Manuka Honey: why this multi action antimicrobial is a valid alternative to silver

KEY WORDS
- Antimicrobial activity
- Bacterial resistance
- Debridement
- Manuka honey

The recent increase in bacterial resistance and decrease in antimicrobial products in development has resulted in greater interest in honey as an antimicrobial solution. Manuka honey has a broad spectrum of antimicrobial activity and effectively reduces bioburden. Its antimicrobial action with no known resistance, no cytotoxicity, promotion of autolytic debridement and odour neutralisation make it a useful treatment in wound care. This article describes how Manuka honey works, and provides an overview of the evidence and benefits in practice.

GINNY DEANE
Tissue Viability Nurse, Midlands Partnership NHS Foundation Trust, Staffordshire

With the development of new antimicrobials significantly slowing and drug resistance increasing, it is important to find treatments that do not contribute to resistance. Antimicrobial stewardship programmes to monitor and evaluate prescribing and local resistance patterns have an important role in optimising outcomes (NICE, 2015), yet all clinicians can apply antimicrobial stewardship within their practice through the selection of appropriate treatment.

Various topical antimicrobial agents are currently used in wound care, see *Table 1*. Silver-impregnated dressings and antimicrobial coatings are commonly used as silver ions have various antimicrobial properties; however, their widespread and uncontrolled use has resulted in the emergence of silver-resistant strains of bacteria that commonly colonise wounds (Muller, 2018; Panáček et al, 2018; Hosny et al, 2019). Silver resistance can develop as a result of genetic mutation, acquisition of plasmids containing silver-resistance genes, phenotypic change or pyocyanin production/use (Muller, 2018; Panáček et al, 2018; Hosny et al, 2019). As a result, alternative antimicrobial agents are needed that should ideally:

- Disrupt and destroy biofilms
- Have a safe and effective antimicrobial action
- Provide a moist healing environment to promote autolytic debridement.

There has been a recent resurgence in the use of honey as a topical wound treatment. *In vivo* and *in vitro* studies have demonstrated that honey has a bactericidal effect on a range of common wound pathogens and there are no known resistant strains (Cooper et al, 2010; Cooper and Gray, 2012; Minden-Birkenmaier and Bowlin, 2018; Mitchell, 2018). Most research to date has focused on Manuka honey.

MANUKA HONEY: HOW IT WORKS

Manuka honey is produced from the nectar of *Leptospermum scoparium*, a plant indigenous to New Zealand and Australia. It contains sugars, proteins, enzymes and amino acids that differ depending on where it comes from and how it is processed. Its complex chemistry results in actions that reduce wound bioburden and promote healing, see *Box 1*. As enzymes break down sugars in the honey, the osmotic potential increases, which draws fluid out of the wound, the pH of the wound bed is lowered and hydrogen peroxide is produced (Cooper and Gray, 2012; Minden-Birkenmaier and Bowlin, 2018). In most honeys, antibacterial activity is due to hydrogen peroxide, much of which is inactivated by the catalase present in blood, serum and wound tissues (Molan and Rhodes, 2015).

In Manuka honey, methylglyoxal (MGO) is responsible for a second type of antibacterial activity. MGO damages the flagella of bacteria, limiting motility and their ability to adhere to cell surfaces (Minden-Birkenmaier and Bowlin, 2018). Unlike hydrogen peroxide, MGO activity is not inhibited by catalase (Molan and Rhodes, 2015; Mitchell, 2018).

MGO is known as Non-Peroxide Activity (NPA) or Unique Manuka Factor (UMF). The quantity of MGO is assigned an NPA rating; medical-grade

Table 1. Topical antimicrobial therapies in wound care (adapted from International Wound Infection Institute, 2016)

