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.
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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).

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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)**

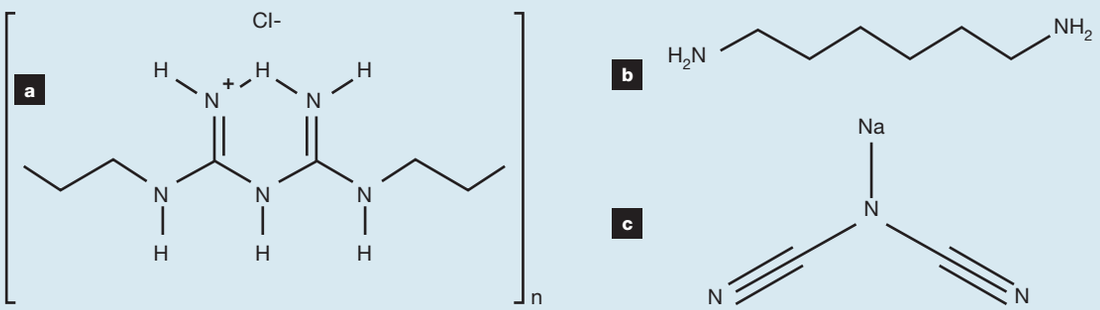


Fig 2. Membrane disruption mechanism of action for polyhexamethylene biguanide (PHMB)

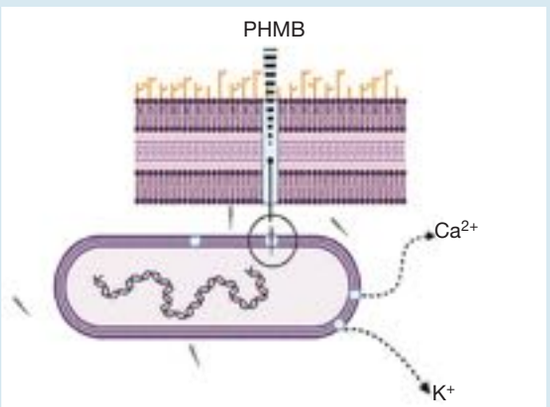
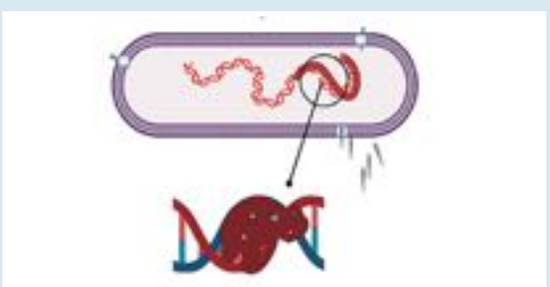


Fig 3. DNA binding/condensation mechanism of action for polyhexamethylene biguanide (PHMB)



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

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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]

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]

Fig 4. Narrative review search strategy results flow diagram

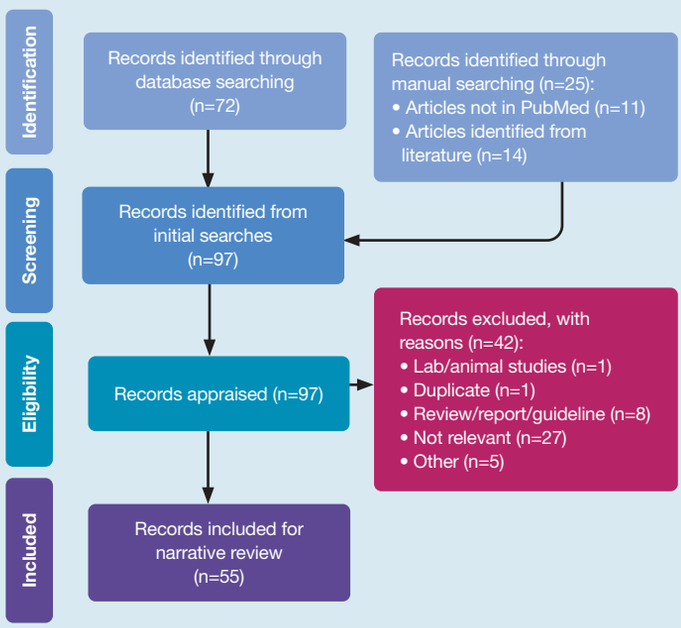

Table 1. Search strategy summary

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

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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

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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

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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

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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

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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

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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

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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

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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

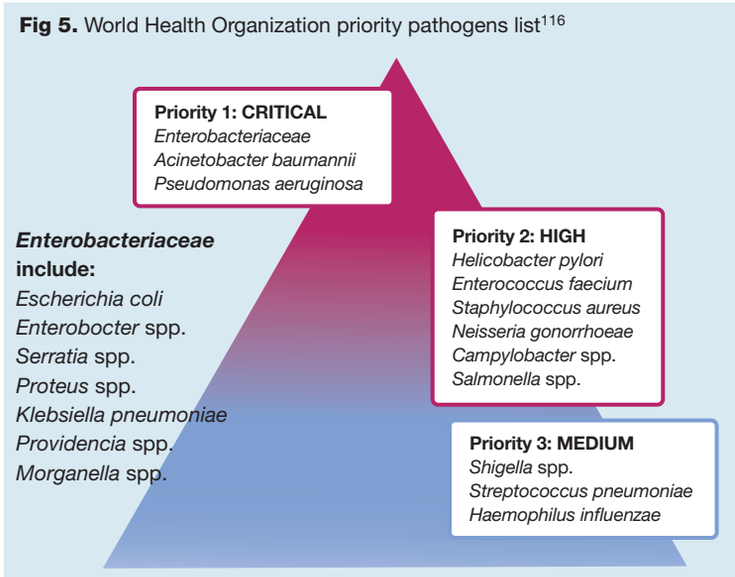
Biofilms are ubiquitous in wounds and are a major cause of delayed healing.[35,103] Their management presents a significant challenge to clinicians treating infected wounds, and a variety of antimicrobials (e.g., iodine, silver, polyhexamethylene biguanide, octenidine, hypochlorous acid, benzalkonium 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] 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.

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



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

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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?

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