THE WOUND INFECTION ISSUE

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A cause for celebration

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A (slightly belated) happy new year to all our visitors. It is already March and we have plenty to celebrate and shout about with 2013 promising to be a most fortunate year for wound healing.

It was with much joy that I learned that the work of Professor Keith Harding had been formally recognised in the UK with the Queen decorating him in her 2013 New Year’s Honours List with a CBE (Commander of the British Empire) for services to medicine and health care. A CBE is awarded to an individual for a number of reasons, one of which is for making a highly distinguished, innovative contribution in his or her area of expertise. For many of us who have witnessed Professor Harding in action, this award comes as no surprise. His enthusiasm, determination, and energy, as well as the profound wealth of his academic contributions, has helped raise the bar in the drive to get stakeholders to take wounds seriously.

There are many amazing initiatives that need to be accepted, shared, and celebrated to make sure that patients all over the world receive the best care and that efforts continue to create appropriate intervention and prevention strategies to reduce the complexity and duration of chronic wounds. Publicly recognising the importance of wound healing is vital for the wound care community as a whole and helps to promote the speciality at many levels, making the collaborative job of improving services easier for all.

In this issue of *Wounds International*, the focus is on wound infection. Authors from the USA, Spain, and the UK report on developments in wound infection and clarify what is, and what is not, known about the subject.

I am delighted that Greg Schultz and Randy Walcott (page 4) lead the Innovations Section of the journal. In their report, they raise hopes that new diagnostics in wound infection are on the way. The diagnostics they describe have great possibilities and will allow a more directed and targeted approach to managing wound infection. This will be well received as Sue Templeton (page 10) stresses that one of the most challenging day-to-day issues facing clinicians in Australia is making best use of topical antimicrobials, especially knowing which topical agent to use when, and for how long. Developments in the form of point-of-care tests will result in a huge improvement to the quality of care provided.

However, these resources are not yet widely available. For now, most clinicians will have to rely on more traditional methods of assessment and diagnosis. The Top Ten Tips in this issue (page 15) is on using silver in wound care. Zena Moore provides a succinct summary guiding clinicians on when and how to use silver dressings effectively.

It is interesting that the Wound Infection Institute has decided to update the TIME document on wound bed preparation (Leaper et al., 2012). The update addresses a number of developments and changes over the past decade in wound care. Most of these changes focus on wound infection (including the role of biofilms), the use of negative pressure wound therapy (NPWT), the use of topical antimicrobials, and advances in the understanding of molecular biological processes, particularly in relation to the use of specific diagnostic tools (see Jacqui Fletcher’s report on page 8). The collaborative work of the international wound care community is discussed in the *Wounds International* webcast TIME to Revisit Wound Bed Preparation [available here](#). More than 1500 of you watched this webcast live on 13 December 2012, with a further 3000 viewing the on-demand version since.

There is no doubt that managing wound infection is complex and places great demands on clinicians, patients, and healthcare resources. It is important to keep as up-to-date as possible, especially on developments that are likely to impact on everyday practice.

Suzie Calne
Editor, Wounds International

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**Wound infection and diagnostics in practice: what is emerging?**

Wound infection unquestionably impairs healing, but many chronic wounds do not have high levels of planktonic bacteria as measured by standard clinical microbiology laboratory culturing methods. Recent research (James et al, 2008; Phillips et al, 2010) suggests this “critical colonisation” state is due to the presence of polymicrobial biofilm communities that are highly tolerant of hosting antibiotics, inflammatory cells, antibiotics, and many antiseptics.

Polymerase chain reaction (PCR)-based identification of multiple bacterial species from wound biopsies appears to be a promising technology that overcomes most of the limitations of traditional bacterial-culturing methods. Methods of utilising improved profiling bacterial and fungal species present in wounds enables customised formulations of antibiotics and other agents that target a specific spectrum of organisms. Topical treatment with personalised antimicrobial formulations appears to substantially improve the healing of complex wounds (Dowd et al, 2011).

