

World Wide Wounds

A review of the evidence for the use of topical antimicrobial agents in wound care

Author(s)	Contents
Published: Feb 2004 Last updated: Feb 2004 Revision: 1.0	<ul style="list-style-type: none">• Historical background• Indications for use• Evidence base: a review• Conflicting evidence• Conclusion• References

Keywords: Antimicrobial agents; wound healing; antibiotic resistance; silver; iodine.

Key Points

1. The development of antibiotics during the 20th century marked the decline of many former remedies, but the emergence of antibiotic resistant strains of pathogens has led to the need to find alternative treatments.
2. The judicious, prophylactic use of antiseptics may prevent the development of infections that will minimise antibiotic use, as well as promoting healing.
3. The evidence concerning the efficacy of topical antimicrobial agents in the management of wounds is confused.
4. Larger better designed trials to assess clinical efficacy and cost implications are necessary.
5. Although reports of resistance are limited, misuse and abuse of antiseptics must be avoided.

Abstract

Antibiotics are potent antimicrobial agents with high specificity. However the relentless emergence of antibiotic-resistant strains of pathogens, together with the retarded discovery of novel antibiotics has led to the need to find alternative treatments. The most frequently used topical antimicrobials in modern wound care practice include iodine and silver containing products. In the past acetic acid, chlorhexidine, honey, hydrogen peroxide, sodium hypochlorite, potassium permanganate and proflavine have been used. Some of these products seem to be making a return, and other alternatives are being investigated. This review attempts to provide insight into the controversy that surrounds the use of topical antimicrobials by describing their respective mechanisms of action, reviewing supporting evidence and outlining perceived limitations.

Historical background

Throughout history man has had to contend with dermal wounds. In primitive societies substances derived from animals, plants and minerals formed the basis of crude remedies [1] needed to staunch bleeding, reduce swelling, minimise pain, remove damaged tissue, treat infections, mask foul smells and promote healing. The earliest documented records of topical wound treatments were found in Mesopotamia; these inscriptions on clay tablets have been dated to approximately 2500 BCE. The development and dissemination of later wound treatments can be traced from the ancient Egyptians, via the Greeks to Roman medicine [1], but the history of progress in wound care during the Middle Ages to the present time is incomplete [2].

Although topical antimicrobial agents were utilised in wound care for thousands of years [3], during the 19th century the discovery of chemical preservatives and disinfectants [4], as well as a better understanding of the nature of infection and inflammation, allowed increased control of wound infection. In particular the use of carbolic acid by Joseph Lister in operating theatres from 1865 significantly reduced mortality rates associated with surgical procedures. Later, when it was accepted that micro-organisms were the causative agents of infections, it became possible to consider more specific targeting. Paul Ehrlich began the search for chemicals with selective toxicity for infectious agents, rather than non-specific inhibitors, such as antiseptics and disinfectants.

The discovery and development of antibiotics during the 20th century provided potent antimicrobial agents with high specificity, which revolutionised clinical therapy and marked the decline of many former remedies. However, the relentless emergence of antibiotic resistant strains of pathogens, often with multiple antibiotic resistance [5], together with the retarded discovery of novel antibiotics [3] has led to the need to find alternative treatments. Faced with the prospect of increased prevalence of antibiotic-resistant pathogens, and the diminished effectiveness of current therapies, careful consideration of treatment options is now important.

Indications for use

Antibiotics are indicated in cases of overt wound infection where the classical signs are evident. Yet even in the treatment of the diabetic foot, where infection may precede amputation, assessment of the whole patient and the rational use of antibiotics as part of an integrated treatment plan is recommended [6]. Antibiotics are not indicated simply to limit microbial numbers in uninfected wounds. Many

wounds support relatively stable mixed communities of micro-organisms [7], often without signs of infection [8]. In chronic wounds reduction of certain microbial species, such as anaerobic bacteria in order to limit undesirable odours [9], or perhaps mixed communities of four or more bacterial species that impede healing [10] may be justified. The eradication of beta-haemolytic streptococci [11], or staphylococci and pseudomonads [12] before grafting is essential, and intervention to prevent the development of systemic infection in critically colonised or locally infected wounds is reasonable. Here systemic antibiotics are not always appropriate and topical antimicrobial treatments may be more suitable.

Evidence base: a review

Controversy has long surrounded the use of topical antimicrobial agents because of reports of cytotoxicity. In this review generic products, rather than named examples will be considered, and topical antibiotics have been excluded. This re-evaluation of accumulated evidence is intended as a basis to help practitioners make informed decisions.

