e4. https://doi.org/10.1016/j.jaad.2016.07.020
65 Roth B, Neuenschwander R, Brill F et al. Effect of antiseptic irrigation on infection rates of traumatic soft tissue wounds: a longitudinal cohort study. J Wound Care 2017; 26(3):79–87. https://doi.org/10.12968/jowc.2017.26.3.79
66 Kim PJ, Attinger CE, Oliver N et al. Comparison of outcomes for normal saline and an antiseptic solution for negative-pressure wound therapy with instillation. Plast Reconstr Surg 2015; 136(5):657e–664e. https://doi.org/10.1097/PRS.0000000000001709
67 Dettmers R, Brekelmans W, Leijnen M et al. Negative pressure wound therapy with instillation and dwell time used to treat infected orthopedic implants: a 4-patient case series. Ostomy Wound Manage 2016; 62(9):30–40
68 Timmers MS, Graafland N, Bernards AT et al. Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis. Wound Repair Regen 2009; 17(2):278–286. https://doi.org/10.1111/j.1524-475X.2009.00458.x
69 Horrocks A. Prontosan wound irrigation and gel: management of chronic wounds. Br J Nurs 2006; 15(22):1222–1228. https://doi.org/10.12968/bjon.2006.15.22.22559
70 Moore M, Dobson N, Cetnarowski W. 0.1% polyhexanide-betaine solution as an adjuvant in a case-series of chronic wounds. Surg Technol Int 2016; 29:85–89
71 Dumville JC, Gray TA, Walter CJ et al. Dressings for the prevention of surgical site infection. Cochrane Database Syst Rev 2016; 2016(12):CD003091. https://doi.org/10.1002/14651858.CD003091.pub4
72 Çeviker K, Canikoğlu M, Tatlıoğlu S, Bağdatlı Y. Reducing the pathogen burden and promoting healing with polyhexanide in non-healing wounds: a prospective study. J Wound Care 2015; 24(12):582–586. https://doi.org/10.12968/jowc.2015.24.12.582
73 Motta GJ, Milne CT, Corbett LQ. Impact of antimicrobial gauze on bacterial colonies in wounds that require packing. Ostomy Wound Manage 2004; 50(8):48–62
74 Muangman P, Nitimonton S, Aramwit P. Comparative clinical study of Bactigras and Telfa AMD for skin graft donor-site dressing. Int J Mol Sci 2011; 12(8):5031–5038. https://doi.org/10.3390/ijms12085031
75 Mueller SW, Krebsbach LE. Impact of an antimicrobial-impregnated gauze dressing on surgical site infections including methicillin-resistant Staphylococcus aureus infections. Am J Infect Control 2008; 36(9):651–655. https://doi.org/10.1016/j.ajic.2007.12.005
76 Wibbenmeyer L, Williams I, Liao J et al. A pilot study of the use of biocide-impregnated gauze as an adjunct to wound care in a burn population. J Burn Care Res 2012; 33(3):358–363. https://doi.org/10.1097/BCR.0b013e31823746d2
77 Durante CM, Greco A, Sidoli O et al. Evaluation of the effectiveness of a polyhexanide and propyl betaine-based gel in the treatment of chronic wounds. Minerva Chir 2014; 69(5):283–292
78 Goertz O, Ring A, Knie U et al. Evaluation of a novel polihexanide-preserved wound covering gel on dermal wound healing. Eur Surg Res 2010; 44(1):23–29. https://doi.org/10.1159/000260040
79 Hunt S. Case 14: Octenilin wound gel versus betadine/PHMB gel. J Wound Care 2016; 25(3 Suppl):S22–S23
80 Kiefer J, Harati K, Müller-Seubert W et al. Efficacy of a gel containing polihexanide and betaine in deep partial and full thickness burns requiring split-thickness skin grafts: a noncomparative clinical study. J Burn Care Res 2018; 39(5):685–693. https://doi.org/10.1093/jbcr/iry019
