Wound management – Chlorhexidine: A WHAM evidence summary

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CLINICAL QUESTION

What is the best available evidence regarding use of chlorhexidine in wound cleansing?

SUMMARY

A review of the evidence on use of chlorhexidine in wound care indicates that research on its effectiveness in reducing bacterial burden is limited to preparations of 1% or less concentration and has primarily been conducted in laboratory settings. While effectiveness in eradicating bacteria has been tested in-vitro and animal studies, the limited research in clinical settings fails to demonstrate an associated improvement in the rate of wound healing. Histological findings indicate toxicity of chlorhexidine to proliferating skin.[1, 2, 3] There is no strong clinical evidence that chlorhexidine significantly impedes wound healing; however selection of alternative antiseptics [e.g. polyhexamethylene biguanide (PHMB)] appropriate for the clinical context should be considered. Evaluation of research findings should consider the appropriateness of the concentration of chlorhexidine preparations being used.

CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the clinical context.

There is insufficient evidence on the safety of and effectiveness of chlorhexidine in reducing bioburden and promoting wound healing in concentrations designed for wound care (i.e. 0.05% or more dilute) to make a recommendation on its use as a wound care product.

SOURCES OF EVIDENCE

This summary was conducted using methods published by the Joanna Briggs Institute.[4-6] The summary is based on a systematic literature search combining search terms related to wound management and chlorhexidine. Searches were conducted in ten relevant third world health care journals for evidence published up to April 2016 in English. Levels of evidence for intervention studies are reported in Table 1.

CLINICAL EVIDENCE

Chlorhexidine preparations

Chlorhexidine is available for two primary purposes:[1]

- Chlorhexidine in a 0.05% dilution is designed for wound cleansing, on which this evidence summary focuses.
- Chlorhexidine in a 2% and 4% dilution is designed for surgical skin preparation and as a hand scrub.

Microbiology

Chlorhexidine, a biguanide, is a broad spectrum anti-bacterial that inactivates gram positive and negative bacteria through penetration of outer and

Table 1: Sources of evidence and the level

Level 1 Evidence	Level 2 Evidence	Level 3 Evidence	Level 4 Evidence	Level 5 Evidence
Experimental Designs	**Quasi-experimental Designs**	**Observational – Analytic Designs**	**Observational – Descriptive Studies**	**Expert Opinion/ Bench Research**
1.c RCT double blinded[16] 1.c RCT (unblinded)[14]	None	None	4.c Case series[18]	*In-vivo* laboratory studies[7, 8, 9, 10, 11] *In-vitro* studies[3, 12, 13, 14]

inner cell membranes.[2] It has an affinity for binding to skin and mucous membranes.[15] However, its antiviral activity is variable, mycobacteria are resistant to it and it has no effect on spores[16] (*Level 5*).

It is commonly used in combination with gluconic acid – chlorhexidine gluconate (CHG). Bactericidal activity of CHG increases as the concentration increases.[16] A controlled in-vitro study[12] demonstrated that a wide range of bacteria were susceptible to CHG at concentrations up to 1%. *Escherichia Coli* and *Salmonella spp.* were most susceptible to CHG, with 100% bacterial inhibition at concentrations below 0.01%. (*Level 5*)

An in-vitro study of the efficacy of 0.05% CHG on five organisms including methicillin- resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA), *E.coli* and *E. aerogenes,* produced a 5-6 log reduction in microbial recovery at one and five minutes.[7] Based on these results, the authors suggested that irrigating a surgical wound and surface of an implantable device with 0.05% CHG for 1 minute followed by a saline rinse was likely to be an effective and safe alternative to antibiotic irrigation.[7](*Level 5*) Chlorhexidine gluconate (with sterile water) is currently the only antiseptic with US Food and Drug Administration (FDA) clearance to use as an irrigating fluid in a medical device.[17]

Four studies[8, 9, 10, 11] (*Level 5*) compared the effectiveness of chlorhexidine acetate 0.5% (CA) with other topical antiseptic dressings in full-thickness rat burn wounds. In *Acinetobacter baumannii* – contaminated burns[10] CA prevented the penetration and systematic spreading of the bacteria. However, neither CA nor silver sulphadiazine were as effective as a nanocrystalline silver dressing in removing the bacteria from the eschar ($p < 0.001$ and $p < 0.05$) respectively. A second study[9] examined the effect of chlorhexidine acetate 0.05%, nanocrystalline silver and fusidic acid 2% on MRSA. Both the nanocrystalline dressing and CA prevented the systemic spread of MRSA but the CA did not prevent deep muscle invasion by the MRSA. The fusidic acid 2% had the added effect of removing the MRSA from the eschar, which in this study the nanocystalline silver dressing did not.