Chlorhexidine

Chlorhexidine was discovered in 1946 and introduced into clinical practice in 1954 [13]. It is widely used as an antiseptic in handwashing, and as a surgical scrub, but in wounds its application has been limited largely to irrigation. The mode of action has been studied extensively.

Chlorhexidine is available as diacetate, digluconate and dihydrochloride; the digluconate is most frequently used in wound management. It has rapid, bactericidal activity against a wide spectrum of non-sporing bacteria by damaging outer cell layers and the semi-permeable cytoplasmic membrane to allow leakage of cellular components. It also causes coagulation of intracellular constituents, depending on concentration [14]. Antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and a range of clinical isolates has been documented [15], however in MRSA, resistance has been observed [16].

Although the efficacy of chlorhexidine as a topical agent in treating wounds is generally not well characterised, a recent evaluation of seven animal studies and three human studies has demonstrated that it is associated with few adverse effects on healing [17]. Despite reports of decreased bacterial counts, increased healing rates, and lack of toxicity, it was concluded that at present there is insufficient data to assess safety and efficacy, and that further clinical trials are required before the use of chlorhexidine on open wounds is either recommended or condemned [17].

Honey

Honey is an ancient remedy [18] which has been re-discovered for the treatment of wounds [19]. Many therapeutic properties have been attributed to honey including antibacterial activity and the ability to promote healing [20]. Evidence of antibacterial activity is extensive, with more than 70 microbial species reported to be susceptible [21]. Later *in vitro* studies have shown that active manuka honey is bactericidal against strains of antibiotic resistant bacteria isolated from infected wounds [22], [23], [24], so adding MRSA, vancomycin-resistant enterococci (VRE) and *Burkholderia cepacia* to the list of susceptible bacteria. Osmolarity, acidity, the generation of hydrogen peroxide on dilution and the presence of unidentified phytochemicals have been suggested to contribute to the antimicrobial potency of honey [21], but geographical location, floral origin, and post-harvesting treatment

conditions may also be important.

Mechanisms of microbial inhibition and cellular target sites have not yet been fully investigated, but multiple, non-specific sites are predicted. Similarly, *in vitro* studies with cell lines exposed to honey solutions have demonstrated modulation of monocytic cell activity. It is thought that this is likely to influence the wound healing process[25], [26], although this is not yet fully explained. Studies with animal models have provided evidence of the stimulation of healing by honey[27], [28], [29], and there are extensive reports of the clinical efficacy of honey in treating a wide range of wounds[20]. Much of this research is, however, with uncharacterised honeys and has therefore been described as anecdotal evidence. In a small number of case reports, sterilised active manuka honey was used [30],[31], [32]. In a review of the clinical evidence, the design of the clinical trials was criticised [33]; there is therefore a paucity of double-blinded, randomised, controlled trials to date.

The development of wound care products containing honey has been limited by the availability of standardised, quality assured preparations, although the situation is changing. Honey can be evaluated *in vitro* for antibacterial potency[34], and the production of registered, sterile dressings impregnated with honey, as well as sterilised honey in tubes and innovative dressings (honey and alginate) will improve reliability and accessibility in the near future.

Hydrogen peroxide

Hydrogen peroxide has been widely used as an antiseptic and disinfectant. A 3% (10 volumes) solution has most often been used to clean wounds. It is a clear, colourless liquid that decomposes in contact with organic matter. It has a broad spectrum of activity against bacteria, with greater effect on Gram positive species than Gram negatives.

Hydrogen peroxide functions as an oxidising agent by producing free radicals that react with lipids, proteins and nucleic acids to affect cellular constituents non-specifically. Its use in cleaning superficial trauma wounds has declined since the formation of air emboli was reported [35], yet analysis of studies in animals and humans [17] failed to find any negative effects on wound healing. At present there seems to be insufficient evidence to base definitive judgements about the merits of hydrogen peroxide on wound healing.

Iodine

Iodine is an element that was discovered in 1811. It is a dark violet solid that dissolves in alcohol and potassium iodide. Its first reported use in treating wounds was by Davies in 1839[36], and later it was used in the American Civil War. Early products caused pain, irritation and skin discolouration, but the development of iodophores (povidone iodine and cadexomer iodine) since 1949 yielded safer, less painful formulations.