A rapid, point-of-care (POC) detector that assesses matrix metalloproteinase (MMP) activity identifies a subpopulation of chronic wounds (approximately 28%) that have a high probability (approximately 90%) of not healing. This could lead to targeted treatments with protease modulating therapies that may increase the chance of healing in those wounds (Serena et al, 2011). POC diagnostic platforms currently under development may be able to simultaneously measure levels of multiple biomarker proteins of impaired healing, as well as numerous bacterial and fungal species in wound fluid samples. The future of wound diagnostics, therefore, looks very promising indeed.

As summarised in the recent consensus document on wound infection in clinical practice (Harding et al, 2008), this area continues to be a hugely challenging one for clinicians and places a considerable burden on health services. The early recognition of a wound, along with prompt, appropriate, and effective intervention, is integral in reducing adverse economic and health consequences, especially in the context of growing levels of antibiotic resistance (Harding et al, 2008). Unfortunately, current standard clinical microbiology tests – which are based on the 100-year-old technique of growth of bacteria on nutrient agar plates – only provide a partial profile of the planktonic bacterial and fungal species present in wounds; essentially, those microorganisms adapted to grow rapidly under specific conditions in an incubator (Dowd et al, 2008). This leads, in most situations, to the identification of only a select few of the many planktonic bacteria present in a wound.

Clearly, there is a need for better diagnostic tests to identify and measure levels of bacteria and fungi in wounds. However, such a test (diagnostic) should meet several parameters. It should be cost-effective, at least in the range of the current standard clinical microbiology tests. Results should be generated in a few hours and provide information that can be used to guide clinical decision-making. In other words, just having more complete information about the bacteria and fungi species present in wound biopsies, curettes or swabs has minimal effect, unless there is a way to use that information to guide specific treatments for that patient, which is the aim underpinning the concept of personalised medicine.

Fortunately, molecular biology technologies have been developed that can replace the standard microbiology culturing technique. It quickly became evident in the 1990s that sequencing the 16S regions of bacteria and 18S region of fungi led to levels of sensitivity and specificity in identifying each microorganism present in a sample. Originally, the sequencing was accomplished using the pyrosequencing technique (Roche) because of its ability to produce long sequences of the 16S region, however, this technology was expensive. Important developments in bioinformatics and PCR techniques allowed for the accurate diagnosis and quantification of either a panel of key microbes (approximately 30) or identification of all the bacteria in a sample (Wolcott and Dowd, 2008).

Currently, it remains difficult to determine which of the bacterial or fungal constituents are implicated in the nonhealing of an individual wound. As PCR-based diagnostics become more established and larger databases are generated, it is highly likely that key patterns of bacteria will emerge that correlate with nonhealing. Also, the use of customised formulations of topical antibiotics and other agents will identify key treatable targets. Data from the co-author’s (RDW) laboratory show that utilising personalised antibiotic
gels prepared by a compounding pharmacy – containing multiple antibiotics targeting the 20–30 bacteria identified in a wound – collapsed the various populations to a level where two to three broad spectrum antibiotics could adequately manage the species present. Most importantly, healing rates of chronic wounds increased from 48% to 62%, following the implementation of molecular diagnostics and customised, targeted antibiotic regimens (Wolcott et al, 2010a).

In addition to the large number of different species of planktonic bacteria in chronic wounds, a high percentage of chronic wounds contain tightly attached polymicrobial biofilm communities that are not effectively cultured by the standard clinical microbiology assay techniques (James et al, 2008). Biofilms are known to cause chronic inflammation in several diseases, including periodontitis, osteomyelitis, cystic fibrosis, chronic otitis media, sinusitis, and Crohn’s disease. This is due, in large part, to the fact that many of the polysaccharides, bacterial DNA, and proteins comprising the biofilm matrix stimulate both the innate immune system (toll-like receptors) and the adaptive immune system (antibodies). This has led some to hypothesise (Phillips et al, 2010) that biofilms are a major contributor to the prolonged inflammation that characterises most chronic wounds and leads to the clinical condition described as “critical colonisation” or “localised infection” in the spectrum of wound bioburden levels.

There is no specific diagnostic test for biofilms in chronic wounds at present, but there is clearly a need for a rapid, POC detector for biofilm communities in wounds. In the absence of such tests for biofilms in chronic wounds, wound care clinicians have had to rely on information from laboratories about the effects of antibiotics and antiseptics on biofilms, and from the outcomes of clinical treatment of biofilms in other diseases.

