journal of wound care JWC
VOLUME 25. NUMBER 3. MARCH 2016

A multi-centre clinical evaluation of reactive oxygen topical wound gel in 114 wounds

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- **Objective:** This article reports the outcomes of the use of Surgihoney RO (SHRO), topical wound dressing in a multi-centre, international setting. The aims were to explore the clinical effects of SHRO, including a reduction in bacterial load and biofilm and improvement in healing in a variety of challenging non-healing and clinically infected wounds.
- **Method:** This was a non-comparative evaluation, where both acute and chronic wounds with established delayed healing were treated with the dressing. Clinicians prospectively recorded wound improvement or deterioration, level of wound exudate, presence of pain, and presence of slough and necrosis. Analysis of this data provided information on clinical performance of the dressing. Semi-quantitative culture to assess bacterial bioburden was performed where possible.
- **Results:** We recruited 104 patients, mean age 61 years old, with 114 wounds. The mean duration of wounds before treatment was 3.7 months and the mean duration of treatment was 25.7 days. During treatment 24 wounds (21%) healed and the remaining 90 (79%) wounds improved following application of the dressing. No deterioration in any wound was observed. A reduction in patient pain, level of wound exudate and in devitalised tissue were consistently reported. These positive improvements in wound progress were reflected in the wound cultures that showed a reduction in bacterial load in 39 out of the 40 swabs taken. There were two adverse events recorded: a stinging sensation following application of the dressing was experienced by 2 patients, and 2 elderly patients died of causes unrelated to the dressing or to the chronic wound. These patients' wounds and their response to SHRO have been included in the analysis.
- **Conclusion:** SHRO was well tolerated and shows great promise as an effective potent topical antimicrobial in the healing of challenging wounds.
- **Declaration of interest:** Matthew Dryden has become a shareholder in Matoke Holdings, the manufacturer of Surgihoney RO, since the completion of this study. Keith Cutting is a consultant to Matoke Holdings.

RO Surgihoney; clinical evaluation; topical antimicrobial gel; chronic wound; acute wound

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Continued page 143

Chronic wounds impose a significant burden on patients, society and healthcare providers.[1,2] A chronic wound has been defined as a wound that has not healed within three weeks of onset.[3] Based on this definition it is reasonable to include acute wounds that have not healed within three weeks, bearing in mind that there is a similar failure of the wound to proceed through an orderly and timely healing process.

The financial costs of wound to the NHS are considerable. A recent and comprehensive health economic evaluation of the burden of wounds has estimated a yearly cost of £5.3 billion to the NHS.[4]

Wound infection occurs in the presence of multiplying bacteria in body tissues. It is not bacterial presence per se that causes infection but the microbial expression of virulence factors that results in tissue damage[5] and delayed healing.[6,7] The host response is commonly inflammation that is easily recognised in the acute wound through the manifestation of redness, swelling, heat and pain.[8] In chronic wounds, more subtle signs of infection have been characterised.[9] These diagnostic criteria have been validated[10] and more recently wound-type specific criteria have also been developed.[11] Treatment of wound infection needs to be prompt and effective if increased morbidity is to be avoided. The widespread misuse of antibiotics together with concerns over the emergence of resistant bacteria[12] are well documented and provide a platform for the development and introduction of effective potent topical therapeutics that are broad-spectrum yet avoid inducing microbial selection for resistance.[13]

Surgihoney RO (SHRO) is a licensed CE marked sterile topical antimicrobial that has been shown to be a potent antimicrobial *in vitro*,[14,15] active against Gram-positive and Gram-negative bacteria, including multidrug resistant (MDR) strains. It is effective in acute and chronic wound infection, in the prevention of surgical wound infection,[16,17] in reducing and preventing intravascular line site colonisation[18] and against biofilm-encased bacteria.[19] SHRO is a pure honey-derived

bioengineered product that was initially developed as a wound care therapy, but may have other clinical applications for the control of bacteria and biofilms on mucosal surfaces and in cavities. It is pure in that it contains no antibiotic residues or agricultural additives, but has undergone a process to enhance its natural antimicrobial activity.[15] During the engineering process the production and activity of the active agent, reactive oxygen species (ROS), which includes hydrogen peroxide (H_2O_2), is enhanced, resulting in a highly potent antimicrobial agent that is effective against a wide range of bacteria and fungi,[15] is non-toxic to human tissue,[14] and delivers ROS over a prolonged period.[14] As a simple treatment it can be applied in all areas of health care from first world critical care units to third world budget rural clinics.