Povidone iodine is a polyvinylpyrrolidone surfactant/iodine complex (PVP-I); cadexomer iodine is composed of beads of dextrin and epichlorhydrin that carry iodine. Both release sustained low concentrations of free iodine whose exact mode of action is not known, but involves multiple cellular effects by binding to proteins, nucleotides and fatty acids. Iodine is thought to affect protein structure by oxidizing S-H bonds of cysteine and methionine, reacting with the phenolic groups of tyrosine and reacting with N-H groups in amino acids (such as arginine, histidine and lysine) to block hydrogen bonding. It reacts with bases of nucleotides (such as adenine, cytosine and guanine) to prevent hydrogen bonding, and it alters membrane

structure by reacting with C=C bonds in fatty acids[37]. It has a broad spectrum of activity against bacteria, mycobacteria, fungi, protozoa and viruses.

Despite prolonged use of iodine, reports of resistance are limited to one [38]. Many authors have commented that resistance to iodine has not become a problem, and the methodology in the case of iodine resistance cited above has been criticised [39].

Povidone iodine is available commercially in several formulations (solution, cream, ointment, dry spray or dressings). There is extensive *in vitro* evidence of the efficacy of PVP-I as a cidal agent, from varying methodology [15], [40],[41], [42]. In one study it was shown that PVP-I lethally damaged >99% cells within 10 seconds of exposure, and as little as 2.36×10^5 atoms of iodine were required to kill one bacterial cell[39]. Activity at low concentration is affected by the presence of organic matter, but not all *in vitro* tests incorporate this factor into their design.

Clinically, PVP-I has application not only in the management of wounds, but as a skin antiseptic prior to surgery, and in the disinfection of inert surfaces [43]. Whereas its efficacy as a skin disinfectant is undisputed, numerous publications describe the use of iodine in cleansing wounds, and as a topical agent to prevent or treat localised wound infections, but controversy surrounds its safety and efficacy[44]. Since 1994 PVP-I has been approved by the US Food and Drugs Administration for the 'first aid' treatment of small, acute wounds, but it was not recommended for use with pressure ulcers by the US Department of Health & Human Services.

A report that absorption of PVP-I gave rise to severe metabolic acidosis, which complicated the management of two burns patients who died of renal failure [45], supported opinion that PVP-I should be restricted to brief topical application on superficial wounds rather than long-term use on large wounds. Two comprehensive reviews of the accumulated evidence for PVP-I derived from *in vitro* studies, animal models and human clinical use have attempted to analyse the confused picture [46], [17].

Overall observations from animal models have indicated cytotoxicity against leukocytes, fibroblasts and keratinocytes, but conversely human studies on balance suggest that PVP-I reduces bacterial load, decreases infection rates and promotes healing[17]. In one study healing rates of chronic venous leg ulcers, each treated with one of three topical agents were compared to untreated control ulcers in each respective patient. All agents were seen to reduce bacterial load; silver sulphadiazine and chlorhexidine digluconate caused slight improvements in healing rates and times, but PVP-I yielded statistically significant increases. Furthermore, histological assessment indicated lack of cytotoxicity because PVP-I induced less changes in microvessels and dendrocytes[47]. Additionally, a report of the ability of iodine released from a dressing to modulate the secretion of cytokines by human macrophages *in vitro* has provided another justification of its role in promoting healing[48].

Cadexomer iodine is available as an ointment, as well as a dressing. Analysis of animal and human studies has shown the emergence of a similar picture to PVP-I, that is reduction of MRSA [49] and *Pseudomonas aeruginosa* [50] respectively, with evidence from clinical reports of efficacy in stimulating healing[17]. Its lack of toxicity for human fibroblasts *in vitro* suggests lack of toxicity for chronic wounds *in vivo*[51].

Proflavine

Proflavine is a brightly coloured acridine derivative that was extensively used during

the Second World War in the treatment of wounds [52]. Modern use is as a prophylactic agent in surgical wounds packed with gauze soaked in proflavine hemisulphate solution, even though calcium alginate has been reported to promote better results [53]. It is an intercalating agent that inhibits bacteria by binding to DNA and prevents unwinding prior to DNA synthesis. Although it is effective against sulphonamide-resistant bacteria [52], strains of MRSA that are resistant to proflavine by possessing efflux pumps (mechanisms associated with bacterial membranes that export materials from cells) have been isolated [54]. Acridines are photosensitive; it has therefore been proposed that new derivatives should be sought for topical therapy promoted by light [55]. However, the ability to induce mutations in bacterial [56] and cell cultures [57] raises suspicion about the safety of proflavine.