Bacteria in polymicrobial biofilms are extremely tolerant to the patient’s own antibodies and phagocytic inflammatory cells, as well as oral antibiotics or topical antiseptics (Phillips et al, 2010). This is due to several factors: including reduced penetration of antibodies or antibiotics into the biofilm matrix; the reaction of antiseptic molecules with components of the biofilm matrix (the reaction-diffusion problem) (Stewart et al, 2001); and to the presence of quiescent persister bacteria that are not metabolically active in mature biofilm communities (Xu et al, 2000).
Given that essentially all antibiotics kill bacteria by interfering with some bacterial enzyme reaction, quiescent bacteria are not destroyed by the presence of antibiotics that are only able to kill bacteria when they are rapidly proliferating (metabolising). These challenges led to the concept of biofilm-based wound care (Wolcott and Rhoads, 2008).

The foundational principle of management of wound biofilm is debridement. Debridement contributes many positive aspects to the suppression of wound biofilms. First, there is physical disruption of the biofilm. It has been demonstrated that this forces the biofilm to reconstitute itself, which opens a time-sensitive window where the biofilm is more vulnerable to biocides and antibiotics. Thus, physically disrupting biofilm gives a 2- to 3-day period during which antimicrobials are more effective (Wolcott et al, 2010b). Second, combinations of agents in topical gels can attack multiple aspects of biofilms, such as inhibitors of quorum molecules that promote biofilm phenotypes in planktonic bacteria, and alcohol sugars, such as xylitol, that impair synthesis of the biofilm polysaccharides. Varying the composition of topical gels based on the bacterial species identified by DNA technologies should reduce the reformation of persistent biofilms.

An important molecular link between planktonic and biofilm bacteria that stimulate chronic inflammation is the elevated protease activities found in most chronic wound fluid and in dehisced acute wounds (Yager and Nwomeh, 1999; Ladwig et al, 2002; Utz et al, 2010; Gibson et al, 2010). This has led to the development of rapid, POC detectors for MMP activities in samples of wound fluids. Currently approved for use in most European countries, the WOUNDCHECK™ (Systagenix) diagnostic device detects the level of MMP activity in wound fluid samples. Current clinical results indicate that approximately 28% of nonhealing wounds have elevated protease activity levels and approximately 90% of those wounds will not heal without appropriate intervention, such as the use of a dressing that inhibits MMPs (Serena et al, 2011).

Other rapid, POC detector technologies are being developed. One of the most promising approaches appears to be in using modifications of surface plasmon resonance (SPR) technology to measure binding between two molecules (Lahav et al, 2004). SPR has several advantages as a diagnostic platform. It is a "label-free" detector system, which means that detection of a target molecule (biomarker) does not require a second labelled molecule (which is always needed in other detector systems, such as a lateral flow strip or an enzyme-linked immunosorbent assay). Also, multiple biomarker proteins can, in theory, be simultaneously measured in a sample using an SPR "chip" that contains multiple separate fields, each conjugated with an antibody to a different biomarker protein.

SPR signals can be generated in less than 10 minutes and detected using a simple illumination source and a spectrometer. Laboratory detection of bacterial species by SPR has been reported (Mazumdar et al, 2007; Baccar et al, 2010). Although much more research and development is required to produce a usable rapid, POC SPR detector for wound biomarkers and bacteria. Advances in SPR surface nanostructures and other components are currently occurring (Chung et al, 2010). The field of wound care may be entering a new phase of diagnostics for wound infection and biomarkers.

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For further reading, click here... The Role of Proteases in Wound Diagnostics
MMPs Made Easy
Hosted by Christine Moffatt, this guest lecture covered:

- Why is wellbeing important?
- What is wellbeing in relation to wound management?
- Can wellbeing be measured?
- What is the role of clinicians, patients, healthcare organisations and industry in optimising wellbeing?