81 Sams-Dodd J, Sams-Dodd F. Micropore particle technology promotes wound healing, whereas polyhexamethylene biguanide causes tissue degeneration: a case report. Wounds 2020; 32(3):E6–E10
82 Wattanaploy S, Chinaroonchai K, Namviriyachote N, Muangman P. Randomized controlled trial of polyhexanide/betaine gel versus silver sulfadiazine for partial-thickness burn treatment. Int J Low Extrem Wounds 2017; 16(1):45–50. https://doi.org/10.1177/1534734617690949
83 Johnson S, Leak K. Evaluating a dressing impregnated with polyhexamethylene biguanide. Wounds UK 2011; 7(2):20–25
84 Motta GJ, Trigilia D. The effect of an antimicrobial drain sponge dressing on specific bacterial isolates at tracheostomy sites. Ostomy Wound Manage 2005; 51(1):60–62
85 Sibbald RG, Coutts P, Woo KY. Reduction of bacterial burden and pain in chronic wounds using a new polyhexamethylene biguanide antimicrobial foam dressing-clinical trial results. Adv Skin Wound Care 2011; 24(2):78–84. https://doi.org/10.1097/01.ASW.0000394027.82702.16
86 Brantley J, Park H, Sanchez PJ, Fitzgerald R. The use of a novel antimicrobial and purified native collagen matrix combination to manage bioburden and support healing in challenging wounds: a clinical evaluation. Wounds International 2016; 7(3):40–45
87 Koullias GJ. Efficacy of the application of a purified native collagen with embedded antimicrobial barrier followed by a placental allograft on a diverse group of nonhealing wounds of various etiologies. Wounds 2021; 33(1):20–27
88 Lintzeris D, Vernon K, Percise H et al. Effect of a new purified collagen matrix with polyhexamethylene biguanide on recalcitrant wounds of various etiologies: a case series. Wounds 2018; 30(3):72–78
89 Oropallo AR. Use of native type I collagen matrix plus polyhexamethylene biguanide for chronic wound treatment. Plast Reconstr Surg Glob Open 2019; 7(1):e2047. https://doi.org/10.1097/GOX.0000000000002047
90 Alblas J, Klicks RJ, Andrlessen A. A special case: treatment of a patient with necrotising fasciitis. Br J Nurs 2013; 22(15):S22–S26. https://doi.org/10.12968/bjon.2013.22.Sup10.S22
91 Eberlein T, Haemmerle G, Signer M et al. Comparison of PHMB-containing dressing and silver dressings in patients with critically colonised or locally infected wounds. J Wound Care 2012; 21(1):12–20. https://doi.org/10.12968/jowc.2012.21.1.12
92 Elzinga G, van Doorn J, Wiersema AM et al. Clinical evaluation of a PHMB-impregnated biocellulose dressing on paediatric lacerations. J Wound Care 2011; 20(6):280–284. https://doi.org/10.12968/jowc.2011.20.6.280
93 Fumarola S, Butcher M, Cooper P et al. A clinical audit of Suprasorb X + PHMB. Wounds UK 2010; 6(3):78–87
94 Lenselink E, Andriessen A. A cohort study on the efficacy of a polyhexanide-containing biocellulose dressing in the treatment of biofilms in wounds. J Wound Care 2011; 20(11):534–539. https://doi.org/10.12968/jowc.2011.20.11.534
95 Napavichayanun S, Ampawong S, Harnsilpong T et al. Inflammatory reaction, clinical efficacy, and safety of bacterial cellulose wound dressing containing silk sericin and polyhexamethylene biguanide for wound treatment. Arch Dermatol Res 2018; 310(10):795–805. https://doi.org/10.1007/s00403-018-1871-3
96 Nielsen AM, Andriessen A. Prospective cohort study on surgical wounds comparing a polyhexanide-containing biocellulose dressing with a dialkyl-carbamoyl-chloride-containing hydrophobic dressing. Adv Skin Wound Care 2012; 25(9):409–413. https://doi.org/10.1097/01.ASW.0000419406.29700.ef