Silver

Silver has a long history as an antimicrobial agent [58], [59], especially in the treatment of burns. An awareness of its role in inhibiting micro-organisms has developed since the late 19th century [60]. Metallic silver is relatively unreactive, but in aqueous environments silver ions are released and antimicrobial activity depends on the intracellular accumulation of low concentrations of silver ions. These avidly bind to negatively charged components in proteins and nucleic acids, thereby effecting structural changes in bacterial cell walls, membranes and nucleic acids that affect viability. In particular silver ions are thought to interact with thiol groups, carboxylates, phosphates, hydroxyls, imidazoles, indoles and amines either singly or in combination, so that multiple deleterious events rather than specific lesions simultaneously interfere with microbial processes [61]. Hence silver ions that bind to DNA block transcription, and those that bind to cell surface components interrupt bacterial respiration and ATP (adenosine triphosphate) synthesis [62]. In *Candida albicans*, but not in *Escherichia coli*, irreversible binding of silver ions to cysteine residues in phosphomannose isomerase interrupts cell wall synthesis, which in turn leads to loss of essential nutrients [63]. The role of 'other' silver radicals in antimicrobial activity remains less clearly understood [60].

The complex issues concerning the toxicity of silver to mammalian systems, and its effects on the healing process, have been considered by Lansdown [64], who concluded that further research into this area is required. Skin discolouration and irritation associated with the use of silver nitrate is well documented; absorption of silver, systemic distribution and excretion in urine has also been reported [64].

In wound care silver has been utilised in several formulations. Silver nitrate is no longer widely used, but silver sulphadiazine (SSD) and silver releasing dressings remain popular. When introduced in 1968 [65], SSD was recommended as a topical treatment for the prevention of pseudomonad infections in burns, but it has since been demonstrated to possess broad-spectrum antibacterial [66], antifungal [67], [68] and antiviral activity [69].

SSD is an established treatment for burns patients, but concern about its efficacy arose when the emergence of sulphadiazine-resistant bacteria was reported in a burns unit in a Birmingham hospital following SSD treatment of patients with extensive burns [70]. Reports of the development of silver resistant strains are rare, but SSD-resistant bacteria have been recovered [71], [72], [73]. Silver resistance has been linked to plasmids [62], and on occasions these plasmids confer multiple antibiotic resistance [74], [75]. Resistance to silver in *Salmonella* has been located in a cluster of seven genes that were organised into three discretely transcribed units. The gene products were deduced to be a periplasmic protein that binds silver ions and two efflux pumps that export silver ions from the bacterial cell [76].

In clean wounds in pigs, SSD increased the rate of epithelialisation by 28%,

indicating a beneficial effect in wounds additional to antimicrobial activity [77]. This model also showed that PVP-I did not affect the rate of healing.

A number of wound dressings containing silver have recently been developed. These function by the sustained release of low concentrations of silver ions over time, and generally appear to stimulate healing, as well as inhibiting micro-organisms. The evaluation of silver impregnated dressings, as with other topical therapies, includes *in vitro* antibacterial studies, animal models, and clinical testing. A number of laboratory studies have made comparisons between different products [78], [79], [80], [81], [82], but varying silver concentrations and differing modes of delivery of silver ions makes direct comparison inappropriate.

At present human studies with silver containing dressings are rather limited, yet trials conducted in Germany [83], [84], France [85] and Italy [86] provide encouraging results. In Canada an uncontrolled, prospective study of a series of chronic wounds treated with an ionised nanocrystalline silver dressing demonstrated improved clinical parameters together with decreased surface wound bioburden, but unchanged deep tissue loads [87]. The implication was that surface flora contributed more significantly to delayed healing than deeper flora.

It has been argued that antimicrobial efficacy alone is insufficient benefit in modern wound dressings [88], and that additional properties promoting wound healing are required. Based on this, the ability to remove any undesirable bacterial products in the wound environment that impinge on healing would be a bonus, for example binding bacterial endotoxin (toxins released on cell death) to a silver dressing would be of benefit [89].

Conflicting evidence

Overall the evidence concerning the efficacy of topical antimicrobial agents in the management of wounds is confusing. It must be remembered that it originates from multiple sources, which are not directly comparable. In laboratory studies the evaluation of an antimicrobial agent often begins with the determination of the Minimum Inhibitory Concentration (MIC) to determine potency, continues with suspension tests (both qualitative and quantitative) to assess rates of inhibition, and may include capacity tests to evaluate persistence. Numerous factors influence activity, such as the concentration tested, temperature, the extent of the contact time, the type of species tested, the number of organisms present and the presence of organic matter. Specifications for *in vitro* tests are not consistent in all countries, although a standardised European suspension test has been proposed for testing antiseptics against clinically significant organisms [15]. Innovative, non-invasive and non-destructive assays of inhibitory activity that give results in real time are becoming available [90], but so far these have limited application.

