# Is manuka honey a credible alternative to silver in wound care?

KEY WORDS

- Manuka honey
- Silver
- Antimicrobial
- Wound management
- *In vitro* evidence
- *In vivo* evidence

Honey and silver are traditional wound therapies that are still used in modern clinical practice. Whereas silver is one of the most common antimicrobial agents used in wound management (Leaper, 2011), more scepticism surrounds the use of honey, despite accumulating evidence of its efficacy *in vitro* and *in vivo*. Both antimicrobial interventions have a place in modern formularies, due to the emergence of antibiotic-resistant bacterial strains. Yet medical devices containing either inhibitor vary in their formulations and delivery mechanisms, making generalisations unwise. In this review, the latest information on the mode of action of manuka honey, which is used for the production of most currently available medical-grade honeys (Kwakman, 2011b), will be compared and contrasted with silver, in an attempt to show that manuka honey is an effective alternative antibacterial product to silver for the prevention and management of wound infection.

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Honey and silver are traditional topical antibacterial agents that have been used on wounds for centuries (Blair et al, 2009). However, their value in wound management largely diminished with the availability of antibiotics, which were initially potent microbial inhibitors with specific target sites and modes of action. Now, following the continued emergence of antibiotic-resistant and multiple drug-resistant microbial strains that limit the number of therapeutic options available, these ancient topical treatments are once more being used in conventional medicine.

A rise in the number of resistant pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious cause for concern not only in wound management but in medicine generally (Bradshaw, 2011), and effective control must be achieved. There are now a number of topical antimicrobial agents in different formulations available for the prevention and treatment of wound infection, with silver-based products being among the most commonly used (Leaper, 2011).

The use of honey in clinical practice is less mainstream, despite its availability in modern wound dressing formulations and the existence of evidence that shows it has antimicrobial efficacy similar to silver, while having none of the silver-associated cytotoxicity issues (DuToit and Page, 2009), and no examples of resistance (Cooper et al, 2010). In addition to its

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antibacterial efficacy (*Table 1*), numerous additional key actions that are beneficial for wound management have been attributed to honey (Molan, 2005). For these reasons, further integration of honey into conventional medicine warrants serious consideration. This paper will discuss the possible reasons for the sceptism that exists in clinical practice concerning the use of honey.

It will present the available evidence for both *in vitro* and *in vivo* antibacterial efficacy of manuka honey, which is used for the production of most currently available medical-grade honeys (Kwakman, 2011a), and will also present comparable evidence for silver, in an attempt to show that manuka honey is a credible alternative antibacterial product for the prevention and management of wound infection.

## THE USE OF MANUKA HONEY AND SILVER IN CLINICAL PRACTICE: INFLUENCING FACTORS

Honey was used for treating wounds in hospitals until the 1970s (Robson, 2005), but often non-sterile honey, sourced from supplies intended for nutritional rather than medical use, were employed.

Later this, coupled with messy application, led to honey being perceived by many clinicians as neither an effective nor user-friendly antimicrobial intervention when compared to more sophisticated, better presented and easier-to-use products, such as those containing silver (White and Molan, 2005). Much of the laboratory and clinical evidence for the use of honey published before 2000 was based upon the use of poorly characterised honeys (White and Molan, 2005), where the geographical and botanical source of the honey was frequently not specified.

However, honey cannot be considered a generic product because, although it has a broad-spectrum antimicrobial action, the chemistry and antimicrobial components differ greatly according to floral source, climate and harvesting conditions (Molan, 1992; Kwakman et al, 2011b). The presence of pesticides, pollutants or additives can also be expected to change the characteristics of a honey sample and make it unsuitable for clinical use. Hence well-characterised medical grade honeys are mostly used in modern licensed wound care products. Such variability in antimicrobial efficacy in clinical practice may also have hampered the acceptance of honey into modern medicine (Kwakman et al, 2008).