Antimicrobial agent	Type	Biofilm efficacy	Guidance for use
Silver	▸▸ Salts (e.g. silver sulfadiazine, silver nitrate, silver sulphate, silver CMC) ▸▸ Metallic (e.g. nanocrystalline, silver-coated nylon fibres) ▸▸ Impregnated wound dressings	▸▸ Denatures existing bacterial biofilm at concentrations over 5µg/ml ▸▸ Silver resistance reported in bacteria commonly colonising wounds (Muller, 2018; Panáček et al, 2018; Hosny et al, 2019)	▸▸ More frequent dressing changes required in wounds with heavy exudate ▸▸ Avoid in individuals with silver sensitivities
Ionic silver combined with EDTA and BEC (antibiofilm agents)	▸▸ Carboxymethylcellulose gelling dressing impregnated with ionic silver enhanced with EDTA and BEC	▸▸ Eradicates mature biofilm ▸▸ Prevents biofilm formation	▸▸ More frequent dressing changes required in wounds with heavy exudate ▸▸ Avoid in individuals with sensitivities to silver, EDTA or BEC ▸▸ High cost
Honey	▸▸ Medical grade ▸▸ Impregnated dressings	▸▸ Eradicates mature biofilm (Merckoll et al, 2009) ▸▸ Inhibits biofilm growth ▸▸ Reduces biofilm colony formation (Alandejani et al, 2009; Okhiria et al, 2009; Sojka et al, 2016) ▸▸ Inhibits quorum sensing of biofilm, thereby reducing ability to proliferate	▸▸ Manuka more effective than other types of honey ▸▸ No cytotoxicity ▸▸ Low cost
Iodine (povidone and cadexomer)	▸▸ Solution ▸▸ Impregnated dressings ▸▸ Powder and paste		▸▸ Contraindicated in individuals sensitive to iodine or with thyroid or renal disorders ▸▸ Contraindicated in those with extensive burns
Enzyme alginogel	▸▸ Alginate gel containing lactoperoxidase and glucose oxidase	▸▸ Prevents formation of biofilms at concentration ≤0.5% (w/v) ▸▸ Inhibits growth of established biofilms at higher concentrations ▸▸ Does not disrupt biofilm biomass	▸▸ Select alginate concentrations of 3–5% depending on exudate level
Surfactant	▸▸ Concentrated surfactant gels with antimicrobial preservatives	▸▸ Prevents biofilm formation ▸▸ Increases antibiotic efficacy ▸▸ Eradicates mature biofilm	▸▸ Can be used between and after debridement to prevent re-establishment of biofilm ▸▸ May require daily application for the first few days

BEC = benzethonium chloride; EDTA = ethyenediamine tetraacetate

Box 1. Actions of Manuka honey in wound care (Cooper and Gray, 2012; Molan and Rhodes, 2015; Minden-Birkenmaier and Bowlin, 2018)

- Forms a barrier, preventing bacteria from entering the wound and maintaining a moist healing environment
- Creates a strong osmotic gradient, drawing fluid containing nutrients and oxygen to the wound surface; removing bacteria, debris, slough and necrotic tissue; inhibiting and killing bacteria
- Lowers wound pH (3.5–4), stimulating macrophage and fibroblast activity, reducing protease activity and increasing local tissue oxidation
- Flavonoids and aromatic acids scavenge free radicals, reducing inflammation and tissue damage
- Hydrogen peroxide kills bacteria and stimulates growth factor production, promoting the formation of new blood vessels
- Methylglyoxal reduces bacterial mobility and ability to adhere to cell surfaces

honeys, such as Activon® Manuka Honey (Advancis Medical), have an NPA rating of 10 or greater (Amaya, 2016; Mitchell, 2018).

ANTIMICROBIAL ACTIVITY

Wounds are often polymicrobial, therefore broad-spectrum antibacterial activity is desirable. Manuka honey inhibits the growth of a range of bacteria that colonise wounds, such as *Escherichia coli* and *Pseudomonas aeruginosa* (which are associated with malodour). including drug-resistant strains – e.g. vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Cooper et al, 2002; Sherlock et al, 2010; Cooper

et al, 2011; Mitchell, 2018). In a study of sloughy infected venous leg ulcers, MRSA was eradicated in 70% of Manuka-honey treated wounds compared to 17% of hydrogel-treated wounds (Gethin and Cowman, 2008).