Study aim

To assess the efficacy of SHRO in the healing process of wounds and in the reduction of bacterial load and inflammatory material associated with biofilm.

Methods

The evaluation design comprised prospective assessment of cases from a number of clinical centres in an international setting. The observation period for each patient varied. Ethics committee approval was not required as this assessment was of a CE-marked medical device (dressing) for use by qualified personnel as intended and is available commercially. All patients provided verbal consent to participate in this evaluation and to wound photography.

Data were collected and stored on a handheld tablet in an encrypted database that was uploaded electronically to a central secure database. Data included:

- Patient age, demographics and number of comorbidities
- Wound type
- Location
- Duration of wound before this treatment
- Subjective assessment of wound at each visit (improved, unchanged, deteriorated)
- Measurement of wound area (length/height/depth)
- Semi-quantitative record of presence of discharge/exudate/slough, and inflammation (+/-,+,++,+++)
- Biopsies to assess biofilm histologically were not collected but the clearance of slough and the presence of healthy granulation tissue was taken as a possible reduction of biofilm
- Level of wound pain (mild, moderate, severe)

Table 1. Geographical location of patients and number of wounds

Hospital/ community sites	Location	No of patients	No of wounds
Hospitals, England	Royal Hampshire County Hospital, Winchester	84	93
	North Hampshire Hospital, Basingstoke		
	Hampshire Hospitals NHS Foundation Trust, Andover		
	Hammersmith Hospital NHS Trust, London		
General practice surgeries, England	Odiham		
	Bishops Waltham		
	Milton Abbas		
Developing world	Ethiopia	10	21
	Uganda	6	
	Tonga	4	
Total		**104**	**114**

Table 2. Patients' characteristics, wound duration and mean length of SHRO treatment

Wound type	Number of patients	Mean age (range) years	Mean number of comorbidities	Mean wound duration	Mean duration of SHRO treatment
Leg ulcers	33	78 (32–91)	4	8 months	24 days
Pressure ulcers	18	75 (45–97)	4	5.4 months	27.4 days
Surgical wounds	14	54 (0–76)	5	1.9 months	34.5 days
Diabetic ulcers	5	68 (53–87)	4	4.2 months	35.5 days
Central catheter site infections	2	44	3	n/a	9 days
Suprapubic catheter site	1	61	2	1 month	12 days
Traumatic wounds	8	67 (21–90)	2	2 months	32.3 days
Other topical infections	3	63 (22–95)	n/a	n/a	37.3 days
Mostly traumatic and surgical wounds (developing world)	20	41 (23–82)	2	3.6 months	19.6 days

n/a–not available; SHRO–Surgihoney RO

Table 3. Changes in wound pain recorded at beginning and end of the evaluation period

Wound type	Wound pain at start of the evaluation	Wound pain at end of the evaluation	Number of patients
Leg ulcers	mild	no pain	8
	mild	mild	1
	moderate	mild	5
	moderate	no pain	5
	moderate	moderate	1
	severe	mild	3
	severe	no pain	1
Pressure ulcers	mild	no pain	5
	mild	mild	1
	severe	no pain	1
Surgical wounds	moderate	mild	1
	mild	mild	1
	severe	no pain	1
Diabetic foot ulcer	mild	no pain	2
	moderate	no pain	2
	severe	no pain	1
Trauma	mild	no pain	3
	mild	mild	1
	moderate	no pain	3
Other topical infections developing world	moderate	no pain	1
	mild	no pain	5
	moderate	no pain	6
	severe	no pain	1

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- Presence of slough or necrosis
- Any debridement of wound
- Duration of treatment
- Reduction in bacterial load as assessed by wound swab with semi-quantitative culture
- Adverse events.

