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Re-introducing Honey in the Management of Wounds and Ulcers – Theory and Practice

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ABSTRACT

Dressing wounds with honey was standard practice in past times but went out of fashion when antibiotics came into use. There has been a renaissance in its usage now that antibiotic-resistant bacteria have become a widespread clinical problem, and laboratory studies and clinical trials have shown that it is a very effective broad-spectrum antibacterial agent with no adverse effects on wound tissues. Modern studies have also shown that as well as having an antibacterial action, honey has several other activities that are beneficial to the wound healing process. It gives rapid autolytic debridement and deodorising of wounds, and stimulates the growth of wound tissues thus hastening healing and starting the healing process in dormant wounds. Its anti-inflammatory activity rapidly reduces pain, edema and exudate and minimises hypertrophic scarring. It also provides a moist healing environment for wound tissues with no risk of maceration of surrounding skin, and completely prevents adherence of dressings to the wound bed so that there is no pain and no tissue damage when dressings are changed. By use of appropriate dressing practices any problems of messiness and difficulty of handling can be easily overcome.

Therapeutic usage of honey is often referred to as "alternative" medicine, but it is in fact an orthodox mode of wound management that has just been out of common use for half a century and has now been "rediscovered". It is actually the oldest wound dressing known[1], but unlike many other ancient remedies it has not been just a fashion of a period

but has been in continuous use throughout the passage of time.[2] Although many of the old practices in medicine are disparaged, modern research is finding rational explanations for their mode of action.[3] This is especially true for honey, where not only has it been found to have various bioactivities important in the process of wound healing, but also a considerable amount of evidence has been presented from clinical trials to demonstrate its standing alongside modern wound management products.[4]

Clinical observations using honey in wound management

Observations reported from clinical usage of honey on wounds show many beneficial features. Topical application of honey has been reported to rapidly clear infection,[5-10] heal deeply infected surgical wounds,[6,9-15] and to halt advancing necrotising fasciitis.[7,16] It has achieved healing of wounds not responding to conventional therapy with antibiotics and antiseptics [8,13,15,17-19], including wounds infected with bacteria resistant to antibiotics,[14] such as MRSA.[20,21] It has also been reported to rapidly deodorise wounds.[7-9,11,16,22,23] and debride wounds to rapidly give a clean granulating wound bed.[5-8,10,24] Wounds dressed with honey are seen to have a rapid rate of healing,[12,16,25,26] and honey is able to start the healing process in dormant wounds.[8,17,18,27,28] Also, honey has been reported to stimulate the growth of epithelium over wounds,[7,8,16,24,29] making plastic surgery unnecessary.[6,7,11,16,24] Honey has also been reported to reduce inflammation,[24,25] edema[7,8,16,30,31] and exudate,[7,8,16,25] having a soothing effect when applied to wounds[23,25,32] and burns.[23,25] It also minimises scarring.[7,19,22,29] In the more than 500 cases reported in publications on using honey on wounds and the more than 140 cases of using honey in ophthalmology there has been no mention of any adverse effects other than a stinging sensation experienced by some patients, which appears to be due to the acidity of honey.[33]

The range of types of wound that have been reported to have been treated by dressing with honey is wide: besides the types mentioned above, honey has been used successfully on: skin grafts,[34] infected donor sites from split-thickness skin grafting,[19,33] infected wounds arising from trauma,[8,11,17,35] necrotising fasciitis (Fournier's gangrene),[7,8,16]

abscesses,[33,36] pilonidal sinuses,[33] pressure ulcers,[8,26,27,33,37] leg ulcers,[17,18,28,33] diabetic ulcers,[8,17,33,38] tropical ulcers,[8] sickle cell ulcers,[8] and malignant ulcers.[8] Honey has also been reported to be a reliable alternative to conventional dressing for management of skin excoriation around stomas (ileostomy and colostomy), givng a more rapid epithelialization of the raw surface.[39]

Evidence for effectiveness of honey

Prospective randomised controlled clinical trials have proven that honey gives significantly more rapid healing of superficial burns than that achieved with polyurethane film (OpSite®), a dressing commonly used for creating a moist healing environment, and with silver sulfadiazine ointment, the "gold standard" dressing for preventing infection developing in burns. The mean times for healing for the 46 patients in each group in the trial comparing honey-impregnated gauze with OpSite® were 10.8 days and 15.3 days respectively, the difference being statistically significant ($p < 0.001$), as was the finding that less than half as many of the cases became infected in the wounds dressed with honey ($p < 0.001$). [23]In the first of two trials comparing honey-impregnated gauze with gauze impregnated with silver sulfadiazine, with 52 patients in each group, there was a statistically significant difference ($p < 0.001$) found in the healing time, 87% of the wounds treated with honey being healed within 15 days compared with 10% of those treated with silver sulfadiazine.[22] A statistically significant difference ($p < 0.001$) was also found in the clearance of bacteria from the burns: of the 43/52 cases giving positive swab cultures on admission in the group treated with honey, 91% became sterile in 7 days, compared with 7% of the 41/52 cases treated with silver sulfadiazine. In the second trial, with 25 patients in each group, also there was a statistically significant difference ($p < 0.001$) found in the healing time, 100% of the wounds treated with honey being healed within 21 days compared with 84% of those treated with silver sulfadiazine.[24] In this trial a statistically significant difference ($p < 0.005$) was also seen in the histopathological evidence of reparative activity observed in biopsy samples from the wound margins after 7 days of treatemnt, this being seen in 80% of wounds treated with honey dressing and 52% of the wounds treated with silver sulfadiazine. Again a statistically significant