97 Piatkowski A, Drummer N, Andriessen A et al. Randomized controlled single center study comparing a polyhexanide containing bio-cellulose dressing with silver sulfadiazine cream in partial-thickness dermal burns. Burns 2011; 37(5):800–804. https://doi.org/10.1016/j.burns.2011.01.027
98 Mancini S, Cuomo R, Poggialini M et al. Autolytic debridement and management of bacterial load with an occlusive hydroactive deressing impregnated with polyhexamethylene biguanide. Acta Biomed 2018; 88(4):409–413
99 Wandhoff B, Schröder C, Nöth U et al. Efficacy of universal preoperative decolonization with polyhexanide in primary joint arthroplasty on surgical site infections. A multicenter before-and after-study. Antimicrob Resist Infect Control 2020; 9(1):188. https://doi.org/10.1186/s13756-020-00852-0
100 Tuncel U, Erkorkmaz Ü, Turan A. Clinical evaluation of gauze-based negative pressure wound therapy in challenging wounds. Int Wound J 2013; 10(2):152–158. https://doi.org/10.1111/j.1742-481X.2012.00955.x
101 Wild T, Bruckner M, Payrich M et al. Eradication of methicillin-resistant Staphylococcus aureus in pressure ulcers comparing a polyhexanide-containing cellulose dressing with polyhexanide swabs in a prospective randomized study. Adv Skin Wound Care 2012; 25(1):17–22. https://doi.org/10.1097/01.ASW.0000410686.14363.ea
102 Hagelstein SM, Ivins N. Treating recalcitrant venous leg ulcers using a PHMB impregnated dressing: a case study evaluation. Wounds UK 2013; 9(4):84–90
103 Nedelea AG, Plant RL, Robins LI, Maddocks SE. Testing the efficacy of topical antimicrobial treatments using a two- and five-species chronic wound biofilm model. J Appl Microbiol 2022; 132(1):715–724. https://doi.org/10.1111/jam.15239
104 Stoffel JJ, Kohler Riedi PL, Hadj Romdhane B. A multimodel regime for evaluating effectiveness of antimicrobial wound care products in microbial biofilms. Wound Repair Regen 2020; 28(4):438–447. https://doi.org/10.1111/wrr.12806

105 Bazire A, Diab F, Jebbar M, Haras D. Influence of high salinity on biofilm formation and benzoate assimilation by Pseudomonas aeruginosa. J Ind Microbiol Biotechnol 2006; 34(1):5–8. https://doi.org/10.1007/s10295-006-0087-2
106 Piatkowska E, Paleczny J, Dydak K, Letachowicz K. Antimicrobial activity of hemodialysis catheter lock solutions in relation to other compounds with antiseptic properties. PLoS One 2021; 16(10):e0258148. https://doi.org/10.1371/journal.pone.0258148
107 Denysko TV, Nazarchuk OA, Gruzevskyi O et al. In vitro evaluation of the antimicrobial activity of antiseptics against clinical Acinetobacter baumannii strains isolated from combat wounds. Front Microbiol 2022; 13:932467. https://doi.org/10.3389/fmicb.2022.932467
108 Bowler P, Murphy C, Wolcott R. Biofilm exacerbates antibiotic resistance: Is this a current oversight in antimicrobial stewardship? Antimicrob Resist Infect Control 2020; 9(1):162. https://doi.org/10.1186/s13756-020-00830-6
109 Ghosh S, Bornman C, Zafer MM. Antimicrobial resistance threats in the emerging COVID-19 pandemic: where do we stand? J Infect Public Health 2021; 14(5):555–560. https://doi.org/10.1016/j.jiph.2021.02.011
110 Giamarellou H, Poulakou G. Multidrug-resistant Gram-negative infections: what are the treatment options? Drugs 2009; 69(14):1879–1901. https://doi.org/10.2165/11315690-000000000-00000