A third study [11] tested the effectiveness of four topical antiseptics against multi-drug resistant *Pseudomonas aeruginosa.* Only two of the antiseptic dressings - nanocrystalline silver coated and silver sulphadiazine 1% dressings - were effective ($p < 0.05$), while the results for chlorhexidine acetate and citric acid were not significant. The fourth study[8] compared the topical antifungal effect of nanocrystalline, silver, chlorhexidine 0.05% and nystatin on *Candida albicans* contaminated burns. Although the results for both the silver and nystatin compared to the control group (no topical agent applied) were statistically significant (both $p < 0.001$), the mean eschar concentrations were not significantly different between the CA and control groups and CA only prevented the penetration and spreading of the fungus in half the rats.

Studies of antimicrobial properties of chlorhexidine in the clinical wound care setting are lacking. Its action is pH dependent within a range that includes wound surfaces[16] (*Level 5*). However, expert opinion proposes that body fluids and tap water inactivate chlorhexidine's antibacterial properties[1] (*Level 5*).

Histological findings

Data from an in-vitro study[3] found that chlorhexidine was cytotoxic to human dermal fibroblasts at concentrations of 5-2400 times below those used in clinical practice (*Level 5*). Evidence from in-vitro studies suggests that fibroblasts and keratinocytes exposed to 0.05% chlorhexidine for 15 minutes are non-viable within 24 hours[1] (*Level 5*). Another in-vitro study found that after 96 hours of exposure to chlorhexidine at a concentration of 0.0032% there was a significant reduction in fibroblast proliferation ($p = 0.05$). However, chlorhexidine at a concentration of 0.0004% was associated with a significant increase in fibroblast proliferation ($16\% \pm 7\%$, $p = 0.05$)[13] (*Level 5*).

One histological study ($n = 17$) showed that after six weeks of treatment with 5% CHG, chronic leg ulcers exhibited a decrease in microvessels, neutrophils, fibroblasts and dendrocytes compared to ulcers treated with normal saline[18] (*Level 1*). Expert opinion suggested that the decrease in microvessels might not be a significant issue as there was an excessive increase in vasculature related to lipodermatosclerosis in the ulcer bed, i.e. although some microvessels may not survive exposure to 5% CHG, this only reduces microvessels from a pathogenically high level to a 'normal' level[18] (*Level 5*).

The effect of chlorhexidine on human articular cartilage has been of particular concern, with a number of cases of marked chondrolysis and subsequent joint damage being reported. An in-vitro study demonstrated that

exposure of non-arthritic human cartilage to chlorhexidine for one-minute reduced cell metabolic activity by 14%, which was not significant, but exposure for one hour had a marked effect – 86% reduction ($p < 0.001$). In arthritic cartilage even exposure of one minute had a significant impact on metabolic activity (43% reduction, $p < 0.05\%$)[14] (*Level 5*).

Effectiveness in promoting healing

In one split-body RCT (n = 24) 12.5% of patients receiving treatment with chlorhexidine diphosphanilate (CHP) cream at concentrations from 0.25% to 1% were assessed as having delayed wound healing (decreased epithelialisation) in leg ulcers[19] (*Level 1*).

One split-body RCT with no blinding (n = 17) found no significant difference in time to complete healing between chronic leg ulcers treated with 5% CHG compared to those treated with normal saline (14 weeks, 95% CI 7 to 17 versus 15 weeks, 95% CI 7 to 19)[18] (*Level 1*). (Note: chlorhexidine at concentrations of 5% is generally not considered to be a wound care product.[1] In the same study an indirect comparison between groups (n = 34) provided evidence that povidone iodine 10% was associated with superior wound healing outcomes compared to 5% CHG after six weeks of treatment [median of 11weeks to complete healing (range 9-17weeks) versus median of 14 weeks (range7-17 weeks)][18] (*Level 1*).

Effectiveness in managing pain

One split-body RCT (n = 24) found no statistically significant difference in pain levels up to 120 minutes following application of CHP cream (0.25% to 1% concentrations) to partial thickness burns compared to 1% silver sulphadiazine or the emollient vehicle alone. Pain ratings were lower for concentrations of CHP less than 0.5% compared with 1% CHP[19] (*Level 1*).

Contraindications and side effects

- Chlorhexidine is reported to be associated with low levels of skin irritation and is generally well tolerated when used at appropriate concentrations. It is also considered to be a weak allergen but there have been reported cases of allergic contact dermatitis, urticaria and anaphylactic reactions[20, 18] (*Level 4*).
- Do not apply to areas adjacent to the eyes[7] (*Level 4*).
- In one RCT, severe pain associated with 2% CHP led to early cessation of its use to manage partial thickness burns. The response appears to be related to the higher CHP concentration[19] (*Level 1*).
- CGH is not recommended for use in infants < 2 months of age.[7]

CONSIDERATIONS FOR USE

Care staff rated CHP cream difficult to remove from partial thickness burns[19] (*Level 1*).