difference ($p < 0.001$) was found in the clearance of bacteria from the burns: of the 23/25 cases giving positive swab cultures on admission in the group treated with honey, 65% became sterile in 7 days and 96% in 21 days, compared with 73% in 7 days and 86% in 21 days of the 22/25 cases treated with silver sulfadiazine.

. Although these trials showed that honey gave a better control of infection than standard treatments, a trial on moderate burns, half of the total burn area full-thickness, in two groups of 25 young adults, showed that honey did not give as good a control of infection as did early tangential excision followed with autologous skin grafting: 34% of swab cultures were positive for the group treated with honey, compared with 10% of the group treated with early tangential excision ($p<0.05$), and antibiotics were needed for 32±18 days compared with 16±3 days ($p<0.001$).[40] However, the mean blood volume replaced was less with the honey treatment (21±15% compared with 35±12%: $p<0.01$), and skin grafting was required on only 11 of the group treated with honey.The poor results obtained with honey controlling infection could have been because the honey used in this trial was not selected to have a good antibacterial activity (see Recommendation 2 below). In recent reports where selected honey was used on an infected surgical wound following surgical treatment of hidradenitis suppurativa[15] and infected skin lesions from meningococcal septicemia,[19] in both cases where over a long period it had not been possible to achieve healing with the many systemic antibiotics and modern dressing materials tried, honey selected to have a good level of antibacterial activity gave rapid clearance of infection and healing of the wounds.

A good control of infection has also been reported in a cross-over study on nine infants with large infected surgical wounds, using honey on the wounds after they s had failed to heal with treatment of at least 14 days using intravenous antibiotics (a combination of vancomycin and cefotaxime, subsequently changed according to bacterial sensitivity), fusidic acid ointment, and wound cleaning with aqueous 0.05% chlorhexidine solution.[13]. Marked clinical improvement was seen in all cases after 5 days of treatment with honey, and all wounds were closed, clean and sterile after 21 days of application of honey. A prospective randomised controlled trial on severe post-operative wound infections (following Caesarean section or abdominal hysterectomy) has also been carried out, in which dressing with honey was compared with washing wounds with 70%

ethanol and applying povidone-iodine.[14]. The group of 26 patients treated with honey had infection eradicated in less than half the time, had the wounds completely healed in less than half the time, had post-operative scars less than half the size,and required less than half of the period of hospitalisation of the 24 patients in the control group, all of these differences being statistically significant ($p<0.05$). Another trial has found that dehisced abdominal wounds from Caesarean section healed in less than half the time (mean length of stay in hospital 4.5 days, range 2–7 days) when the wound margins were held together by micropore tape and the wounds dressed with honey, compared retrospectively with the usual treatment of wound cleaning (with hydrogen peroxide, Dakin's solution, and packing with saline-soaked gauze) and subsequent resuturing (mean length of stay in hospital 11.5 days, range 9–18 days).[9]

Antibacterial action of honey

With infection or a heavy bacterial burden in a wound being a major impediment to healing,[41] the ability of honey to rapidly clear bacteria from a wound is an important factor in its therapeutic action. The antibacterial property of honey has been recognised since 1892, and there has been a large amount of laboratory research carried out investigating this in the intervening period.[42] In addition to the high osmolarity due to the sugar content of honey, which is sufficient in undiluted honey to stop the growth of all microbial species, honey contains an enzyme, glucose oxidase, which when honey becomes diluted produces low levels of hydrogen peroxide.[42] Because the production is continuous, the low level is sufficient to be antibacterial even though the concentration typically achieved in diluted honey, around 1 mmol/l,[43] is about one thousand times less than in a 3% solution of hydrogen peroxide as is commonly used as an antiseptic. In some honeys there is augmentation of the antibacterial activity by phytochemicals in the nectar collected by the bees.[42] Usually this is a minor factor, but in honey from Leptospermum species from Australia and New Zealand this can make a major contribution.[42]