In addition to destroying planktonic bacteria, Manuka honey is effective against biofilms. It inhibits established MRSA, VRE and methicillin-sensitive *S aureus* biofilms at 40% concentration and prevents their formation at concentrations above 10% (Cooper et al, 2011). Studies have demonstrated that Manuka honey successfully prevents or destroys biofilms consisting of MRSA, methicillin-susceptible *S aureus*, *P aeruginosa*, methicillin-resistant *Staphylococcus epidermidis*, extended-spectrum ß-lactamase and *Klebsiella pneumoniae* (Alandejani et al, 2009; Merckoll et al, 2009; Okhiria et al, 2009; Sojka et al, 2016). Its active ingredients penetrate biofilm matrices, killing embedded bacteria in a dose-dependent manner (Merckoll et al, 2009). MGO inhibits biofilm formation at concentrations above 0.53mg/mL, which is equivalent to 33% w/v level of Manuka honey (Minden-Birkenmaier and Bowlin, 2018).

DEBRIDEMENT OF NECROTIC TISSUE AND SLOUGH

Necrotic tissue and slough can harbour bacteria and impede wound healing, therefore timely debridement is important, see *Box 2*. Manuka honey promotes autolytic debridement and can be applied by generalist as well as specialist healthcare practitioners (Wounds UK, 2013). It is useful for the treatment of infected wounds when other methods of autolytic debridement are contraindicated.

The osmotic action of honey draws water from the wound, selectively rehydrating, softening and liquefying necrotic tissue and slough, safely and effectively lifting it from the wound bed (Wounds UK, 2013; Minden-Birkenmaier and Bowlin, 2018). The osmolarity prevents maceration of the periwound skin (Molan, 2009). Patients may experience discomfort or a drawing sensation at the application site as a result of the osmotic action. They should be informed of this effect and offered appropriate analgesia if required (Mitchell, 2018).

A review of the literature found the application of honey effectively debrided a wide range of wounds, resulted in significantly better debridement than hydrogel, and was a suitable alternative to surgical debridement in necrotising fasciitis in the genital area (Molan, 2009). In addition to debridement, honey prevented the formation of slough and necrosis, and was more effective than silver sulfadiazine in preventing eschar formation in burns (Molan, 2009; Mitchell, 2018). A multicentre study of neonatal and paediatric patients reported successful debridement of 86% of wounds treated with Manuka honey and was well tolerated, with two out of 115 patients reporting a transient stinging sensation that did not prevent additional honey applications (Amaya, 2016). A smaller study of diabetic foot wounds found the application of 100% medical-grade Manuka honey debrided at a significantly faster rate than a chemical debriding agent, 80% and 100% preparations of Manuka honey (Barcic and Haesley, 2013). Molan (2009) noted that the efficacy of Manuka honey and low incidence of adverse reactions result in it being very acceptable to patients.

Box 2. Effects of debridement (Wounds UK, 2013)

- Enable accurate wound assessment
- Remove biofilms and prevent infection
- Reduce bioburden
- Reduce malodour
- Reduce exudate
- Progress wound healing/ encourage granulation tissue formation
- Increase the effectiveness of topical treatments (e.g. antimicrobials and pain relief)

CYTOTOXICITY

Unlike silver and iodine, honey is not associated with cytotoxicity (Paddle-Ledinek et al, 2006; du Toit and Page, 2009; Cooper and Gray, 2012). Silver is highly cytotoxic to fibroblasts and keratinocytes, which are essential for tissue repair (du Toit and Page, 2009; Cooper and Gray, 2012; Liao et al, 2019). Silver nanoparticles exert dose-, size- and time-dependent cytotoxicity on various human cell lines (Liao et al, 2019) and silver-impregnated dressings, such as Acticoat® (Smith and Nephew), Aquacel® Ag (ConvaTec), Avance® (Mölnlycke Health Care) and Contreet-H (Coloplast), significantly impair keratinocyte proliferation and morphology (Paddle-Ledinek et al, 2006). An *in vitro* study found honey had excellent cytocompatibility and promoted cell proliferation and silver-impregnated dressings consistently caused culture and cell toxicity (du Toit and Page, 2009). These findings collectively suggest that using silver to treat wounds containing rapidly proliferating cells, such as donor sites or superficial burns, may result in cytotoxicity; whereas honey supports healing without being cytotoxic.