**Table 1**
**Key actions of honey**

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|---|
| *Broad spectrum antimicrobial activity* |
| *Provides a moist wound environment* |
| *Autolytic debridement* |
| *Wound deodoriser* |
| *Stimulation of wound healing* |
| *Anti-inflammatory activity* |
| *Immuno-modulatory properties* |
| *Reduces oedema* |

It is now widely recognised that different honeys have different antimicrobial properties (Kwakman et al, 2011b), and that experimental data from one type of honey cannot be applied generally to all honey products. The first modern medical-grade honey-based wound care product was registered in Australia in 1999, with Activon 100% manuka honey becoming the first honey product registered as a medical device in the UK in 2004. Products are now registered throughout Australasia, Hong Kong, Europe and North America.

Medical grade honey is distinguished from supermarket honey by its proven antibacterial activity, traceability of its source, and lack of contaminants. It is gamma-irradiated to kill bacterial spores that may be present in raw honey (Cooper and Jenkins, 2009). Honeys that are used clinically include buckwheat, chestnut, manuka, multifloral, tualang and some that do not disclose their floral source.

Medical grade manuka honey often carries a UMF (unique manuka factor) rating that represents its antimicrobial activity against *S. aureus* in an agar well diffusion assay (Allen et al, 1991). As the antimicrobial efficacy of manuka honey can vary from batch to batch, the rating gives an indication of its anti-*staphylococcal* activity. A rating of 10 or more is considered to be suitable for medical use.

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The increasing availability of standardised, quality assured honey preparations in a range of user-friendly products, including sterile tubes of honey, ointment, honey-impregnated tulles, alginates, gels and meshes, has resulted in honey being used increasingly in clinical practice. Similarly, dressings containing silver increased in usage by 200% between 1996 and 2009, due in part to strong marketing campaigns backed by large companies (Michaels et al, 2009) and also in response to an increasing awareness of the risks to vulnerable patients from wound infection. They, too, are available in a range of formulations including creams, ointments and dressings impregnated with elemental silver or silver-releasing compounds.

As is the case for differing honey products, there is variation in the antimicrobial efficacy of the silver products that are currently available (Ip et al, 2006). However, the popularity of silver compared to that of honey over the last decade, indicates that this was not an obstacle to clinical use. More recently, there have been concerns raised over the use of silver dressings because of questions related to efficacy, cost-effectiveness and safety (International Consensus, 2012).

Whatever their active component, all antimicrobial agents require safe preparation, knowledge of the composition of antibacterial factors, knowledge of the mechanism of action and standardised antibacterial activity (Kwakman, 2011a; Kwakman et al, 2011b). It is a clinician's duty to be familiar with these factors so that appropriate management decisions can be made and antimicrobial dressings selected that are best suited for the patient's needs.

## ANTIBACTERIAL MODE OF ACTION OF MANUKA HONEY AND SILVER

Many wounds support diverse communities of micro-organisms without adverse effects — they do not have to be sterile to heal uneventfully (Bowler et al, 2001). Infection can arise in acute and chronic wounds and always interrupts the healing process. Wounds are often polymicrobial with Gram-positive cocci such as Streptococcus and Staphylococcus being the most common isolates. However, Enterococci, Enterobacteriaceae, anaerobes and *Pseudomonas* species may also be responsible for causing infection (Bradshaw, 2011).

Many studies exist that outline the antimicrobial efficacy of honey (Molan, 1992) and 80 species are known to be inhibited by honey (Cooper, 2007). Manuka honey has been shown to have a bactericidal effect on a wide range of common wound pathogens *in vitro*, with antibiotic-sensitive strains and their respective antibiotic-resistant strains exhibiting equal susceptibility (Cooper et al, 2002).

A study to evaluate the activity of the medical grade honeys (manuka honey and Revamil®; B Factory) on *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and MRSA showed that manuka honey had rapid activity (within two hours) against *B. subtilis* only, compared with Revamil which displayed rapid activity against *B. subtilis, E.coli* and *P. aeruginosa* (Kwakman et al, 2011b). Both honeys lacked rapid activity against MRSA. After 24 hours, manuka honey displayed potent slow bactericidal activity compared to Revamil, most noticeably against MRSA and *B. subtilis*. It was concluded that the antibacterial activity of each honey was attributed to its distinct set of individual components, which in turn gave each honey different bactericidal properties. Silver ions have also been shown to be active against a broad range of potential wound pathogens, including many antibiotic-resistant bacteria, such as MRSA and vancomycin-resistant enterococci (VRE) (Parsons et al, 2005).