The antibacterial factors in honey additional to the osmolarity are important because the osmotic inhibition of bacterial growth is lost when honey becomes diluted by wound exudate. Also, the osmotic action on bacteria is only of effect on the wound surface whereas the other antibacterial factors can diffuse into wound tissues. But the potency of the additional antibacterial factors varies as much as a hundred-fold from honey to honey.[43] Although the reason for it was not known, it was empirical knowledge of the Ancient Greeks that some honeys were better than others for wound care. Dioscorides (c.50 AD) stated that a pale yellow honey from Attica was the best,[44] and Aristotle (384-322 BC), discussing differences in honeys, referred to pale honey being "good as a salve for sore eyes and wounds".[45] In present-day folk medicine in various parts of the world there is also recognition of particular local honeys being the best for use.[43] Discovery of the antibacterial activity over and above the osmotic effect of honey on bacteria came from research on honey as far back as 1937, and a system of rating the antibacterial activity of honeys, the "inhibine number", was devised in1955.[42,43] Yet in present times almost all of the clinical reports of usage of honey show no recognition of the variance in the potency of the antibacterial activity of honey.

Failure to take this variance into account has complicated conclusions on the sensitivity of different species of bacteria to the antibacterial activity of honey, but from the large number of microbiological studies carried out it can be seen that honey has a very broad spectrum of action.[42] This is of advantage in management of infected wounds, as sensitivity testing prior to selection of the antibacterial agent to be used is not required if honey is used. More recently studies have been carried out with honeys with standardised antibacterial activity (near the median level in the normal range of potency) tested against some common wound-infecting species of bacteria, and these have shown that the antibacterial activity of honey is quite significant. A study of type culture collection specimens of seven common wound-infecting species of bacteria found the MIC (minimum inhibitory concentration) of honey ranged from 1.8% to 10.8% (v/v), *i.e.* the honey was still able to stop bacterial growth if diluted nine to fifty-six times.[46] A study of 58 clinical isolates of *Staphylococcus aureus* found the MIC of honey to range from 2% to 4%,[47] and a study of 20 isolates of *Pseudomonas* from infected wounds

found the MIC of honey to range from 5.5% to 9.0%.[48] A study of 82 epidemic strains of MRSA found the MIC of honey to range from 3% to 8%, and for 56 strains of VRE to range from 5% to 10%.[49]. In a similar study the MIC of honey for 8 strains of MRSA isolated from swabs collected from acute and chronic wounds, and for 16 strains of VRE isolated from the hospital environment was below 10%, as it was for 15 strains of β-haemolytic streptococci and 7 strains of vancomycin-sensitive enterococci isolated from swabs collected from acute and chronic wounds.[50]

It is probably more than just the antibacterial action that is responsible for the rapid deodorising of wounds that is observed when honey dressings are used. The malodorous substances produced by bacteria are ammonia, amines and sulfur compounds formed from the metabolism of amino acids from decomposed serum and tissue proteins. Honey provides a copious quantity of glucose, a substrate which bacteria metabolise in preference to amino acids.[51]

The clearance of infection may also involve more than the antibacterial action of honey – recent research findings indicate that honey may work also by stimulating the activity of the immune system. Honey at concentrations as low as 0.1% has been found to stimulate proliferation of peripheral blood B-lymphocytes and T-lymphocytes in cell culture, and activate phagocytes from blood.[52] Also, honey at a concentration of 1% has been reported to stimulates monocytes in cell culture to release the cytokines TNF-α, IL-1 and IL-6 which are intermediates in the immune response.[53,54]

In addition to the reported stimulation of leukocytes, honey has the potential to further augment the immune response by supplying glucose. This is essential for the 'respiratory burst' in macrophages that generates hydrogen peroxide, the dominant component of the bacteria-destroying activity of these cells.[55] The sugars in honey also provide substrates for glycolysis, the major mechanism for energy production in the macrophages. This would allow them to function in damaged tissues and exudates where the oxygen supply is often poor.[55]

Debriding action of honey

Like any other moist wound dressing it is to be expected that honey would induce debridement of wounds, by allowing the autolytic action of tissue proteases. But unlike other wound dressings, honey creates a moist environment by drawing out lymph from the wound tissues by its strong osmotic action. This would give a constantly replenished supply of proteases at the interface of the wound bed and the overlying necrotic tissue, which may be one of the explanations for the notably rapid debridement brought about by honey. Another advantage of the osmotic action of honey drawing out lymph from the wound tissues is that it washes the surface of the wound bed from beneath. This would account for the long-known feature of honey dressings of removal of dirt with the dressing.[56] It would also aid in the painless lifting off of slough and necrotic tissue that is observed.[7,8,16,22,23,30]

Another possible explanation for the rapid debridement brought about by honey could be activation of the proteases by the hydrogen peroxide that is liberated by honey. The proteases in wound tissues are normally in an inactive state but can be activated by oxidation. The matrix metalloproteases of the connective tissue are normally present in a conformation that is catalytically inactive, but hydrogen peroxide changes the conformation of these and makes them active.[57,58] The neutrophil serine proteases are normally inactive because of the presence in wound tissues of an inhibitor, but hydrogen peroxide inactivates the inhibitor, so the protease becomes active.[59]