Dressings and SHRO gel were changed at the discretion of the attending clinician and patient circumstances, but the recommendation was for gel change every 2–3 days. The gel is applied to the wound bed in an even layer up to approximately 2mm thick and covered with a suitable sterile secondary dressing. If the wound was heavily exuding it is advised to use a highly absorbent secondary dressing to avoid the gel being sluiced from the wound.

Results

A total of 114 wounds/104 patients were recruited. Of these, 84 patients (81%) were from four secondary care hospitals and three general practice surgeries in England and 20 patients (19%) from countries in the developing world (Table 1).

A range of wound types were included, these together with the number of wounds, mean patient age, average wound duration and number of comorbidities are presented in Tables 2. Across all wound types the mean age of the patients was 61 years old (range: 32–91). The highest number of patients was the leg ulcer cohort. This group also had the highest mean age of patients (78 years old) and the longest mean wound duration at 8 months.

On enrolment, 109 wounds were recorded as deteriorating and five wounds were static. At the end of the evaluation period, all wounds were recorded as having improved following treatment with SHRO with 24 wounds (21%) closed (re-epithelialised).

The duration of treatment with SHRO varied from patient to patient as did the observation period. Treatment with SHRO ranged from 1 to 19 weeks, the mean duration being 25.7 days.

The type and level of exudate was identified as a clinical problem in 47 (41%) wounds. Following treatment the type of exudate changed from (unhealthy) green-tinged or purulent/haemopurulent/seropurulent, to clear serous exudate in all 47 wounds. Likewise, the level of exudate calculated semi-quantitatively as heavy or moderate at the start of treatment resolved to low/negligible in all 47 wounds.

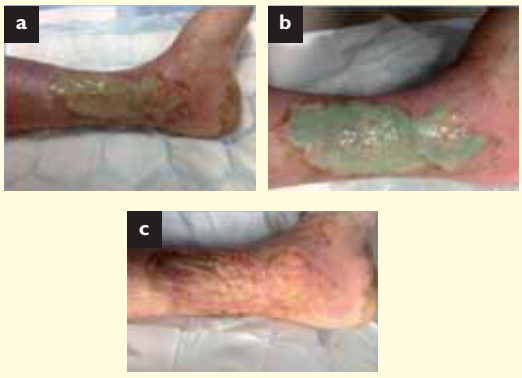
The wound type and associated changes in wound pain are seen in Table 3. A clear decrease in pain between the beginning and end of the evaluation period was recorded in 54 patients.

In this evaluation the presence of slough, necrotic material and increasing exudate was equated with a raised suspicion of the presence of biofilm. A total of 41 wounds were initially recorded as having slough or necrotic tissue present. The breakdown of wound type and debridement outcomes are seen in Table 4 and illustrated in Fig 1 and 2. In this evaluation debridement was achieved through larvae therapy in two patients, sharp debridement in three patients and through the topical application of SHRO in conjunction with a simple retentive dressing in all remaining evaluation patients (Table 4).

It is not known why the quantity of slough increased in one patient in the PU group. Nonetheless, by day 22 wound size had decreased by 60% and the wound was recorded as 'progressively healing'. Overall the results indicate excellent debridement and possible biofilm reduction following use of SHRO

The majority of wounds treated with SHRO were noted to have reduced in size and shown positive improvement towards wound healing criteria. These criteria were observed in conjunction with reduction in the level of wound exudate, pain, slough and inflammation (Table 5). A total of 40 wounds from patients resident in England had serial microbiological sampling. A reduction in bacterial load was demonstrated in 39 (98%) of the wounds. The number of swabs taken according to wound type may be seen in Table 5.

Fig 1. A 77-year-old man with ischaemic ulcer heavily colonised with *Pseudomonas* sp, methicillin-resistant *Staphylococcus aureus*, Coliforms and enterococci. SHRO Surgihoney treatment. Photographs on days 0 (a), 4 (b) and 8 (c). The clinical team wanted antibiotics to cover all microbes and were considering debridement surgery. SHRO was used topically which eliminated all multidrug-resistant organisms.