111 Barreto R, Barrois B, Lambert J et al. Addressing the challenges in antisepsis: focus on povidone iodine. Int J Antimicrob Agents 2020; 56(3):106064. https://doi.org/10.1016/j.ijantimicag.2020.106064
112 Davis SC, Harding A, Gil J et al. Effectiveness of a polyhexanide irrigation solution on methicillin-resistant Staphylococcus aureus biofilms in a porcine wound model. Int Wound J 2017; 14(6):937–944. https://doi.org/10.1111/iwj.12734
113 Lachapelle JM, Castel O, Casado AF et al. Antiseptics in the era of bacterial resistance: a focus on povidone iodine. Clin Pract 2013; 10(5):579–592. https://doi.org/10.2217/cpr.13.50
114 Wessels S, Ingmer H. Modes of action of three disinfectant active substances: a review. Regul Toxicol Pharmacol 2013; 67(3):456–467. https://doi.org/10.1016/j.yrtph.2013.09.006
115 Renzoni A, Von Dach E, Landelle C et al. Impact of exposure of methicillin-resistant Staphylococcus aureus to polyhexanide in vitro and in vivo. Antimicrob Agents Chemother 2017; 61(10):e00272-17. https://doi.org/10.1128/AAC.00272-17
116 World Health Organization. Antimicrobial resistance. 2021. https://tinyurl.com/ydecub73 (accessed 1 December 2022)
117 Maillard JY, Kampf G, Cooper R. Antimicrobial stewardship of antiseptics that are pertinent to wounds: the need for a united approach. JAC Antimicrob Resist 2021; 3(1):dlab027. https://doi.org/10.1093/jacamr/dlab027
118 Roberts CD, Leaper DJ, Assadian O. The role of topical antiseptic agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. Adv Wound Care 2017; 6(2):63–71. https://doi.org/10.1089/wound.2016.0701
119 Edwards-Jones V, Spruce P. Antimicrobial stewardship: what it means in tissue viability? Wounds UK 2019; 15(1):64–69
120 Uzer Celik E, Tunac AT, Ates M, Sen BH. Antimicrobial activity of different disinfectants against cariogenic microorganisms. Braz Oral Res 2016; 30(1):e125. https://doi.org/10.1590/1807-3107bor-2016.vol30.0125
121 Hafner S, Ehrenfeld M, Storz E, Wieser A. Photodynamic inactivation of Actinomyces naeslundii in comparison with chlorhexidine and polyhexanide—a new approach for antiseptic treatment of medication-related osteonecrosis of the jaw? J Oral Maxillofac Surg 2016; 74(3):516–522. https://doi.org/10.1016/j.joms.2015.09.014
122 Paleczny J, Junka A, Brozyna M et al. The high impact of Staphylococcus aureus biofilm culture medium on in vitro outcomes of antimicrobial activity of wound antiseptics and antibiotic. Pathogens 2021; 10(11):1385. https://doi.org/10.3390/pathogens10111385
123 Ali S, Wilson AP. Effect of poly-hexamethylene biguanide hydrochloride (PHMB) treated non-sterile medical gloves upon the transmission of Streptococcus pyogenes, carbapenem-resistant E. coli, MRSA and Klebsiella pneumoniae from contact surfaces. BMC Infect Dis 2017; 17(1):574. https://doi.org/10.1186/s12879-017-2661-9
124 Mencucci R, Favuzza E, Bottino P et al. A new ophthalmic formulation containing antiseptics and dexpanthenol: In vitro antimicrobial activity and effects on corneal and conjunctival epithelial cells. Exp Eye Res 2020; 201:108269. https://doi.org/10.1016/j.exer.2020.108269
125 Medvedec Mikić I, Cigić L, Kero D et al. Antimicrobial effectiveness of polyhexamethylene biguanide on Enterococcus faecalis, Staphylococcus epidermidis and Candida albicans. Med Glas (Zenica) 2018; 15(2):132–138. https://doi.org/10.17392/959-18