There is a strong association between high protease activity and impaired wound healing, which may suggest that activation of proteases by honey would be harmful rather than beneficial. However, a causal effect has never been proved,[60]and it could be that the association is the result of both the impaired healing and the high protease activity together being caused by the same factor. Excessive inflammation prevents healing and the attraction of inflammatory leukocytes gives rise to high levels of proteolytic enzyme activity at the site of the inflammation.[60] The potent anti-inflammatory action of honey (see the next section) would resolve such a situation and prevent excessive proteolytic activity. It has also been suggested that high levels of proteolytic activity and high levels of inflammation are both caused by a lack of secretory leukocyte protease inhibitor,

which is an inhibitor both of serine proteases and the production of TGF-β, a potent chemoattractant of inflammatory cells. Yet proteolysis in wound tissues is a normal part of the healing process, as well as being responsible for autolytic debridement. Also it is standard practice to add proteolytic activity to a wound to debride it, either as streptokinase preparations or as larval therapy (maggots). Honey provides a much less expensive (and more comfortable) alternative.

Anti-inflammatory action of honey

As well as the clinical observations of reduction of inflammation by application of honey to a wound, studies in animal models have demonstrated that honey gives reduced inflammation compared with various controls. The evidence for this is in the form of histological observation of reduced numbers of inflammatory cells present in wounds dressed with honey: deep[61] and superficial[25] burns, and full-thickness wounds.[62-64] It was shown that these effects were due to components other than the sugar in honey.[25,61] Evidence has also come from similar findings in biopsy samples from burn wound tissue of hospital patients.[24] That the reduction in inflammation was due to an anti-inflammatory component of honey, and not just a secondary effect of the honey clearing infection and debriding the wound, could be concluded from it being observed in experimental wounds in which there were few or no bacteria present.[25,61-64] There has also been a direct demonstration of the anti-inflammatory properties of honey reported, where honey decreased the stiffness of inflamed wrist joints of guinea pigs.[65]

Although inflammation is a vital part of the normal response to infection or injury, when it is excessive or prolonged it can prevent healing or even cause further damage to tissues. Suppression of inflammation, as well as reducing pain for the patient, reduces the opening of blood vessels and thus reduces edema and exudate. The pressure building up in tissues from edema restricts the flow of blood through the capillaries,[66] thus starving the tissues of the oxygen and nutrients that are vital for leukocytes to fight infection and for fibroblasts to multiply for wound healing. The swelling also increases the distance for diffusion of oxygen and nutrients from the capillaries to the cells.[67] In these ways

inflammation impairs healing. But a more serious consequence of excessive inflammation is the production of reactive oxygen species (free radicals) in the tissues,[68] side products of the activity of phagocytes in the inflammatory process. These free radicals are very reactive and can break down proteins, nucleic acids and cell membrane lipids, thus damaging or destroying tissue. Reactive oxygen species also serve to recruit more leukocytes into areas of inflammation, as a self-amplification of the inflammatory response.[68] The mechanism of self-amplification of the inflammatory response is by way of activating the transcription factor NF-κB, which then promotes the production of the pro-inflammatory cytokines IL-1, IL-8 and TNF. [69] Further amplification would come from the activation of proteases by reactive oxygen species, [57-59]and their increased activity resulting from activation of macrophages by oxidative activation of the transcription factor NF-κB,[70] as the powerful chemoattractant TGF-β present in wounds requires proteolysis to become active. Although the hydrogen peroxide produced in honey may be thought to have the potential to itself cause inflammation, it is produced at very low levels. In a discussion of the sense of cells using reactive oxygen species as messengers, it has been pointed out that there is a narrow concentration range in which they can function without being harmful.[70] The antioxidant content of honey (see below) would also help prevent inflammation being caused, as it has been found that it oxidative species formed from hydrogen peroxide, rather than hydrogen peroxide itself, that are responsible for the activation of the transcription factor NF-κB:[70] this activation can be prevented by antioxidants.[69] In experiments on monocytes[53] and lymphocytes[52] in cell culture it has been found that honey gives a mild stimulation of mitogenesis compare with classical mitogens (lipopolysaccharide or concanavalinA), but gives no additional stimulation if the cells are stimulated by the classical mitogens, and gives a reduction in production of reactive oxygen species in cells stimulated by lipopolysaccharide. [53]

Burn wounds characteristically have a large amount of inflammation, which can lead to worsening of the tissue damage from that caused by the initial thermal injury. A study carried out on burn wounds has shown that application of antioxidants to mop up free radicals reduces inflammation.[71] Honey has a significant content of antioxidants that mop up free radicals,[72] which may account for the finding in a clinical trial that honey

dressings prevented partial-thickness burns from converting to full-thickness burns which would have needed plastic surgery.[24]

Whether it is the antioxidants in honey breaking the feed-back loop of self-amplification of inflammation, or whether there is another anti-inflammatory component involved, the anti-inflammatory action of honey is likely to be involved in the notable effectiveness of honey in healing venous leg ulcers. In these there is a state of continual reperfusion injury, a condition in which there is a large amount of production of reactive oxygen species. This is because when there is ischemia (which occurs in a leg ulcer when there is venous stasis) xanthine oxidase is formed in tissues, which then produces reactive oxygen species from the oxygen supplied when tissues are re-perfused (which in a venous leg ulcer occurs when the leg is elevated).