One study (Ip et al, 2006) evaluated the antibacterial activity of five commercially available silver-coated or impregnated dressings on nine common wound pathogens including MRSA, *S. aureus*, *Enterococcus faecalis*, *P. aeruginosa*, and *E. coli*. The rapidity and extent of killing *in vitro* was investigated. Results showed that while all five silver-impregnated dressings exerted bactericidal activity particularly against Gram-negative bacteria, the spectrum and rapidity of action ranged widely for different dressings. Two dressings had rapid and broad-spectrum antibacterial activity, with one demonstrating bactericidal

action within 30 minutes against Gram-negative bacteria particularly. Other dressings displayed a much narrower range of bactericidal activities. These findings were confirmed by Edwards-Jones (2006).

Similarly, Bradshaw (2011) investigated the *in vitro* antimicrobial efficacy of one honey dressing and a range of silver and iodine dressings and suggested that there were no differences in antibacterial nature of the constituent inhibitors, but that there were significant differences between dressings within each category. In other words, all silver dressings did not elicit equivalent magnitudes of inhibitory effects and this was likely to have been the result of structural properties of the individual dressing affecting silver delivery (Bradshaw, 2011).

These studies again highlight the need for the characteristics of individual dressings to be better understood so that they can be used to maximum effect in clinical practice. It is important that clinicians appreciate differences in dressing formulations, because they may influence clinical outcomes with some products having a rapid, broad spectrum of activity, while others have a slower or narrower range of activity.

## Antibacterial mode of action of manuka honey

Manuka honey is derived from European honey bees that forage on the nectar of manuka bushes (*Leptospermum scoparium*) that are indigenous to New Zealand, and it is this that gives it its unique antibacterial properties. The complex chemistry of manuka honey has complicated attempts to define its antibacterial mode of action. Like all honeys, manuka honey can restrict microbial growth due to its high sugar content, low water content and acidity (Molan, 1992). All micro-organisms require nutrients to survive and any restriction in supply will compromise growth and division (Cooper, 2006). Low acidity and low pH also make honey unsuitable to support bacterial growth, as most microbes prefer a neutral pH. Honey is a super-saturated solution of sugars with low water content, so the sugars readily bind the water molecules, making them unavailable for micro-organisms (Cooper, 2006).

Even though undiluted honey prevents the growth of a wide range of bacteria, honey may be used at varying concentrations in different dressings/formulations and it will always become diluted during clinical use as the osmotic pressure of its constituent sugars attracts fluid from wounded tissue. Honeys do not depend exclusively on sugars and organic acids for their antibacterial action. The honey bee produces an enzyme, glucose oxidase, which is mixed with nectar during collection and deposited into the honeycomb within the hive. The enzyme is not active in whole honey, but it becomes activated upon dilution with wound fluid and oxidizes glucose to gluconic acid and hydrogen peroxide. Hydrogen peroxide generation also confers antibacterial properties to many honeys (Bang et al, 2003; Brudzynski et al, 2011), but its production has not been observed in manuka honey (Kwakman et al, 2011b).

The unique antimicrobial properties of manuka honey have been attributed in large part to the presence of methylglyoxal (MGO), which has been shown to originate from the high levels of dihydroxyacetone present in the nectar of manuka flowers (Adams et al, 2009; Mavric et al, 2008). MGO was found to be present in 100-fold higher concentrations in manuka than in other honeys (Mavric et al, 2008) and was confirmed as a significant bactericidal component of manuka honey (Kwakman et al, 2011b). However, when MGO was neutralised, bactericidal activity was still detected. This suggested the presence of additional antibacterial components in manuka honey. Reduced ability of this neutralised manuka honey to inhibit MRSA was noted, suggesting that MGO was not wholly responsible for inhibitory activity at low concentrations.