This lecture coincides with the launch of a new consensus on patient wellbeing. Trudie Young, Lecturer in Tissue Viability at Bangor University, Wales, and chair of the working group said: “This document provides a practical framework for clinicians, patients, organisations and industry to understand and promote wellbeing as a fundamental aspect of good wound care. We think it can really make a difference.”

Download the document at: www.woundsinternational.com
TIME for an update? Potential changes to wound assessment

The concept of TIME has been discussed for 10 years and is widely accepted in clinical practice. However, since it was originally proposed in 2003, much has changed in both the fields of research and clinical practice. Therefore, it was felt necessary by the International Wound Infection Institute to provide an update to the TIME framework (Schultz et al, 2004).

A review was carried out of each of the core concepts: tissue (nonviable); infection/inflammation; moisture balance; and edge/epithelial advancement, to determine whether any significant changes had occurred since the original publication. Where differences were identified, they were investigated and the findings included in the updated version of the framework (Leaper et al, 2012).

The most important differences are in four key areas:

- The role of biofilms
- The use of negative pressure wound therapy (NPWT)
- The use of topical antimicrobials
- The increased understanding of molecular biological processes, particularly in relation to the use of specific diagnostic tools.

The management of infection and biofilms—an area where it was evident that a considerable amount of literature had been published over the past 10 years—has undergone major changes. Central to this was the suggestion that biofilm management may be crucial in wound healing, particularly in chronic wounds.

Attention to biofilm management heralds a step change in what has been considered the norm in wound care for the past 30 years. Whereas care used to be taken by clinicians not to disturb the wound bed and fragile new cells, how biofilm management advocates regular and aggressive debridement, and the more frequent use of topical antimicrobials. This fits with the current ethos seen in many areas of wound management and health care in general, where the focus has shifted to preventative action.

The review identified a range of ways of carrying out debridement, including the use of hydrotherapy, but also more familiar options, such as debridement pads. It also advocates the use of a range of antimicrobials, including silver and iodine, and some less well known, such as polyhexamethylene biguanide. Certain new products combine debridement and antimicrobial activities by including a surfactant in the liquid, which helps disperse and loosen debris (e.g. Prontosan®; B. Braun; octenilin®; schülke).

The role of NPWT in the treatment of highly exuding wounds has increased significantly during the period in question. Enhanced understanding of the biological components of wound exudate has highlighted the importance of removing exudate as quickly as possible and thus controlling bioburden at the wound surface and removing corrosive matrix metalloproteinases (MMPs), which may perpetuate the inflammatory process and delay healing.

The range of wounds in which NPWT is being used has increased exponentially as clinicians continue to gain confidence with this modality. As greater understanding is achieved, more clinical scenarios are tested. Recently, this has included the prophylactic use of NPWT in post-operative wounds to splint the suture line and reduce the frequency of post-surgical wound breakdown.

The most recent development to be included (Leaper et al, 2012) is the use of point-of-care diagnostics, which allow clinicians to target and individualise treatment by identifying factors such as elevated levels of MMPs. This encourages the cost-effective use of more expensive products.

The original TIME framework (Leaper et al, 2012) is firmly focused on assessment; the identification of what is preventing wound healing. The second TIME model introduces a new concept: consideration of the importance of controlled and systematic wound management that identifies the correct treatment, ensures consistent implementation of that treatment, which is regularly monitored, and then evaluated against the treatment goal.

This TIME update should be of interest to all clinicians involved in wound management. For those undertaking wound management on a daily basis, it provides a clear and precise summary of new assessment and treatment modalities. For those organising services, it identifies how wound care can be undertaken in a cost-effective manner.

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60% of chronic wounds contain a biofilm,¹ which could delay healing. IODOSORB’s unique 4 in 1 action has been shown to disrupt and substantially eradicate mature biofilms of P. aeruginosa (in-vitro).²,³ IODOSORB has also been shown to accelerate wound healing in randomised controlled trials.⁴-⁹

Unlike the biofilm, the results are clear to see.

References
Wounds Infection. Those two words have been the source of much debate in recent years. Like many other countries, Australia has been swept up in the tide of products and strategies to minimise the burden of this ever-present scourge. The more cynical side of me sometimes wonders how any wound in the past ever healed without the vast armamentarium of resources available to manage modern wound infection! The past couple of years have been particularly interesting, as the phenomenon of silver has been tempered somewhat and management of wound infection has become more broadly focused.