The anti-inflammatory action of honey is also the most likely explanation for the reduction in hypertrophic scarring that is a feature of dressing wounds with honey. The reactive oxygen species formed in inflammation stimulate the activity of the fibroblasts which produce the collagen fibres of scar tissue, and in situations where there is prolonged inflammation their over-stimulation can lead to hypergranulation and fibrosis.[73] Fibroblasts are also responsible for the contraction that occurs in wound healing, so the anti-inflammatory action of honey may also account for the reduction in contractures seen when honey is used to dress burn wounds.

Bioactivity of honey: stimulation of tissue growth

Honey is a bioactive wound dressing, having a stimulatory effect on the rate of healing. It has been observed that it gives rapid healing of wounds,[12,25,26] and there have been many reports that it promotes the formation of clean healthy granulation tissue[5-8,10,24,31,36] and hastens epithelialization,[7,8,16,24,29], making skin grafting unnecessary.[6,7,11,16,24] The stimulation of cell growth by honey is probably also responsible for the "kick-starting" of the healing process observed in chronic wounds which have remained non-healing for long periods[8,17,18,27,28].

The property of topically applied honey of stimulating tissue growth in wounds has been confirmed by measurements and histological observations in many studies of

experimental wounds in animals.[12,25,61-63,74] Of these where there has been statistical analysis of the results, the honey treatment has been shown to give significant improvements. In one of these studies, on rats, the rate of decrease in wound size improved by 43% over the first 4 days ($p<0.001$; $n=6$), and the period required for complete epithelialisation decreased by 15% ($p<0.05$; $n=6$), with topically applied honey compared with untreated controls.[74] In another study, on mice, topically applied honey compared with a saline control was found after 6 days to give a 114% increase in the extent of epithelialisation ($p<0.001$; $n=12$) and a 69% increase in the thickness of granulation tissue ($p<0.01$; $n=12$).[12] Studies on experimental wounds in animals have also demonstrated that topically applied honey, compared with untreated controls, stimulates the synthesis of collagen (by 24% after 6 days; $p<0.001$; $n=6$)[75] and other connective tissue components (hexosamine by 13 % after 8 days; $p<0.01$; $n=6$: uronic acid by 23% after 8 days; $p<0.001$; $n=6$),[74] and gives an improvement of the strength (cross-linking) of collagen (by 23% after 6 days; $p<0.05$; $n=6$)[75] and the tensile strength of the wounds (by 21% after 10 days; $p<0.05$; $n=6$)[74]. Stimulation of angiogenesis by honey has also been observed in histological studies of experimental wounds in animals.[62,63] This is an important feature for promotion of healing, as the supply of oxygen is the rate-limiting factor,[76] granulation tissue being granules of fibroblasts growing where new capillary beds form. The acidity of honey would also help with oxygenation, as acidification of wounds speeds the rate of healing by increasing the release of oxygen from haemoglobin.[77] The new capillaries formed also supply essential nutrients to growing fibroblasts, another factor limiting the rate of healing. It has been demonstrated that wounds heal faster if a nutrient mixture is applied topically.[78-81] Honey supplies sugars and a wide range of amino acids, vitamins and essential minerals.[82] It also, by its osmotic action drawing out lymph, provides a constant flow of nutrients from the functioning capillaries deeper down. Another way in which honey may promote healing is by supplying glucose to the epithelial cells, as these have to build up an internal store of carbohydrate to provide the energy they need to migrate across the surface of a wound to restore skin cover[76].

Another factor that is probably involved in the stimulation of cell growth by honey is the low level of hydrogen peroxide produced enzymically in honey. There is a large amount of evidence for hydrogen peroxide being involved in many cell types in the body as a stimulus for cell multiplication, acting at various points in the mechanisms of the cells that control the cycle of cell growth and division.[83] It is produced as part of the normal inflammatory response to injury or infection, and serves to stimulate the growth of fibroblasts and epithelial cells to repair the damage.[83] The application of creams containing hydrogen peroxide has been found to stimulate the development of new capillaries in wound tissue.[84] It has been proposed that low concentrations of hydrogen peroxide might be used to stimulate wound healing, in place of the expensive cell growth factors used for this purpose,[83] but it has pointed out that this is feasible only if the concentration could be carefully controlled to avoid tissue damage[85] (as occurs in honey). There has also been a proposal that honey be used in place of recombinant growth factors to provide hydrogen peroxide to stimulate the healing of burns.[86] The action of exogenously supplied hydrogen peroxide augments that involved in an intracellular mechanism of response to growth factors binding to receptors on cells. The pathway of response to growth factors is via the Ras protein, and it has been found that this protein activates a second pathway as well as the previously known pathway of tyrosine phosphorylation of MAP kinase which then activates transcription factors.[87] This second pathway involves the activation of the Rac protein, which then forms a complex which produces superoxide. The superoxide, possibly via other reactive oxygen species, activates the transcription factor NF-κB and thus stimulates mitosis. It has also been found that in vascular smooth muscle cells the hydrogen peroxide endogenously produced as part of the signal transduction process in response to stimulation by platelet-derived growth factor activates MAP kinase, and that exogenous hydrogen peroxide in the concetration range of 0.1 to 1.0 mmol/l will do this also

