When antibiotics can be avoided in skin inflammation and bacterial colonization: a review of topical treatments

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Purpose of review
This review looks at the recent evidence on the safety, toxicity, microbiology and the prevention and management of acute and chronic wound infections with regard to antiseptics and antiseptic wound dressings. It is timely and relevant because of the global concerns of antimicrobial resistance and the need to address the inappropriate use of antimicrobials in the healthcare setting.

Recent findings
There have been a number of recent Cochrane reviews that have concluded that there is little evidence to delineate clinical outcomes between antiseptics and antiseptic dressings. Published in-vitro evidence offers some new techniques and evaluates some new dressings and antiseptics. There are no economic evaluations of antiseptics and antiseptic dressings.

Summary
Better clinical trials on the effectiveness and cost-effectiveness of wound dressings are needed to ensure evidence-based guidance is developed for optimizing the treatment of patients. It is surprising that with the paucity of evidence of clinical effectiveness, healthcare organizations continue to spend considerable resources on poorly evaluated topical wound products.

Keywords
antibiotics, antimicrobials, antiseptics, bacterial colonization, skin and soft tissue infections, skin inflammation, topical treatments, wounds

INTRODUCTION
Resistance to antimicrobials (antibacterials, antifungals and antivirals) has become a global problem in recent years [1,2*], leading to governments adopting programmes of antimicrobial stewardship [1]. Indeed, the financial burden of this problem is likely to be considerably underestimated [3]. One of the early moves to address antimicrobial resistance was to discourage the use of agents that are used systemically being applied topically to skin infections.

Thus, over recent years there has been a development of a range of skin antiseptics that have been employed clinically for the management and prevention of skin infections. This review will address the place of these agents through an up to date examination of the published literature that addresses in-vitro performance [minimum inhibitory concentrations (MIC), minimum bactericidal concentrations (MBC), log kill and biofilm prevention and disruption], clinical studies and the safety and toxicity associated with topical preparations.

LITERATURE REVIEW
A literature search was undertaken in October 2013 using the following databases and keywords.

Databases
EMBASE: Excerpta Medica (Ovid), Journals@Ovid Full Text (Ovid), PubMed, MEDLINE (Ovid), Highwire

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Skin and soft tissue infections (SSTIs), antiseptics, iodine, silver, medical grade honey, chlorhexidine, polyhexanide, dialkylcarbamoyl chloride, flaminal, octenidine hydrochloride, betaine and polyhexanide.

Articles were considered, if they had been published within the last 12 months.

REVIEWS

The Cochrane Collaboration has published reviews on the clinical effectiveness of a number of groups of antiseptic agents and dressings, and has found the evidence to be equivocal for the use in clinical practice of silver dressings [4,5], honey dressings [6,7], and skin preparation for preventing infection following caesarean section, as well as the evidence to suggest either that one dressing type was better than any other, or that covering these wounds with dressings at all was better at preventing surgical-site infection, or that any dressing type improves scarring, pain control, patient acceptability or ease of removal [8,9]. Furthermore, it is not clear what sort of skin preparation may be most efficient for preventing postcaesarean wound and surgical-site infection [10].

However, Cochrane reviews tend to only include clinical studies that have a randomized controlled design and studies that do not have this design or are observational cohort, before and after, or in-vitro studies tend not to be included. Indeed, it is frequently difficult to mount such clinical studies in patients with complex chronic wounds and multiple comorbidities.

Another review looked at studies on the neuro-toxic effects of medicines and some antiseptics that are administered topically. The authors identified seven drugs with either central or peripheral neurotoxicity from topical use, including lindane, retinoic acid, benzalkonium chloride, hexachlorophene, clioquinol, metronidazole and topical mercury compounds. Topical medications are often dismissed as benign, assuming minimal absorption and limited systemic effects, and may be omitted from most medical documentation. These results led the authors to conclude that ‘physicians should remain aware of their potential neurotoxicity and consider discontinuation if warranted’ [11].

MICROBIOLOGICAL AND CYTOLOGICAL STUDIES

An in-vitro study examined whether extended-spectrum-beta-lactamase (ESBL)-producing clinical isolates of Klebsiella pneumoniae and Escherichia coli displayed greater resistance to a number of antiseptics used as topical agents. Octenidine dihydrochloride, chlorhexidine digluconate and polyhexanide (PHMB) were able to kill ESBL-producing bacteria sufficiently at concentrations well below those concentrations that are usually applied in wound treatment [12].