PATIENT-RELATED ISSUES
In many areas of Australia, prevention and treatment of wound infection has become increasingly holistic. In the surgical area, risk minimisation strategies are being implemented to identify and manage patients at risk of wound infection. Negative pressure wound therapy (NPWT) is being used post-operatively by some clinicians on high-risk surgical incisions – although this is still relatively isolated.

There is an increasing focus on identifying and managing wound pathology. Australia has recently published evidence-based guidelines for venous leg ulcer management (Australian Wound Management Association, 2011) and diabetic foot ulcers (National Health and Medical Research Council [NHMRC], 2011), both of which were endorsed by Australia’s leading research body, the NHMRC. As wound pathologies are diagnosed more often and managed by appropriately skilled clinicians, the detrimental consequences of wound infection are reduced.

CLINICIAN-RELATED ISSUES
There has been significant growth in the number of wound management nurses in recent years. In Australia, “nurse practitioner” is a legally protected title that can only be used by registered nurses who have been endorsed by our authorised regulatory body (the Nursing and Midwifery Board of Australia) as meeting the required professional and educational standards. Wound management nurse practitioners have considerable local influence in areas of practice, policy, and standards. In the management of wound infection, wound management nurse practitioners work within the multidisciplinary team to ensure wound infection risk is minimised, and when infection occurs, that appropriate, evidence-based strategies are implemented to optimise outcomes.

WOUND MANAGEMENT: DEBRIDEMENT
The role of wound debridement in managing wound infection has led to significant changes in practice. When I began my career in wound management, debridement meant applying wet gauze, waiting for it to dry out, and literally ripping it off. Today, I consider this to be a form of legalised torture!

While it saddens me to acknowledge that there are some clinicians who still use this as their primary method of wound debridement, I am pleased to report that the vast majority have adopted alternative methods. Autolytic and sharp debridement remain the mainstay of wound debridement in Australia. However, sharp debridement is under-utilised, as many clinicians remain fearful of it and view it as a high-risk intervention.

Performing sharp debridement is not specifically regulated under the Health Practitioner Regulation National Law Act in Australia, but the clinician must possess the requisite skills to perform it. Serial sharp debridement is often difficult to achieve, particularly in out-patient settings. Sometimes, it is challenging to even get the average clinician to perform adequate wound cleansing and use mechanical debridement – such as scraping off loose nonviable tissue and debris.

The use of hydrosurgery and/or ultrasonic wound debridement has been incorporated into several specialist wound clinics. While these techniques are providing excellent outcomes, the considerable costs associated with them is limiting their availability and use. I am not aware of any community-based services offering these techniques and as a community-based practitioner myself, I am envious of my colleagues who have access to these resources.

Another wound debridement strategy enjoying increased resurgence is the use of maggots. Australia has one controlled maggot farm, located in Westmead Hospital, New South Wales. From here, medical-grade maggots are supplied to all Australian states and territories, and other countries in the Pacific (Geary et al, 2009).
Unfortunately, in many instances, maggot debridement therapy is only used as a last resort and not until all other options have been exhausted. Despite this, several wound care clinics are reporting success in reducing amputation rates through the use of maggot debridement therapy (Geary et al, 2009).

**WOUND MANAGEMENT: DRESSINGS AND THERAPIES**

It was not long ago that almost every patient had a silver-containing dressing applied to their wound, irrespective of wound pathology or clinical appearance. Similarly, some clinics embraced cadexomer iodine with similar fervour. Any foot wound was plastered with cadexomer iodine, whether there was an adequate amount of exudate to activate the product or not.

Use of these products was often continued for extended periods and clinicians were fearful of ceasing their use in case infection developed. The market became flooded with silver wound care products and many service providers became concerned by the costs. However, in some areas of Australia, where community patients have to pay for their own wound care products, usage of silver-containing products in out-patient settings was very limited.