ACTIVON® PRODUCT RANGE

The products in the Activon® Manuka Honey range enable the clinician to select the most suitable option for the management of each patient's wound, see

Table 2. Activon Honey products and their use

Product	Description	Most suitable use
Activon® Tube 	100% Medical Grade Manuka Honey	›› Wounds with slough or necrotic tissue ›› Cavity wounds ›› Topping up other Activon Manuka Honey dressings
Activon® Tulle 	Knitted viscose impregnated with 100% Medical Grade Manuka Honey	›› Shallow wounds in need of debridement ›› Reducing bacterial colonisation risk in vulnerable patients ›› Skin tears ›› Partial-thickness burns ›› Low-to-moderate exudate
Algivon® 	Soft alginate dressing impregnated with 100% Medical Grade Manuka Honey	Wounds with moderate-to-high volume of exudate: ›› Sloughy wounds ›› Infected wet wounds – e.g. chronic venous leg, pressure or diabetic foot ulcers
Algivon® Plus and Algivon® Plus Ribbon 	Reinforced soft alginate dressing impregnated with 100% Medical Grade Manuka Honey	Wounds with moderate-to-high volume of exudate: ›› Sloughy wounds ›› Infected wet wounds – e.g. chronic venous leg, pressure or diabetic foot ulcers ›› Cavities or sinuses – e.g. pilonidal sinuses, pressure ulcers, dehisced surgical wounds (Algivon® Plus Ribbon)
Actilite® 	Viscose net dressing impregnated with 100% Medical Grade Manuka Honey and Manuka oil	›› Shallow wounds with a low volume of exudate to clear infection or reduce bacterial burden

Table 2. All dressings contain 100% Manuka honey with a guaranteed NPA rating of 10+. As there is no known bacterial resistance to pure Manuka honey, the dressings can be used to treat all infected wound types. The osmotic nature of Activon Manuka Honey dressings can result in increased exudate that will need to be appropriately managed.

Activon Tube is a topical treatment that can be directly applied to any wound or cavity. It should be covered with a secondary dressing suitable for the volume of exudate expected. Activon Tube can be used to top up Activon Manuka Honey dressings when the honey has been diluted or washed away by exudate. Activon dressings are suitable for use on all types of wounds, with the only contraindication being allergy to bee venom.

The dressings can be left in place for up to a week. Activon Tulle is suited to debriding or desloughing shallow wounds, and for use in wounds where exudate levels have started to decrease. Exudate is able to pass through the dressing, maintaining a moist wound bed. Algivon and Algivon Plus contain alginate fibres, which slowly release honey into the wound and absorb some exudate. The reinforced

alginate in Algivon Plus pad and ribbon allows the dressing to be removed in one piece. Actilite is ideal for shallow wounds and its application is particularly useful in immunocompromised patients, as there is evidence that it stimulates immune response and reduces inflammation (Molan and Rhodes, 2015; Cooper, 2016).

CONCLUSION

Manuka honey is a broad-spectrum antimicrobial agent that is effective against planktonic bacteria and biofilms, while promoting autolytic debridement of slough and necrotic tissue, which can harbour bacteria. Unlike silver, there are no reports of honey-resistant organisms and it has low cytotoxicity. Evidence from the literature and the case studies highlight its suitability for the treatment of a wide range of wounds. WUK

REFERENCES

Alandejani T, Marsan J, Ferris W et al (2009) Effectiveness of honey on Staphylococcus aureus and Pseudomonas aeruginosa biofilms. *Otolaryngol Head Neck Surg* 141: 114–8

Amaya R (2015) Safety and efficacy of active Leptospermum honey in neonatal and paediatric wound debridement. *J Wound Care* 24(3): 95–103