In a simulated controlled in-vitro wound study, flexible methacrylate powder dressing (Altrazeal) was shown to transform into a wound contour conforming matrix once in contact with wound exudate. The model examined the dressing in combination with PHMB, PHMB and betaine, povidone–iodine and octenidine dihydrochloride and phenoxyethanol [13].

In a study of Staphylococcus aureus SSTIs, 1089 patients were examined before and after mupiricin and chlorhexidine. Small numbers (2.1%) of patients carried a mupirocin-resistant S. aureus strain, and 0.9% of patients carried chlorhexidine-resistant S. aureus, however these could not be eradicated [14].

The in-vitro bactericidal activity against S. aureus of four commonly used topical antiseptics using a modified version of the European Standard, (EN 1276), a quantitative suspension test for the evaluation of bactericidal activity of chemical disinfectants and antiseptics. The standard for antiseptic effectiveness of EN 1276 requires at least a 105-fold reduction in bacteria counts within 5 min of exposure. Although 0.1% benzalkonium chloride and 6% hydrogen peroxide both achieved this
105-fold reduction in *S. aureus* counts, neither 2% aqueous eosin nor 1:10,000 potassium permanganate showed significant bactericidal activity, when compared with controls, at exposure periods of up to 1 h. Aqueous eosin and potassium permanganate may have desirable astringent properties, but these results suggest they lack effective antiseptic activity, at least against *S. aureus* [15].

Co-operative inhibitory activities (synergism, additive effects and modes of growth inhibition) of hydrogen peroxide and iodine used concurrently were studied against three bacterial and 16 yeast species. Synergistic or additive inhibitory effects were shown for hydrogen peroxide and iodine mixtures against all 19 species used in the study. Both biocides were mostly cidal individually and in mixtures against *Pseudomonas aeruginosa* and *S. aureus*. Both compounds manifested static inhibitory effects individually, but their mixtures were synergistically cidal for *Saccharomyces cerevisiae* and *E. coli*. However, cells of *S. cerevisiae* treated with hydrogen peroxide and iodine--hydrogen peroxide mixture produced increased numbers of respiratory-deficient mutants indicating genotoxic effects [16].

The effects of ionic silver (Ag⁺) on the viability, macromolecular synthesis and membrane integrity of *S. aureus* showed rapid and extensive loss of membrane integrity observed following challenge with Ag⁺. The authors suggest that antibacterial activity results directly from damage to the bacterial membrane and that susceptibility of staphylococci to Ag⁺, and failure to select for resistance to Ag⁺ suggest that silver compounds remain a viable option for the prevention and treatment of topical staphylococcal infections [17].

In an *in vitro* chronic wound model, biofilm inhibitory and eradicating activity of wound care products were studied against *S. aureus* and *Staphylococcus epidermidis* biofilms. The authors claim their model can be used to compare the efficacy of wound care products to inhibit biofilm formation and/or eradicate mature biofilms. In addition, the results indicate that treatment of infected wounds should be started as soon as possible and that novel products with more potent antibiofilm activity are needed [18].

**TOXICITY OF ANTISEPTICS**

To assess the toxic effects of chlorhexidine and PHMB at concentrations commonly applied in clinical practice, human osteoblasts were cultivated *in vitro* and assayed. Both antiseptics promoted lactic dehydrogenase activity after incubation with osteoblasts, and the evaluation of vital osteoblasts showed a significant decrease of vital cells, demonstrating toxicity [19].

The effects of albumin on antibacterial potency can be a problem, as shown in an *in vitro* study that found albumin causes a significant decrease of the antibacterial potency of PHMB-based antiseptics [20]. However, a contrary finding demonstrated that addition of up to 4% albumin to the test medium did not change the MICs and MBCs of PHMB against *S. aureus* [21].