SHRO treatment was very well tolerated. Patients were asked to report adverse effects at each dressing change; the majority (102/104) patients reported no adverse effects at all with SHRO treatment, two reported stinging, one with a chronic venous ulcer refused any further SHRO treatment on day 4 and was withdrawn from the evaluation. There were two other patients with severe comorbidities who did not report adverse effects while being treated with SHRO, but died as a result of other causes during treatment: one due to left ventricular cardiac failure, the other due to organ failure with widespread malignancy.

Discussion

Many of the patients included in this evaluation had multiple comorbidities. These patients and their wounds present a challenge to the clinicians in terms of achieving progression to healing.

It is widely accepted that wound infection causes pain[20] and that there are established links between wound pain, stress, delayed healing and patient quality of life.[21] Achieving a reduction in wound pain following application of a topical antimicrobial agent is a positive indication the reduction in pain following application with SHRO is consistent with earlier reports.[17,22]

Recent findings indicate that when sharp debridement is regularly performed the chance of healing increases 2.5-fold.[23] However the precise relationship between slough, infection and biofilm is still being investigated. In a rat model, infection was associated with slough, necrotic tissue and wound pocketing. All these features delayed healing compared with a control or colonised group.[24] Other reports show that when wounds become colonised with bacteria that can form biofilms, healing is delayed.[25,26] The efficacy of SHRO in the reduction of wound biofilm has already been demonstrated *in vitro*.[19]

Table 4. Effect of SHRO treatment on slough and necrosis

Wound type	At start	At end	Notes
Leg ulcer (n=14)	7 slough++	2 slough+	1 patient died (day 11)
		5 no slough	
	2 slough+++	2 no slough	
	2 slough/necrosis	1 no slough/ necrosis	
		1 slough+	
	3 necrosis+++	3 no necrosis	2 patients initially received larvae therapy
Pressure ulcer (n=7)	1 slough+	1 slough++	Decrease in overall wound size
	5 slough++	5 no slough	2 patients initially received sharp debridement
	1 necrosis++	1 no necrosis	
Surgical (n=6)	2 slough++	2 no slough	
	2 slough+++	2 slough+	
	2 necrosis+++	2 necrosis+	1 patient received sharp debridement, wound contracting
Diabetic foot ulcer (n=4)	3 slough++	3 no slough	
	1 necrosis	1 no necrosis	
Trauma (n=3)	3 slough++	2 no slough	
		1 slough+	
Developing world (n=7)	5 slough++	5 no slough	
	2 necrosis++	2 no necrosis	

SHRO–Surgihoney RO

When attempting to establish if there are clinical signs of biofilm in wounds the findings are more tenuous, particularly without a biopsy of the wound for histological examination. An increase in the level of exudate, failure of wound closure despite appropriate therapy, build up of slough despite debridement and the presence of the subtle signs of infection have been proposed.[27] In addition a glazed/shiny/translucent appearance of the wound bed has also been suggested.[28] Although these latter signs are clinically related to delayed wound healing a robust validation relating these to the presence of biofilm has yet to be undertaken.

Topic antimicrobial preparations are available to treat or prevent wound infection. Silver impregnated dressings appear to possess good localised antimicrobial activity;[29] however, they also display cytotoxicity compared with honey preparations.[30,31] Iodine analogues also possess good antimicrobial

Table 5. Type of wound, response to SHRO treatment and reduction of bacterial load demonstrated by semi-quantitative bacterial culture

Wound type	Number of patients	Number of wounds	Reduction in wound size documented (%)	Improvement in healing criteria documented (%)	Number of wounds swabbed	Reduction of bacterial load (number of wounds)
Leg ulcers	33	37	25 (68)	34 (92)	17	17
Pressure ulcers	18	19	12 (63)	17 (89)	9	9
Surgical wounds	14	14	10 (71)	12 (86)	8	7
Diabetic ulcers	5	9	9 (100)	9 (100)	1	1
Central catheter site Infections	2	2	n/a	2 (100)	2	2
Suprapubic catheter site	1	1	n/a	1 (100)	1	1
Traumatic wounds	8	12	5 (42)	12 (100)	2	2
Other topical infections	3	3	n/a	n/a	n/a	n/a
Developing world	20	21	15 (71)	16 (76)	n/a	n/a