Barcic M, Heasley D (2013) Evaluation of a 100% Manuka honey (free of color additives and preservatives) in the debridement of diabetic foot ulcers versus a pharmaceutical chemical debrider and two other Manuka honey based products. Poster presentation. https://us.advancismedical.com/uploads/files/documents/resources/US/Evaluation%20100%25%20manuka%20honey%20debridement%20of%20foot%20ulcers%20vs%20pharmaceutical%20debrider%20&%202%20other%20honeys.pdf

Cooper R (2016) Honey for wound care in the 21st century. *J Wound Care* 25(9): 544–52

Cooper RA, Molan PC, Harding KG (2002) The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. *J Appl Microbiol* 93(5): 857–63

Cooper RA, Jenkins L, Henriques AFM et al (2010) Absence of bacterial resistance to medical grade manuka honey. *Eur J Clin Microbiol Infect Dis* 29: 1237–41

Cooper R, Jenkins L, Rowlands R (2011) Inhibition of biofilms through the use of manuka honey. *Wounds UK* 7(1): 24–32

Cooper R, Gray D (2012) Is manuka honey a credible alternative to silver in wound care? *Wounds UK* 8(4): 54–64

Du Toit DF, Page BJ (2009) An in vitro evaluation of the cell toxicity of honey and silver dressings. *J Wound Care* 18(9): 383–9

Gethin G, Cowman S (2008) Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: An RCT. *J Wound Care* 17: 241–7

Hosny AE, Rasmy SA, Aboul-Magd DS et al (2019) The increasing threat of silver-resistance in clinical isolates from wounds and burns. *Infect Drug Resist* 1: 1985–2001

International Wound Infection Institute (IWII) (2016) *Wound infection in clinical practice: Principles of best practice.* Wounds International, London. Available at: www.woundinfection-institute.com/wp-content/uploads/2017/03/IWII-Wound-infection-in-clinical-practice.pdf (accessed 28.09.20)

Liao C, Li Y, Tjong SC (2019) Bactericidal and cytotoxic properties of silver nanoparticles. *Int J Mol Sci* 20(2): 449

Merckoll P, Jonassen TØ, Vad ME et al (2009) Bacteria, biofilm and honey: A study of the effects of honey on 'planktonic' and biofilm-embedded chronic wound bacteria. *Scand J Infect Dis* 41: 341–7

Minden-Birkenmaier BA, Bowlin GL (2018) Honey-based templates in wound healing and tissue engineering. *Bioengineering (Basel)* 5(2): 46

Mitchell T (2018) Use of Manuka honey for autolytic debridement in necrotic and sloughy wounds. *Journal of Community Nursing* 32(4): 38–43

Molan PC (2009) Debridement of wounds with honey. *J Wound Technol* 5: 12–7

Molan PC, Rhodes (2015) Honey: a biologic wound dressing. *Wounds* 27(6): 141–51

Muller M (2018) Bacterial silver resistance gained by cooperative interspecies redox behavior. *Antimicrobial Agents and Chemotherapy* 62(8): e00672–18

NICE (2015) NG15. Antimicrobial stewardship: Systems and processes for effective antimicrobial medicine use. Available at: www.nice.org.uk/guidance/ng15/chapter/1-Recommendations (accessed 10.09.2020)

Paddle-Ledinek JE, Nasa Z, Cleland HJ (2006) Effect of different wound dressings on cell viability and proliferation. *Plast Reconstr Surg* 117(7 Suppl): 1105–85

Panáček A, Kvítek L, Smékalová M et al (2018) Bacterial resistance to silver nanoparticles and how to overcome it. *Nature Nanotechology* 13: 65–71

Sherlock O, Dolan A, Athman R et al (2010) Comparison of the antimicrobial activity of Ulmo honey from Chile and Manuka honey against methicillin-resistant Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa. *BMC Complement Altern Med* 10: 47

Sojka M, Valachova I, Bucekova M, Majtan J (2016) Antibiofilm efficacy of honey and bee-derived defensin-1 on multispecies wound biofilm. *J Med Microbiol* 65: 337–44

Wounds UK (2013) *Effective debridement in a changing NHS: A UK consensus.* Wounds UK, London. Available at: www.wounds-uk.com (accessed 25.09.2020)