Another action of hydrogen peroxide on cells is activation of insulin receptor complexes.[88-90] Activation triggers a chain of molecular events in the cell that stimulates the uptake of glucose and amino acids, and promotes anabolic metabolism, giving cell growth. It has been shown that intravenous infusion of insulin or its topical application to

wounds stimulates the rate of wound healing.[91-93] Thus this indicates another possible mechanism by which honey promotes the healing process, stimulating uptake and anabolic metabolism of the nutrients it supplies to wound tissues.

Physical properties of honey as a wound dressing

Honey differs from other wound dressings providing a moist healing environment in that it has an osmotic action which draws fluid out from the wound bed. This creates beneath the dressing a layer of fluid in contact with the wound surface which is a dilute solution of honey in plasma or lymph, so there is no adherence possible, hence when dressings are changed there is no pain and no tearing away of newly grown repair tissues. Although it may be thought that the osmotic effect would dehydrate wound tissues, where there is a circulation of blood underneath to replace fluid lost from cells then the osmotic effect of sugar on the surface just creates an outflow.[94] The osmotic action of honey also removes any risk of the skin surrounding a wound becoming macerated by the moisture accumulating under a dressing – even when dilute, honey will induce a withdrawal of moisture rather than a hydration of skin.

The high viscocity of honey provides a physical barrier to infection of wounds from external contamination. This is particularly useful where there would normally be a requirement to use gauze dressings to avoid occluding the wound and thus encouraging growth of Pseudomonas in the moist conditions created, as in the treatment of burn wounds. As long as the honey used has sufficient antibacterial activity (see Recommendation 2) there will be no danger of Pseudomonas growing in the moist conditions created by occluding the wound with honey. The antibacterial activity of honey also prevents growth of any bacteria already present on the surface of the wound, so there is not the problem of odour when dressings are changed like there is with hydrocolloid dressings.

The stickiness and fluidity of honey can be a practical challenge in dressing wounds, especially in retaining the honey when it is further liquefied by absorption of wound exudate.[95] This issue was addressed by the Ancient Egyptians, who used honey mixed with fat covered with fibres for dressing wounds,[96] but in more recent times it has not

usually been dealt with in a satisfactory way. The usual practice is to spread the honey on a wound and cover it with gauze, or to spread the honey on gauze and place that on the wound,[4] although occasionally honey-impregnated gauze has been used. The disadvantage of these practices is that gauze does not absorb much honey. Practices which overcome the problems of messiness of honey are described in Recommendation 3.

Recommendation 1

Do not leave it too late to start using honey on a wound

Many clinicians resort to trying honey when all of the orthodox treatments have failed to work. If a wound infection has been allowed to progress to a systemic infection then honey cannot be of any help, and if the infective organism is antibiotic-resistant then the patient's life could well be at risk by that stage. Although the antibacterial components of honey are capable of diffusing into a wound bed, honey is most effective before a wound has been allowed to become deeply infected, as the antibacterial activity is greatest near the surface. If used from the outset, honey provides a barrier to infection both through its viscosity and its antibacterial action. This is particularly useful where there is a risk of cross-infection. Allowing a wound to become very inflamed and heavily exudative before honey is used makes much more frequent dressing changes necessary to bring the inflammation under control. (See Recommendation 8.) If a hard eschar is allowed to form before honey is used it will take longer for honey to debride the wound. (See Recommendation 10.)

Recommendation 2

Use only honey that has been selected for use in wound care

Although it has been pointed out by Greenwood[97] that the clinical significance of the additional antibacterial activity in honey will be unequivocally proven only if a clinical trial is conducted to determine this, since the presence of bacteria in wound tissues is often an impediment to wound healing it seems wise to select for use in wound management a honey with a high level of antibacterial activity, especially since this can

vary so much. Although any honey, when undiluted, will through its high osmolarity stop the growth of bacteria colonising the surface of a wound, honey usually gets diluted by exudate and thus a honey of low potency may not maintain an effective level of antibacterial activity. Another consideration is that the antibacterial substances diffusing from honey on the surface of the wound down into infected tissues give a gradient of decreasing concentration. Thus the higher the potency of the honey on the surface, the further down into the tissues will be the minimum effective level of the antibacterial substances, down into the depth of the wound tissues where the infection lies.