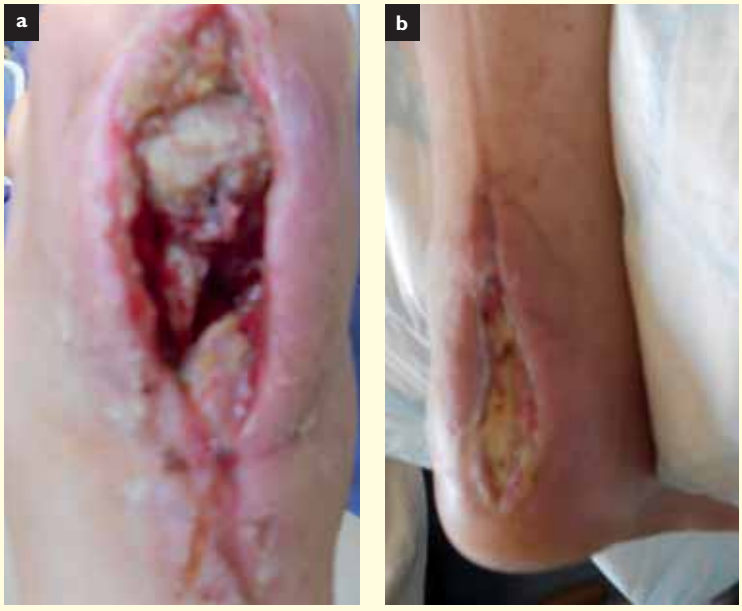
n/a–not available

activity[31] but have been reported to be toxic in certain situations.[31–36] There is also increasing concern about the use of chlorhexidine preparations in wound dressings due to the development of antimicrobial resistance and toxicity.[37,38]

A Cochrane Collaboration report stated that honey may be superior to some conventional dressing materials,[39] but there is considerable uncertainty about the replicability and applicability of this evidence. This Cochrane review was compiled before the published evidence of efficacy with SHRO.

This evaluation supports the idea that SHRO helps clear the bacterial bioburden assessed by semi-quantitative culture. This possible biofilm reduction, as assessed through reduction of slough and necrotic material adhering to ulcer base, supports wound contraction, reduction in exudate, inflammation, pain, and facilitates debridement.

Fig 2. Soft tissue cavity in a young diabetic following fractured, pinned calcaneum: days 0 and 14 of Surgihoney RO treatment



Evaluation limitations

This observational evaluation included subjective reporting. Sampling bias occurred naturally as the patients were 'enrolled' at the discretion of the clinician. There was neither randomisation nor control of treatment. The patients' wounds and conditions were highly varied. Furthermore, biofilm is difficult to assess without histological biopsy and so a reduction in biofilm was assumed to occur by reduction in slough and necrotic material. Bacterial culture assessments were semi-quatitative and were not undertaken in every patient.

Further possible benefits from SHRO gel that are difficult to measure in this evaluation but are important aspects of wound healing could be wound deodorisation, stimulation of tissue growth, synthesis of collagen, stimulation of development of new blood vessels and nerve endings in the bed of wounds. Further research is being undertaken to establish this.

Recommendations

The clinical use of a topical antimicrobial, on skin, in wounds and cavities and possibly on other mucosal surfaces and internal structures at surgery, both to prevent infection and treat low grade localised infection

is recommended. A topical agent with broad antimicrobial activity and clear *in vitro* evidence in the reduction of biofilm could play an important therapeutic role in infected soft tissue lesions and possibly mucosal surfaces. SHRO can support antimicrobial management in reducing the use of systemic antibiotics in these areas. *In vitro* studies and clinical evaluations have demonstrated the potential of SHRO as a wound treatment with high antimicrobial activity.