**CLINICAL STUDIES**

In a well designed multicenter, prospective, open label, randomized controlled trial undertaken in 26 centres in Australia and New Zealand, participants undergoing peritoneal dialysis were randomly assigned to daily topical exit-site application of antibacterial honey (Medihoney) and standard exit-site care (186 patients) or intranasal mupirocin prophylaxis (only in carriers of nasal *S. aureus*) and standard exit-site care (control group – 185 patients). The primary end-point was time to first infection related to peritoneal dialysis (exit-site infection, tunnel infection or peritonitis). With an 80% statistical power to detect an increase in median infection-free survival, the results were equivocal, and the authors felt they could not endorse the routine use of Medihoney [22**]. However, independent commentary felt that the results from the honey group were as good as the control group, did not record any antiseptic resistance, unlike the control group, and that the honey was applied daily, whereas most centres recommend changing exit-site dressing much less frequently [23**].

Initial experience of a modified honey, Surgihoney, showed considerable *in vitro* enhanced antimicrobial activity compared with regular medicinal honey preparations, and together with safety and efficacy studies in a cohort of patients with acute and chronic wounds suggests it might offer a nontoxic solution as an antiseptic wound dressing [24]. In addition, in a pilot study looking at the prevention of surgical-site infection in patients undergoing caesarean section surgery, this modified honey was observed to reduce surgical-site infections substantially compared with normal wound dressings, and thus offered considerable cost-effectiveness over other preparations [25].

Anything that reduces surgical-site infections will also reduce the need for broad spectrum antibiots, and thus contribute to antimicrobial stewardship programmes in helping to reduce the rise in antibiotic resistance.

A small study of 69 patients with partial thickness burn wounds with total body surface area less...
than 40% randomized patients to nanocrystalline silver nylon wound dressing or silver sulfadiazine cream. The results showed that silver nylon wound dressing significantly reduced length of hospital stay, analgesic use, wound infection and inflammation compared with silver sulfadiazine [26].

In a blinded study of 112 adults undergoing elective colorectal cancer surgery at two university-affiliated hospitals, patients were randomly assigned to have the surgical incision dressed with Aquacel Ag Hydrofiber dressing or a commonly used dressing. The primary end-point of the study was the occurrence of any surgical-site infection within 30 days of surgery. The results did not confirm a statistically significant superiority of Aquacel Ag Hydrofiber dressing in reducing surgical-site infection after elective colorectal cancer surgery [27].

In a small volunteer study, the in vivo antiseptic potential of particle-associated and aqueous PHMB on the human skin was investigated by monitoring bacterial growth kinetics under an antiseptic over a period of 2.5 h. The results suggest that the use of a particle-bound antiseptic might achieve a better and longer lasting antisepsis of the human skin than the non-particulate form [28].

A before and after comparison of 477 patients undergoing on-pump cardiac surgeries at one institution showed a significant reduction in surgical wound infection rates over a 6-month period with ChloroPrep antiseptic [29].

In a study to determine the prevalence of resistance to antiseptics and mupirocin among invasive coagulase-negative staphylococci from very preterm neonates in neonatal intensive care units, 51 coagulase-negative staphylococci (CNS) isolated from catheter-associated bloodstream infections in very preterm neonates were investigated. In total, 41.2% exhibited decreased susceptibility to at least one antiseptic (chlorhexidine 12%, benzalkonium 24% and acriflavine 33%), and 61% were resistant to mupirocin. Both genes QacA/B and mupA were detected by polymerase chain reaction in 59, 63 and 49% of CNS, respectively. Seventy-six percent of S. epidermidis and 11% of Staphylococcus capitis were multiresistant [30].

In a before and after study comparing 1298 patients with historic controls, a chlorhexidine-containing dressing significantly decreased central venous line-associated bloodstream infection rates [31].

CONCLUSION

This review has identified the importance of increasing antimicrobial resistance to systemic agents and the contribution that effective topical antiseptic agents might offer to help stem this rise. Cochrane Reviews continue to report the failure of evidence to differentiate between antiseptics and antiseptic dressings in clinical trials. Future research should seek to investigate whether the results that appear to differentiate between antiseptic agents in microbiological testing can be repeated in the clinical environment for the prevention and management of infections in acute and chronic wounds. Effective economic evaluations need to be conducted to inform healthcare organizations of the clinical value of antiseptics and antiseptic dressings.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


Important editorial in high-impact journal.


Cochrane review.


Cochrane review.


Cochrane review.