Animal models may also yield inconsistent evidence as they utilise different species, different types of wound and different challenge organisms. Two landmark studies that demonstrated cytotoxicity of topical agents *in vivo* have probably influenced practitioners to limit the use of antiseptics on wounds since the late 1980s. One study used a rabbit ear chamber [91], and the other cultured human fibroblasts, followed by acute wounds in adult rats [92]. It is debateable whether such models are relevant to the situation in chronic wounds. The development of a fibroblast model using cells from non-healing equine wounds may have advantages over models utilising cell lines or cells from acute wounds [93], but *in vitro* models will never faithfully mimic *in vivo* conditions.

While *in vitro* testing is required to screen and eliminate agents that are likely to be

unsuitable for *in vivo* testing, only those agents with greater potential are selected for clinical trials. Ultimately such studies provide the best evidence of efficacy, providing that appropriate control groups and statistically empowered studies are designed. Of the agents discussed here, there is insufficient evidence to make conclusive judgements about efficacy in the treatment of chronic wounds, except perhaps for silver sulphadiazine[94]. A systematic review of the effectiveness of antimicrobial agents used for chronic wounds debated the difficulties in making comparisons between studies and called for larger, better designed trials to assess clinical efficacy and cost implications [94].

Conclusion

The future threat of ineffectual control of wound infections caused by antibiotic-resistant strains of pathogens is sufficient reason to consider modifying our present reliance on antibiotics. The impact of micro-organisms on the healing process is not fully understood, but infection is known to interrupt healing and at worst can lead to death. In chronic wounds, it has been suggested that bacteria delay healing. If this is true, then reducing the wound bioburden should reduce adverse influences that impede healing. In cases of infections, antibiotics may be indicated, but holistic assessment of the patient is required. The judicious, prophylactic use of antiseptics may prevent the development of infections that will minimise antibiotic use, as well as promoting quicker healing. Topical antimicrobial therapy may be especially helpful to overcome the deleterious effects of bacteria in specific circumstances, for example, the eradication of bacteria [12] prior to grafting. Another application, as yet hardly considered, might be in the removal of biofilms, where bacteria encased in slime layers are less susceptible to antibiotics and have been implicated in persistent infections [95]. Already *in vitro* tests on biofilms with iodine[96] show inhibition, and hydrogen peroxide (and hence peroxide generating honeys) also offer potential for their disruption.

Topical antimicrobial agents usually have a non-specific mode of action and therefore the opportunity for unwanted patient effects exist, but there is a lesser chance of the development of resistance in microbial species. The development of antiseptic resistance, however, has already been noted with chlorhexidine, and it has been linked to antibiotic resistance [14]. Misuse and abuse of antiseptics must, therefore, be avoided, and additional antimicrobial therapies will always be needed. Tea tree oil has already been assessed for *in vitro*[97] and *in vivo*[98] activity, and antimicrobial peptides isolated from amphibian skin offer promise in treating infections[99].

The removal of infectious agents provides another approach to controlling infection, and two therapies in particular are suitable candidates for wound care. In biosurgery the ingestion and subsequent digestion of bacteria in the gut of greenbottle larvae (maggots) not only reduces the bioburden in difficult to heal wounds, but also reduces the risks of hospital acquired infection[100]. In addition, maggot therapy is beneficial in the debridement of necrotic tissue and the production of substances that stimulate the healing process[100]. Bacteriophage therapy began soon after the discovery of bacterial viruses in the early 20th century, but it was overlooked, except in Georgia and Poland, when antibiotics became widely available for clinical use. Because bacteria, such as staphylococci, pseudomonads and enterococci, are killed by infection with their respective viruses, topical application of viral suspensions has the potential to limit bacterial colonisation and infection of wounds [101]. This therapy has yet to be fully evaluated, but may be appropriate for the management of burns.

This review extends the information included in a previous publication [102], and hopes to give insight into past, present and future topical treatment strategies for

wound infection. Future wound care products are likely to be sophisticated formulations that incorporate not only antimicrobial components, but will be designed to maintain a moist wound environment and optimise the wound environment to promote healing. Since evolution is faster in microbial species than in other species, there will be a continual need to search for novel treatments.

This article is supported by an educational grant from Johnson & Johnson. The views expressed in this article are those of the author and do not necessarily reflect those of Johnson & Johnson.

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