Conclusions

This evaluation reports positive outcomes on 104 patients with 114 wounds who received topical SHRO gel as a treatment in a wide range of chronic wounds, line sites, surgical and traumatic wounds. The report shows that 24 wounds healed and 90 wounds improved within the evaluative period. There was a positive reduction in wound pain, exudate production, devitalised tissue, wound bacterial load as assessed by reduction of slough and necrotic material. The dressing was well tolerated by the patients and shows much promise as an effective topical antimicrobial dressing in challenging wounds. ■

References

1 Augustin, M., Schmitt, J., Herberger, K. et al. The German national consensus on wound documentation and outcomes: Rationale, working programme and current status. Wound Medicine 2014; 7: 8–13.

2 Phillips, C.J., Humphreys, I., Fletcher, J. et al. Estimating the costs associated with the management of patients with chronic wounds using linked routine data. Int Wound Journal 2015; doi: 10.1111/iwj.12443. [Epub ahead of print].

3 Hermans, M.H.E., Treadwell, T. An introduction to wounds. In: Percival, S., Cutting, K. (eds). Microbiology of wounds. CRC Press, Taylor & Francis Group, 2010.

4 Guest, J.F., Ayoub, N., Mcilwraith, T.et al. Health economic burden that wounds impose on the National Health Service in the UK. BMJ open 2015; 5:e009283.

5 Barczak, A.K., Hung, D.T. Productive steps toward an antimicrobial targeting virulence. Curr Opin Microbiol 2009;12: 5, 490–496.

6 Schlüter, B., König, W. Microbial pathogenicity and host defense mechanisms - crucial parameters of posttraumatic infections. Thorac Cardiovasc Surg 1990; 38: 6, 339–347.

7 Thomson, P.D. Immunology, microbiology, and the recalcitrant wound. Ostomy Wound Manage 2000; 46: 1A Suppl, 77S-82S.

8 White, R.J., Cutting, K., Kingsley, A. Topical antimicrobials in the control of wound bioburden. Ostomy Wound Manage 2006; 52: 8, 26–58.

9 Cutting, K.F., Harding, K.G. Criteria for identifying wound infection. J Wound Care 1994; 3: 4, 198–201.

10 Cutting, K.F. The identification of infection in granulating wounds by registered nurses. J Clin Nurs 1998; 6: 539–546.

11 Cutting, K.F., White, R.J., Mahoney, P. et al. Clinical identification of wound infection: a Delphi approach. Identifying criteria for wound Infection EWMA Position Document. MEP, 2005.

12 Levin, S.A., Andreasen. a V. Disease transmission dynamics and the evolution of antibiotic resistance in hospitals and communal settings. Proc Natl Acad Sci U S A 1999; 96: 3, 800–801.

13 Edwards-Jones,.V., Flanagan, M., Wolcott, R. Technological advancements in the fight against antimicrobial resistance. Wounds International 2015; 6: 2, 47–51.

14 Cooke, J., Dryden, M., Patton, T. et al. The antimicrobial activity of prototype modified honeys that generate reactive oxygen species (ROS) hydrogen peroxide. BMC Res Notes 2014; 8: 20.

15 Dryden, M., Lockyer, G., Saeed, K et al. Engineered honey: In vitro antimicrobial activity of a novel topical wound care treatment. Journal of Global Antimicrobial Resistance 2014; 2: 3, 168–172.

16 Dryden, M., Goddard, C., Madadi, A. et al. Using antimicrobial Surgihoney to prevent caesarean wound infection. British Journal of Midwifery 2014; 22: 2, 111–115.

17 Dryden, M., Hudgell. L., Saeed. K. et al. (23013) Surgihoney - Modified honey wound treatment: first report of in-vitro and early clinical evaluation. Federation of Infection Societies. Birmingham. Available at bit.ly/1mV0sih (accessed February 2016).

18 Dryden, M., Tawse, C., Adams, J. et al. The use of Surgihoney to prevent or eradicate bacterial colonisation in dressing oncology long vascular lines. J Wound Care 2014; 23; 6, 338–341.

19 Halstead, F.D., Webber, M.A., Rauf, M. et al. In vitro activity of an engineered honey, medical-grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates. J Wound Care 2016; 25: 2, 93–102.