Also, consideration needs to be given to the quality of any honey used on a wound. Honey produced for use as a food may not be well filtered, so may contain various particles in it. Although honey does not allow vegetative bacteria to survive, it does contain viable spores, including Clostridia. Various brands of honey with standardised antibacterial activity, processed as a medical product and sterilised by gamma-irradiation, are available commercially for use in wound management: *Apiban* (Apimed: Cambridge, New Zealand), *Woundcare 18+* (Comvita: Te Puke, New Zealand), *Medihoney* (Capilano: Richlands, Queensland, Australia). These are all packed in squeeze-out tubes. Apimed also manufacture other honey wound-care products: honey packed in syringes, and honey-impregnated dressings (Gamgee type and alginate type). All three of these companies use manuka honey (and honey from a related Leptospermum species in *Medihoney*) in their products.

Manuka honey has a unique, unidentified, antibacterial component in addition to the enzymically generated hydrogen peroxide that is common to all honeys. The level of the manuka factor, like the level of hydrogen peroxide in all honeys, can vary markedly from batch to batch, so it is important that any honey be tested in a microbiology laboratory if a good antibacterial activity is to be obtained. Although some floral types of honey characteristically have higher antibacterial activity than others, individual batches still vary a lot, so testing of each batch is necessary. It is also to be noted that the enzyme in honey that produces hydrogen peroxide is easily destroyed by exposure to heat and light, so it is important that the minimum of heating is used in the processing of honey for use in wound care, and that the honey is stored in a cool place and packaged to protect it from light.

Recommendation 3

Use dressings that will hold sufficient honey in place on a wound to get a good therapeutic effect

Although honey is very viscous, or even solid, at room temperature, it becomes very fluid at body temperature. If it is applied directly to the wound it tends to run off before a secondary dressing can be applied to hold it in place. Because of its viscosity and lack of free water, honey does not readily soak into absorbent dressings so tends to be squeezed out when a secondary dressing is applied. It is important to hold sufficient honey in place on a wound to get a good therapeutic effect, providing a "reservoir" of sufficient quantity such that its antibacterial and other bioactive components are not excessively diluted by exudate and not substantially depleted by diffusion into the wound tissues. Because the antibacterial activity of honey is of relatively low potency compared with that of the usual antibacterial agents used on wounds, the amount required on a wound is greater.

In some situations a "blister" of honey can be held on a wound using an adhesive membrane dressing. Honey can also be held in a small cavity in this way. However, this is not a suitable form of dressing if the wound is exuding heavily.

On most wounds the best practice is to use an absorbent dressing impregnated with honey, which allows an effective amount of honey to be easily applied and held in place. As long as the amount of honey impregnated does not exceed the amount that the dressing will absorb, the honey does not run out even under pressure bandaging. Impregnating dressings with honey is facilitated by warming the honey to body temperature and adding 1 part of water to 20 parts of honey to make the honey more fluid. Typically, 20 ml of honey would be used in a 4 inch x 4 inch dressing. Alternatively, commercially available dressing pads (cellulose or alginate fibre) pre-impregnated with honey with a standardised level of antibacterial activity and sterilised by gamma irradiation can be used. Dressings impregnated with honey still retain their capacity for absorbing exudates.

Recommendation 4

Ensure that honey is in full contact with the wound bed

Contact between the wound bed and the honey is essential for the antibacterial and other bioactive components of the honey to be able to diffuse into the wound tissues. Dressing pads impregnated with honey have a tendency to bridge over depressions in the wound bed, so any cavities or depressions need to be filled with honey before the dressing is placed on the wound. (Honey sold for use in wound management is packaged in squeeze-out tubes or syringes, which avoids the messiness of using honey from a jar to do this.) Abscesses and sinuses can be filled with honey before a covering dressing is applied – honey is water-soluble and easily rinsed out, and any residues are biodegradable (as long as the honey has been suitably filtered in processing so that there are no foreign bodies in it.) For sinuses with small openings, a catheter on a syringe filled with warmed honey is an effective way of inserting honey.

Recommendation 5

If a non-adherent dressing is used between the honey dressing and the wound bed it must be sufficiently porous to allow the active components of the honey to diffuse through

Honey dressings normally do not adhere to wound tissues, but there are occasions when dressings cannot be changed frequently enough to prevent adhesion occurring. (See Recommendation 8.) Also there are occasions when disturbance of the wound surface is to be avoided when honey dressings are changed (*e.g.* when used on skin grafts). In these situations a non-adherent dressing may be placed between the wound bed and the honey dressing. It is important that the non-adherent dressing is sufficiently porous to allow the antibacterial and other bioactive components of the honey to diffuse freely into the wound bed, and that honey is spread on this dressing so that there is continuous contact between the wound bed and the honey dressing on top of the non-adherent dressing.