Kwakman et al (2011b) also showed that higher concentrations of MGO-neutralised manuka honey were needed to inhibit *B. subtilis* and *P. aeruginosa* (eight- and two-fold respectively) compared to MRSA, and that antibacterial activity was not due to sugars alone. Activity against *E. coli* was not affected by MGO neutralisation, indicating that other components of the honey were responsible for action against this bacterial species. When

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the compound sodium polyanethole sulphonate (SPS), which is able to neutralise cationic compounds, was added to the MGO-neutralised manuka honey, all residual activity against *P. aeruginosa* was lost, suggesting that this activity had been due to the presence of cationic compound(s). Activity against *B. subtilis* and *E. coli* was also reduced. When pH was neutralised, all remaining activity against *E. coli* was abolished. Activity against *B. subtilis* was decreased but was still substantial, therefore, low pH was considered to be responsible for non-cationic bacterial activity of MGO-neutralised manuka honey against *B. subtilis*. In summary, Kwakman et al (2011a) showed that MGO contributed to the activity of manuka honey against *S. aureus* and *B. subtilis*, but not against *E. coli* and *P. aeruginosa*, which involved unidentified cationic and non-cationic compounds.

Leptosin, a glycoside, has recently been discovered as a characteristic compound of manuka honey. Furthermore, the concentration of leptosin positively correlates with the UMF of manuka honey, indicating that leptosin may have the potential to be a good chemical marker for the identification of manuka honey and used to assess its antimicrobial efficacy (Kato et al, 2012). In addition to laboratory investigations aimed to determine the antibacterial constituents of manuka honey, the effects of manuka honey on the bacterial structure of common wound pathogens have been explored.

### *S. aureus*

Manuka honey has been shown to interrupt cell division of *S. aureus* (Henriques et al, 2009). Structural changes observed with transmission electron microscopy showed that manuka honey-treated *S. aureus* cells failed to progress through the cell cycle and could not separate effectively. This bactericidal effect was independent of component sugars in manuka honey, and indicated that the staphylococcal target site of manuka honey involved the cell division machinery (Henriques et al, 2009). Analysis of the proteins expressed by *S. aureus* treated with manuka honey has recently shown that multiple cellular effects occurred which were distinct from those induced by other bacterial inhibitors (Packer et al, 2012).

### *MRSA*

Manuka honey also interrupts cell division in MRSA (Jenkins et al, 2011a). Using electron microscopy, enlarged cells containing septa were observed in MRSA exposed to inhibitory concentrations of manuka honey (5%, 10% and 20%w/v). The effect was not caused by either constituent sugars or MGO, indicating the presence of additional antibacterial components, possibly acting synergistically with other components in the honey. Cell division in MRSA was prevented just before the point at which the bacteria would normally separate because the enzymes responsible for digesting cell wall in the bacterial *septa* had been inactivated. Manuka honey has also been shown to elicit down-regulation of a universal stress protein in MRSA, which compromises its ability to overcome environmental insults (Jenkins et al, 2011b) and to work synergistically with oxacillin to reverse oxacillin resistance in MRSA (Jenkins and Cooper, 2012). These multiple inhibitory effects of manuka honey on MRSA indicate that it may play an important clinical role in managing patients with, or at risk of, MRSA infection (Cooper and Jenkins, 2012). Indeed, case reports that demonstrate MRSA eradication following topical application of manuka honey to colonised wounds have been published (Natarajan et al, 2001; Eddy and Giddeonsen, 2005; Chambers, 2006; Blaser et al, 2007; Gethin and Cowman, 2008).

### *P. aeruginosa*

In *P. aeruginosa* cells treated with manuka honey, extensive structural damage was observed using scanning and transmission electron microscopy (Henriques et al, 2010). Loss of structural integrity and changes in cell shape and surface were noted in honey-treated cultures, along with evidence of cell disruption and lysis. These effects were different to those seen in *Staphylococci* (Henriques et al, 2010) and agree with the deductions that different components in manuka honey contribute to lethal events in bacteria (Kwakman et al, 2011a). Recently changes in cell surface layers of *P. aeruginosa* exposed to manuka honey have been found to result from the down-regulation of an outer membrane protein, which is important in anchoring

membranes to the underlying wall (Roberts et al, in press).

*E. coli*

A blend of *Leptospermum* honeys induced a unique response that involved multiple cell targets in *E. coli* (Blair et al, 2009), resulting in disturbed protein synthesis and a bacterial cell stress response.