20 Bjarnsholt, T., Kirketerp-Moller, K., Jensen, P. et al. Why chronic wounds won't heal: a novel hypothesis. Wound Repair Regen 2008; 16: 2, 1–10.

21 Cutting, K., White, R., Mahoney, P. Wound infection, dressings and pain, is there a relationship in the chronic wound? Int Wound J 2013; 10: 1, 79–86

22 Heyes, I., Hughes, R., Hussein, A. et al. Poster presentation Surgihoney: Biotechnological honey wound treatment: first clinical report of its use in the tropics. British Society for Antimicrobial Chemotherapy spring meeting & AGM. Royal College of Physicians, London, 2013. Available at: bit.ly/1p0DuaZ (accessed February 2016.)

23 Karavan, M., Olerud, J., Bouldin, E. et al. Evidence-based chronic ulcer care and lower limb outcomes among Pacific Northwest Veterans. Wound Repair Regen 2015; 23: 5, 745–752.

24 Asada, M., Nakagami, G., Minematsu, T. et al. Novel models for bacterial colonization and infection of full-thickness wounds in rats. Wound Repair Regen 2012; 20: 4, 601–610.

25 Scali, C., Kunimoto, B. An update on chronic wounds and the role of biofilms. J Cutan Med Surg 2013; 17: 6, 371–376.

26 Percival, S.L., Hill, K.E., Williams, D.W. et al. A review of the scientific evidence for biofilms in wounds. Wound Repair Regen 2012; 20: 5, 647–657.

27 Cutting, K.F., Wolcott, R., Dowd, S.E. et al. Biofilms and significance to wound healing. In: S. L. Percival, S.L., Cutting, K.F. (eds). The microbiology of wounds. CRC Press, Taylor and Francis Group, 2010.

28 Cutting, K.F., White, R.J. Criteria for identifying wound infection--revisited. Ostomy Wound Manage 2005; 51: 1, 28–34.

29 Aramwit, P., Muangman, P., Namviriyachote, N., Srichana, T. In Vitro Evaluation of the Antimicrobial Effectiveness and Moisture Binding Properties of Wound Dressings. Int J Mol Sci 2010;11: 8, 2864–2274.

30 Du Toit, D.F., Page, B.J. An in vitro evaluation of the cell toxicity of honey and silver dressings. J Wound Care 2009; 18: 9, 383–389.

31 Bradshaw, C.E. An in vitro comparison of the antimicrobial activity of honey, iodine and silver wound dressings. Bioscience Horizons 2011; 4: 1, 61–70.

32 Béji, S., Kaaroud, H., Ben Moussa, F. et al. Insuffisance rénale aiguë secondaire à la povidone iodée. La Presse Médicale [In French] 2006; 35: (1, Part 1), 61–63.

33 Colpaert, K., Tromp, F., Vandecasteele. E. Iodine toxicity as a cause of total atrioventricular block in burn patients. Burns 2009; 35: S45–S6.

34 Ramaswamykanive, H., Nanavati, Z., Mackie, J. et al. Cardiovascular collapse following povidone-iodine wash. Anaesth Intensive Care 2011; 39: 1, 127–130.

35 3Waran K, Munsick R. Anaphylaxis from povidone-iodine. Lancet 1995; 345: 8963, 1506.

36 Wong, R.H.L., Wong, V.W.Y., Hung, E.C.W. et al. Topical application of povidone-iodine before wound closure is associated with significant increase in serum iodine level. Surgical Practice 2011; 15: 3, 79–82.

37 Horner, C., Mawer, D., Wilcox. M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? J Antimicrob Chemother 2012; 67: 11, 2547–2559.

38 MHRA. Medical Device Alert - All medical devices and medicinal products containing chlorhexidine. (2012) Ref: MDA/2012/075. Available at http://bit.ly/1R9Ykhd (accessed Feburay 2015).

39 Jull AB, Walker N, Deshpande S. Honey as a topical treatment for wounds. Cochrane Database Syst Rev 2013;2:CD005083.