CONFLICTS OF INTEREST

The author declares no conflicts of interest in accordance with International Committee of Medical Journal Editors (ICMJE) standards.

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ABOUT WHAM EVIDENCE SUMMARIES

WHAM evidence summaries are consistent with methodology published in

Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach, Worldviews Evid Based Nurs. 2015;12(3):131-8.

Methods are provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer-review by an international review panel.

WHAM evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

PUBLICATION

This evidence summary has been published in:

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REFERENCES

1. Main R. Should chlorhexidine gluconate be used in wound cleansing? J Wound Care, 2008;17(3):112-4.
2. McDonnell G, Russell A. Antiseptics and disinfectants: activity, action and resistance. Clin Microbiol Rev, 1999;12:147-79.
3. Hidalgo E, Dominguez C. Mechanisms underlying chlorhexidine-induced cytotoxicity. Toxicology in Vitro, 2001;15:271-6.
4. Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. https://reviewersmanual.joannabriggs.org/. The Joanna Briggs Institute, 2017.
5. Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party. New JBI Grades of Recommendation. Adelaide: Joanna Briggs Institute, 2013.
6. The Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party. Supporting Document for the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation. The Joanna Briggs Institute, 2014.
7. Edmiston C, Bruden B, Rucinski M, Henen C, Graham M, Lewis B. Reducing the risk of surgical site infection: does chlorhexidine gluconate provide a risk reduction benefit? Amer J Infect Control, 2013;41:S49-S55.
8. Acar A, Uygur F, Diktas H, Evinc R, Ulkur E, Oncul O, Gorenek L. Comparison of silver-coated dressing (Acticoat). chlorhexidine acetate 0.5% (Bactigrass) and nystatin for topical antifungal effect in *Candida albicans*-contaminated, full-thickness rat burn wounds. Burns, 2011;37:882-5.
9. Ulkur E, Oncul O, Karagoz H, Yeniz E, Celikoz B. Comparison of silver coated dressing (Acticoat TM), chlorhexidine acetate 0.5% (Bactigrass), and fusidic acid 2% (Fucidin) for topical antibacterial effect in methiciliin-resistant Staphylococci-contaminated, full-skin thickness rat burn wounds. Burns, 2005;31:874-7.
10. Uygur F, Oncul O, Evinc R, Diktas H, Acar A, Ulkur E. Effects of three different topical antibacterial dressings on *Acinetobacter baumannii*-contaminated full-thickness burns in rats. Burns, 2009;35:270-3.
11. Yabanoglu H, Basaran O, Aydogan C, Azap O, Karakayali F, Moray G. Assessment of the effectiveness of silver-coated dressing, chlorhexidine acetate(0.5%), citric acid (3%) and silver sulfadiazine (1%) for topical antibacterial effects against multi-drug resistant *Pseudomonas aeruginosa* infecting full-skin thickness burn wounds on rats. Int Surg, 2013;98:416-23.
12. Mengistu Y, Erge W, Bellete B. *In -vitro* susceptibility of gram-negative bacterial isolates to chlorhexidine gluconate. East African Med J, 1999;76(5):243-6.
13. Thomas G, Rael L, Bar-Or R, Shimonkevitz R, Mains C, Slone D, et.al. Mechanisms of delayed wound healing by commonly used antiseptics. J Trauma, 2009;66(1):82-90.
14. Best A, Nixon M, Taylor G. Brief exposure of 0.05% chlorhexidine does not impair non-osteoarthritic human cartilage metabolism. J Hosp Infect, 2007;67:67-71.
15. Atiyeh B, Dibo S, Hayek S. Wound cleansing, topical antiseptics and wound healing. Int Wound J, 2009;6(6):420-30.
16. Eardley W, Watts S, Clasper J. Limb wounding and antisepsis: iodine and chlorhexidine in early management of extremity injury. Int J Lower Extremity Wounds, 2012;11(3):213-33.
17. Barnes S, Spencer M, Graham D, Boehm Johnson H. Surgical wound irrigation: a call for evidence-based standardization, 2014;42:525-9.
18. Fumal I, Braham C, Paquet P, Pierard - Franchimont C, Pierard G. The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora; a proof-of-concept study. Dermatology, 2002;204:70-4.
19. Miller L, Loder J, Hansbrough J, Peterson H, Monafo W, Jordan M. Patient tolerance study of topical chlorhexidine diphosphanilate: a new topical agent for burns. Burns, 1990;16(3):217-20.
20. Lachapelle J. A comparison of the irritant and allergenic properties of antiseptics. Eur J Dermatol, 2014;24(1):3-9.