*Biofilm*

The ability of manuka honey to inhibit established biofilms has been demonstrated in studies conducted in Canada (Alandejani et al, 2009), Norway (Merckoll et al, 2009), and in the UK (Okhiria et al, 2009; Cooper et al, 2011). Generally, manuka honey was more effective than other honey samples, and higher concentrations of honey were required to inhibit established biofilms than those required to inhibit planktonic cells.

In one study, the effect of manuka honey on six biofilms of *P. aeruginosa* over a 24-hour period was determined (Okhiria et al, 2009). One culture from a reference collection and five clinical isolates from chronic wounds infected with *P. aeruginosa* were grown into established biofilms. The effects of two concentrations of manuka honey were tested over 24 hours. Exposure of *P. aeruginosa* biofilms to 40%w/v manuka honey resulted in significantly reduced biofilm biomass for all cultures ($p>0.05$), compared to growth medium alone and 20%w/v manuka honey. Maximum inhibition was noted after 9–11 hours of exposure and increased biomass at 24 hours. Since honey contains sugars that bacteria could utilise for growth, it is important that the amount of active honey within the wound is maintained at inhibitory levels if biofilm is to be inhibited, rather than stimulated in a wound. Length of exposure is also crucial. The authors concluded that as most dressings contain 80–100% manuka honey, it is probable that application would initially reduce biofilms (Okhiria et al, 2009).

In another study it was demonstrated that biofilms of *S. aureus*, MRSA and VRE were prevented and inhibited *in vitro* by Activon manuka honey at concentrations that could be used in clinical practice (Cooper et al, 2011). However, exposure to concentrations below 10% w/v promoted growth of biofilms of S. aureus, MRSA and VRE. The authors concluded that as honey is unlikely to be diluted by factors of 10 in the wound, there should be no problem in clinical use, but highlighted the importance of applying and maintaining appropriate concentrations *in vivo* (Okhiria et al, 2009; Cooper et al, 2011).

Manuka honey has also been shown to inhibit *Streptococcus pyogenes* biofilms by the downregulation of two fibrinogen-binding proteins located on the bacterial surface, which are necessary for bacterial aggregation and adherence. Interference in these processes is likely to prevent acute wound infections, as well as preventing and disrupting biofilms that typify chronic wounds (Maddocks et al, 2012).

## Antimicrobial mode of action of silver

Elemental silver (Ag) is ionised in the presence of wound fluid to form Ag+, whereas silver compounds contain positive silver ions bound to negatively charged ions or molecules, which dissociate when in contact with wound fluid to form Ag+. These positively charged ions are attracted to the negatively charged structures in the bacterial cell membrane, which they bind to and enter, affecting multiple sites within the bacterial cells.

Silver ions have a strong affinity to electron donor groups containing sulphur, oxygen and nitrogen and binding to these groups results in the blockage of key pathways such as cell respiration, structural disruption of the cell membrane and blockage of the enzyme and transport systems (Percival et al, 2005). Bacterial ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) may also be denatured, preventing transcription and replication (Michaels et al, 2009). At present, the precise mechanisms by which silver inhibits bacteria have not yet been well characterised, but there is consensus that surface binding and damage to membrane function are the most important bactericidal mechanisms of silver (Percival et al, 2005). A maximum concentration of approximately 1 part per million (1µg/ml) silver ions is thought to be achievable in wound exudate exposed to different silver dressings. This maximal

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concentration is due in part to chloride ions in exudate that bind silver ions limiting their availability to the wound bed.

Data from some studies indicate this concentration is sufficient to achieve bactericidal effects, whereas others show that over 80% of organisms tested have minimal inhibitory concentrations that exceed 1ppm of silver (Thomas and McCubbin, 2003). It is not clear how silver content and availability measured in experimental settings relates to clinical performance.

### *Biofilms*

*In vitro* studies of the effects of silver on biofilms indicate that silver may destabilise the biofilm matrix, kill bacteria within the biofilm, and increase susceptibility of bacteria to certain antibiotics, but that this effect also varies according to the silver species and dressing carrier used. It has been shown that silver ions can destabilise biofilm matrices by binding to biological molecules responsible for the biofilm stability (Chaw et al, 2005). The attachment of silver to these molecules leads to a reduction in the number of binding sites for stabilising bonds to form and interactions to occur, leading to destabilisation of the overall structure.