I am pleased to report that use of antimicrobial products has become less a standard treatment and more a specialised strategy, reserved for wounds at very high risk of infection or exhibiting clinical signs of infection. However, products containing silver are still widely used in Australia. Many healthcare providers have introduced criteria for their use, restricting their use to locally authorised clinicians who regularly review their ongoing use. This has helped promote a more judicious use of silver-containing dressings in many areas.

Generally, Australia has not felt the same pressure that the NHS in the UK experienced following the release of the VULCAN Trial (Michaels et al, 2009) and has not had to broadly defend the continued use of, and access to, silver-containing dressings (Leaper and Drake, 2011). Despite this, there is still work to be done in some areas to establish more comprehensive patient and wound assessment, rather than treating all chronic wounds with silver-containing dressings. As most readers would acknowledge, silver-containing dressings are an adjunct to wound management, not the answer.

The range of antimicrobial products used to manage wound infection has also broadened, with honey and polyhexamethylene biguanide (PHMB) being increasingly used to manage wound infection. Products containing PHMB have become incorporated into the routine management of chronic wounds in a range of settings for its ability to assist in the disruption of wound biofilms. The integration of honey into different delivery systems, and the availability of several honey wound management products as registered medical devices in Australia (Molan, 2011), has resulted in increased use in clinical practice (Freeman et al, 2010).

**CONCLUSION**

Developments in recent years have seen an increasing range of strategies to both reduce the risk of infection and better manage infection if it develops in wounds. Clinicians have never had a wider range of products and strategies available to them. Australia, like most countries, faces increasing stress on health budgets, so the challenge for the future is to ensure that wound care can be both cost-effective and improve patient outcomes.

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**References**


The need for topical antimicrobials in the treatment of wounds is self-evident. Acute injuries will often be contaminated by the surroundings where the injury occurred and the risk of subsequent infection developing in these wounds is high, while chronic wounds will be contaminated, colonised, critically colonised, or infected due simply to their chronicity, and so requires local management of bioburden.

Antibiotics selectively target micro-organisms and, in general, should not be used topically, due to the risk of inducing resistant strains. On the other hand, antiseptics are nonselective and may damage all cells they come into contact with.

In recent decades, the topical antiseptics iodine and silver have been widely used in wound care, but – given the relative novelty and wide variety of products containing these agents – selecting the most appropriate topical antimicrobial and the most appropriate formulation for a specific wound can be challenging (Sibbald et al, 2011; MacGregor, 2012). In this review, innovations in topical antimicrobials will be discussed with special attention to Prontosan® (B. Braun), Flaminal® (Crawford Healthcare), and Cutimed® Sorbact® (BSN Medical).

NEW TOPICAL ANTISEP TICS

Prontosan

Prontosan is an irrigant containing polyhexamethylene biguanide (PHMB; an antimicrobial) and undecylenamidopropyl betaine (a surfactant). It is available as a solution and a gel.

PHMB is a polymeric cationic agent that was recognised as having superior antimicrobial properties to other cationic biocides, but could only be poorly defined chemically. Early attempts to rationalise PHMB mixtures were unsuccessful and precluded their use in pharmaceutical products. While it shares many attributes with the simpler cationic agents, it has additional mechanisms of action that render it unique among this class of antimicrobials (Arch Chemicals, 2008). Nevertheless, PHMB was marketed as a broad-spectrum antimicrobial agent in a number of diverse applications and has been available in consumer applications for more than 40 years (Horrocks, 2006; Kaehn and Eberlein, 2009).

As with the bisbiguanides, PHMB was shown to rapidly bind to the envelope of both Gram-positive and -negative bacteria and so displace the otherwise stabilising presence of Ca²⁺ (Messick et al, 1999). PHMB binds to the cytoplasmic membrane itself, as well as to the lipopolysaccharide and peptidoglycan components of the cell wall (Kaehn, 2009).

The toxicity profile of both the biguanides and polymeric biguanides is excellent; neither molecule is a primary skin irritant, nor a hypersensitising agent (Gilbert et al, 1990). With respect to the deployment of PHMB as part of a wound care system, there is little or no evidence to suggest that this would lead to the emergence of PHMB-resistant strains.