Recommendation 6

Ensure that honey dressings extend to cover any area of inflammation surrounding wounds

Honey dressings need to be of a size that not only covers the wound bed but also extends beyond any area of inflammation or cellulitis surrounding a wound. This allows diffusion through the skin of the antibacterial components to clear infection in peri-wound tissue, and of the anti-inflammatory components to reduce inflammation and edema.

Recommendation 7

Use a suitable secondary dressing to prevent leakage of honey

If a wound is exuding, honey becomes diluted and very fluid. If the absorptive capacity of the primary dressing is exceeded then the diluted honey will seep out, so a secondary dressing may be needed. If it is compatible with the condition of the skin and the location of the wound then an occlusive dressing is best for this. (Maceration of the surrounding skin does not occur in the presence of the honey.) Absorbent secondary dressings can be used, but tend to draw the honey away from the wound surface. This means that honey is replaced with exudate in the dressing in contact with the wound bed. (See Recommendation 8.) Occlusive dressings trap the diluted honey in the primary dressing and thus tend to keep more honey in contact with the wound bed.

If an adhesive secondary dressing cannot be used to hold the honey dressing in place then bandaging or body stocking can be used. On venous leg ulcers where inelastic or elastic compression bandaging is used a secondary dressing is needed under the bandaging to stop honey seeping out into the bandaging.

Recommendation 8

Change the dressings frequently enough to prevent the honey being washed away or excessively diluted by wound exudate

Unlike many of the other antibacterial agents used on wounds, honey is a water-soluble material that readily takes up wound fluid and thus becomes diluted. It can do

this to some degree by osmosis even when a wound is not noticeably exudating. Although bacterial growth in the dressing and on the wound surface will be prevented even when the honey is diluted as much as ten-fold, control of infection in deeper wound tissue is not likely to be maintained if the honey becomes greatly diluted. (See Recommendation 2.) This applies also to the other bioactivities of honey such as the anti-inflammatory action and the stimulation of tissue growth. Thus when there is a lot of exudate from a wound it may be necessary to change honey dressings quite frequently (up to three times daily) in cases of heavily exuding wounds. However, the anti-inflammatory action of honey usually gives a marked reduction in the amount of exudation within a few days. The best guide is the appearance of the dressing when removed – if honey is not visibly present then the dressing has been left on the wound too long. If the dressing sticks to the wound this is a clear indication that more frequent changes are required, as the honey in the dressing has been replaced with plasma in which a fibrin clot has formed. When cotton/cellulose dressing materials impregnated with honey are used the honey tends to get washed towards the outer surface by wound exudate, but if honey-impregnated alginate dressings are used the alginate fibres convert to a honey-containing soft gel in which the honey is more evenly distributed.

Honey in dressings may also become diluted or washed away by external fluids such as water or urine, so where waterproof covering of the dressing is not possible it will be necessary to change dressings that have become wet in this way.

Even where there is no exudate and the honey does not become diluted, the dressings need to be changed at least weekly to maintain a "reservoir" of bioactive components as these diffuse away into the wound tissues and deplete the content in the honey on the surface, thus decreasing the concentration gradient down into the wound tissues.

Recommendation 9

When using honey to debride hard eschar, scoring and softening the eschar by soaking with saline will allow better penetration of the honey

Because if its high osmolarity, honey will not hydrate eschar. Thus the penetration of its components through the eschar is slow if the eschar is hard, and autolytic debriding may take more than one week to occur. Scoring the eschar and/or softening it by soaking

with saline will speed up the debriding action of honey. An alternative way of speeding up the process is to apply dressings soaked in diluted honey (1 volume of honey to three volumes of saline) until debridement is achieved.

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KEY POINTS

- Honey has a broad-spectrum antibacterial activity, effective also against antibiotic-resistant bacteria, with no adverse effects on wound tissues.
- Honey gives rapid debridement and deodorising of wounds.
- Honey has an anti-inflammatory activity that reduces pain, edema and exudation, and minimises hypertrophic scarring.
- Honey stimulates healing in dormant wounds and speeds the healing process by stimulating cell growth.

TABLE 1

QUICK REFERENCE GUIDE TO THE 9 RECOMMENDATIONS FOR PRACTICE: DRESSING WOUNDS WITH HONEY

1. Do not leave it too late to start using honey on a wound.
2. Use only honey that has been selected for use in wound care.
3. Use dressings that will hold sufficient honey in place on a wound to get a good therapeutic effect.
4. Ensure that honey is in full contact with wound bed.
5. If a non-adherent dressing is used between the honey dressing and the wound bed it must be sufficiently porous to allow the active components of the honey to diffuse through.
6. Ensure that honey dressings extend to cover any area of inflammation surrounding wounds.
7. Use a suitable secondary dressing to prevent leakage of honey.
8. Change the dressings frequently enough to prevent the honey being washed away or excessively diluted by wound exudate.
9. When using honey to debride hard eschar, scoring and softening the eschar by soaking with saline will allow better penetration of the honey.

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