Percival et al (2008) found that silver was effective in killing biofilms consisting of bacterial populations commonly found in chronic wounds. In both monomicrobial biofilms, each consisting of *P. aeruginosa*, *Enterobacter cloacae* and *S. aureus,* and polymicrobial biofilms, containing a mixed bacterial community, 90% of all bacterial species died within 24 hours and total kill was achieved after 48 hours.

Kostenko et al (2010) evaluated the long-term antimicrobial efficacy of silver dressings against bacterial biofilms *in vitro* over seven days. Findings demonstrated that after one day all of the dressings evaluated significantly reduced the bacteria present in the biofilm and disrupted biofilm structure. Dressings with hydrophilic base materials and loaded with ionic or metallic silver showed short-term efficacy, with their antimicrobial efficacy diminishing and the bacterial populations recovering with time. Dressings with hydrophobic base materials loaded with nanocrystalline or metallic silver, however, sustained their antibiofilm activity for at least seven days. It was also found that biofilm bacteria that survived initial silver treatment were susceptible to certain antibiotics, including tobramycin, ciprofloxacin and trimethoprim-sulfamethoxazole, in contrast to untreated biofilms that were totally tolerant of these antibiotics. It was concluded that the differences in antimicrobial efficacy could be explained by the diversity of silver species and base materials making up the dressings (Kostenko et al, 2010).

Similarly, a study by Thorn et al (2009), which compared the *in vitro* antimicrobial activity of iodine and silver dressings against biofilms of *P. aeruginosa* and *S. aureus* found that both dressings killed bacteria in the first eight hours of treatment in both samples, with iodine exerting a significantly greater antimicrobial effect than silver during this time. In both populations, iodine achieved total kill after 24 hours of treatment. In *P. aeruginosa* biofilms treated with silver, only a low-level, residual bacterial population remained after 24 hours, whereas for the *S. aureus* population, the bacteria beneath the silver dressing had recovered to a population size similar to that of the untreated control group after 24 hours.

## CLINICAL EVIDENCE

The extent of clinical evidence for the antibacterial efficacy of honey is often under-estimated (Molan, 2011). Despite increasing amounts of evidence of the efficacy of manuka honey in inhibiting wound pathogens *in vitro*, clinicians and purchasers require objective clinical evidence before manuka honey is likely to be used as a first-choice topical treatment.

A review by Gethin (2004) of the RCTs carried out to date using honey stated that the trials were small, focused upon burns, did not sufficiently discuss wound aetiology, or did not state type or concentration of honey used for general conclusions to be drawn about the antimicrobial efficacy of honey. Gethin and Cowman (2008) carried out the first randomized *in vivo* study that compared the efficacy of manuka honey with that of a hydrogel dressing in desloughing venous

leg ulcers. As a secondary outcome, the qualitative bacteriological changes that occurred during a four-week period of treatment with either manuka honey or hydrogel were determined.

At baseline, MRSA was isolated in 10 ulcers in the honey group and six in the hydrogel group. After four weeks, this reduced to 3/10 ulcers in the honey group compared to 5/6 in the hydrogel group. The authors concluded that the ability of manuka honey to eradicate MRSA was a positive finding that may have implications for wound management and infection control and is in line with the findings of Natarajan et al (2001), Dunford et al (2000), Visavadia et al (2006), Chambers (2006) and Eddy and Giddeonsen (2005) that honey successfully eradicates MRSA from colonised chronic wounds.

The RCT is seen as providing a high level of evidence for practitioners because randomisation minimises the risk of bias and counteracts the placebo effect (International Consensus, 2012). However, they are expensive and time-consuming so are less likely to be undertaken. As a result, other forms of evidence need to be considered, including observational studies, and expert and patient opinion. Systematic reviews of RCTs and meta-analysis evaluate the strength of available clinical evidence in order to guide future clinical practice. A systematic review of antimicrobial agents used in chronic wounds (O'Meara et al, 2001) identified a small number of topical agents of limited value, but suggested that larger, better-designed studies were needed. Since then several more reviews have been conducted on silver (Bergin and Wraight, 2006; Vermeulen et al, 2007; Storm-Versloot et al, 2010; Carter et al, 2010; Toy and Macera, 2011; Aziz et al, 2012) and honey (Moore et al, 2001; Jull et al, 2008; Bardy et al, 2008), but none have provided definitive evidence to recommend either of them over other treatments.