126 Minnich KE, Stolarick R, Wilkins RG et al. The effect of a wound care solution containing polyhexanide and betaine on bacterial counts: results of an in vitro study. Ostomy Wound Manage 2012; 58(10):32–36
127 Jin J, Chen ZL, Xiang Y et al. Development of a PHMB hydrogel-modified wound scaffold dressing with antibacterial activity. Wound Repair Regen 2020; 28(4):480–492. https://doi.org/10.1111/wrr.12813
128 Shoukat K, Pilling S, Rout S et al. A systematic comparison of antimicrobial wound dressings using a planktonic cell and an immobilized cell model. J Appl Microbiol 2015; 119(6):1552–1560. https://doi.org/10.1111/jam.12967
129 Loose M, Naber KG, Purcell L et al. Anti-biofilm effect of octenidine and polyhexanide on uropathogenic biofilm-producing bacteria. Urol Int 2021; 105(3-4):278–284. https://doi.org/10.1159/000512370
130 López-Rojas R, Fernández-Cuenca F, Serrano-Rocha L, Pascual Á. In vitro activity of a polyhexanide–betaine solution against high-risk clones of multidrug-resistant nosocomial pathogens. Enferm Infecc Microbiol Clin 2017; 35(1):12–19. https://doi.org/10.1016/j.eimc.2016.02.008
131 Fabry WH, Kock HJ, Vahlensieck W. Activity of the antiseptic polyhexanide against gram-negative bacteria. Microb Drug Resist 2014; 20(2):138–143. https://doi.org/10.1089/mdr.2013.0113
132 Reddersen K, Finger S, Zieger M et al. Cytocompatibility testing of cyclodextrin-functionalized antimicrobial textiles—a comprehensive approach. J Mater Sci Mater Med 2016; 27(12):190. https://doi.org/10.1007/s10856-016-5804-4
133 Zheng Y, Wang D, Ma LZ. Effect of polyhexamethylene biguanide in combination with undecylenamidopropyl betaine or PslG on biofilm clearance. Int J Mol Sci 2021; 22(2):768. https://doi.org/10.3390/ijms22020768
134 Heaselgrave W, Hamad A, Coles S, Hau S. In vitro evaluation of the inhibitory effect of topical ophthalmic agents on Acanthamoeba viability. Transl Vis Sci Technol 2019; 8(5):17. https://doi.org/10.1167/tvst.8.5.17
135 Sudano Roccaro A, Asero A. An original use of a bioluminescence assay to test the in vitro efficacy of polihexanide in the eradication of Acanthamoeba cysts. Cornea 2020; 39(7):892–897. https://doi.org/10.1097/ICO.0000000000002308
136 Romanowski EG, Yates KA, O'Connor KE et al. Evaluation of polyhexamethylene biguanide (PHMB) as a disinfectant for adenovirus. JAMA Ophthalmol 2013; 131(4):495–498. https://doi.org/10.1001/jamaophthalmol.2013.2498
137 Lehner B, Fleischmann W, Becker R, Jukema GN. First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study. Int Orthop 2011; 35(9):1415–1420. https://doi.org/10.1007/s00264-011-1274-y
138 Monteiro Vasconcelos F, Cabral Pereira da Costa C, Peres E et al. Microbiological identification and resistance profile of microorganisms in pressure injuries after the use of polyhexamethylene biguanide: a series of fourteen cases. Wounds 2022; 34(2):51–56. https://doi.org/10.25270/wnds/2022.5156
139 Payne B, Simmen HP, Csuka E et al. Randomized controlled clinical trial on the antiseptic efficacy of polihexanide 0.04% on acute traumatic wounds. J Hosp Infect 2018; 98(4):429–432. https://doi.org/10.1016/j.jhin.2017.12.020
140 Vallejo A, Wallis M, McMillan D. Use of low-frequency contact ultrasonic debridement with and without polyhexamethylene biguanide in hard-to-heal leg ulcers: an RCT. J Wound Care 2022; 31(8):670–681. https://doi.org/10.12968/jowc.2022.31.8.670

notes