Although silver dressings have been assessed in many different types of studies, the lack of consistent clinical evidence of their antimicrobial efficacy to support their use in practice may have arisen because different endpoints have been utilised (International Consensus, 2012). Endpoints relating to healing are perhaps unrealistic and measurement of bioburden or assessment of indicators of infection would give more meaningful insight into the antimicrobial efficacy of agents such as honey and silver. Difficulties in comparing available studies arise for several reasons, including:

- Small numbers of patients
- Wide range of inclusion criteria
- Study protocols
- Endpoints.

As a result, systemic reviews and meta-analyses for silver have come to differing conclusions, or have failed to find sufficient comparable data (International Consensus, 2012). Further clinical studies into the antimicrobial efficacy of both honey and silver are needed.

## DEVELOPMENT OF RESISTANCE

With few exceptions, the introduction of new antimicrobial agents into clinical practice has selected for resistant strains. However, to date, no honey-resistant bacteria has been isolated from wounds (Cooper et al, 2010). Training experiments with manuka honey (Cooper et al, 2010) did not select for honey-resistant mutants and the risk of bacteria acquiring resistance to honey was thought to be low, provided that high concentrations of honey were maintained clinically. Unlike antibiotics, antimicrobial agents such as manuka honey and silver affect more than one bacterial target site and, although this does not prevent the emergence of resistance, it is less likely to develop as multiple mutations are needed. There is well-documented evidence for bacterial resistance to silver (Maillard, 2006) with experimental and clinical evidence (in chronic wounds and burns) showing that bacteria can develop resistance to silver (Gupta and Silver, 1998). Bacteria with known silver resistance include *E. coli*, *E. cloacae*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Salmonella typhimurium* and *Pseudomonas stutzeri* (Percival et al, 2005).

## SAFETY PROFILE OF HONEY

Honey-based treatments have been found to be preferential to silver or iodine due to comparative lack of toxicity (DuToit and Page, 2009). Dutoit and Page (2009) observed that silver-impregnated dressings are potentially cytopathic and cytotoxic to proliferating cells *in vitro*, and that this may

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be relevant *in vivo* and in clinical decision-making. Studies by DuToit and Page (2009) and Burd et al (2007) have demonstrated significant cytotoxicity of silver towards fibroblasts and keratinocytes — cells that are essential for tissue repair. These findings are in line with those of Fraser et al (2004) and Poon and Burd (2004) that also showed evidence of keratinocyte cytotoxicity following exposure to silver. A study by Paddle-Ledinek et al (2006) reported on cell toxicity arising from dressings such as Aquacel® Ag (ConvaTec), Avance® (Mölnlycke Health Care) and Contreet-H (Coloplast). Collectively, these findings infer that rapid proliferating cells such as donor sites and superficial burns are at risk of cytotoxicity if exposed to silver. Honey, by comparison, favours cell proliferation and was not shown to be cytotoxic (DuToit and Page, 2009).

## CONCLUSION

Due to the emergence of antibiotic-resistant bacteria, topical antimicrobial agents have seen a resurgence in use over the last decade. During this time, many silver dressings have been developed and marketed by large companies, with the result that their uptake into clinical practice made them an established antimicrobial intervention in wound management. However, the popularity of silver has recently met considerable challenges, including a perceived lack of efficacy, cost-effectiveness and concerns surrounding safety and resistance (International Consensus, 2012).

While further substantive *in vivo* data are required, collectively the increasing evidence to demonstrate efficacy of manuka honey in a number of wound types, its broad-spectrum activity against wound pathogens, lack of selection of honey-resistant mutants and lack of cytotoxicity are all good reasons to consider using manuka honey as an alternative to silver in clinical practice for the reduction of wound bioburden (Cooper and Jenkins, 2012). WUK


## DECLARATION

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