The other key ingredient of Prontosan is undecylenamidopropyl betaine, which is a mild, active surfactant with dual water and oil solubility. It is a highly pure betaine based on undecylenic acid, developed for the specific demands of the wound care industry. This betaine is used to reduce surface tension and allow wound contaminants to lift (Burnett et al, 2012).

A number of case studies in which Prontosan has been used to manage a range of wound types is available online (Andriessen and Eberlein, 2008). A case study booklet comprising 29 cases is also available (B. Braun, 2010).

Flaminal

Flaminal is available in two hydrogel formulations with a high alginate content, which are indicated for the reduction of bacterial growth in wounds. Flaminal hydrogels are based on alginate gel, not on other polymers, and use the enzymes glucose oxidase and lactoperoxidase to control bioburden in a similar way to honey (van den Plas et al, 2006; White, 2006).

Flaminal contains lactoperoxidase, an enzyme derived from milk, and acts as an important natural antimicrobial. It has been shown to be bacteriostatic against Gram-positive organisms and exhibits pH-dependent bactericidal action against Gram-negative organisms in the presence of hydrogen peroxide and thiocyanate. Peroxidases are enzymes that belong to the natural, non-immune defence systems found in milk and in the secretions of exocrine glands, such as saliva, tears, intestinal secretions, cervical mucus, and the thyroid (Thomas and Hay, 1996; White, 2006). The combination of glucose oxidase with lactoperoxidase serves to provide a sustained source of safe and effective broad-spectrum antimicrobial protection in a manner similar to the human body’s own natural white cell defences (Vandenbulcke et al, 2006).
Flen Pharma introduces a new class in wound healing: Enzyme Alginogels®. Enzyme Alginogels® can be applied to any type of chronic or acute wounds at any stage, whether they are contaminated or infected. Enzyme Alginogels® provide simply better wound care.

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Clinical innovations

From the available laboratory and clinical evidence, it is clear that Flaminal products are safe and effective, both clinically and microbiologically, although some studies have shown methicillin-resistant Staphylococcus aureus is not always eradicated (de la Brassinne et al, 2006). However, there is currently little published evidence in support of Flaminal products (Lacarrubba et al, 2005; Kyripoulos et al, 2010; Durante, 2012).

Sorbact

Sorbact is a non-allergic, non-toxic hydrophobic fibre dressing made of acetate or cotton fabric impregnated with a fatty acid ester that makes it strongly hydrophobic (Ljungh et al, 2006). It is available in ribbons, foams, absorbent dressings, and gels. The green Sorbact surface binds with, and deactivates, pathogenic microorganisms, and, as such, is recommended for use in colonised and infected wounds, as well as for fungal skin infections (Ljungh et al, 2006).

Sorbact is indicated for the treatment of colonised and infection wounds as well as fungal infection (Wadström et al, 1985; Johansson et al, 2009; Powell, 2009; Derbyshire, 2010; Skinner and Hampton, 2010; Lee et al, 2011). As with Flaminal, there is currently limited published evidence in support of this product.

CONCLUSION

Despite topical antiseptics being used in a wide range of clinical situations, evidence supporting their efficacy in the treatment of wound infection is more limited. For newer products, it is important that clinical research be undertaken and published to validate their efficacy in wound management. The problem arises in that bacteria not only develop resistance to certain antimicrobials, but also produce biofilms to prevent their destruction. It is important that new agents continue to be developed that have the ability to penetrate biofilm and, in doing so, lessen the burden of wound infection and improve outcomes.

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How does silver work?
Silver can be placed into three categories: inorganic, nanoparticles, or nanocrystalline. When exposed to wound fluid or moisture, silver is released in its ionic form (Ag+) (Canadian Agency for Drugs and Technologies in Health, 2010).

Silver ions are highly reactive and affect multiple sites within bacterial cells, ultimately causing cell death. They bind to bacterial cell membranes, causing disruption of the bacterial cell wall and cell leakage. Silver ions transported into the cell disrupt cell function by binding to proteins and interfering with energy production, enzyme function, and cell replication. Silver ions are active against a broad range of bacteria, fungi, and viruses, including many antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* (International Consensus Group, 2012).

Types of silver dressing
A variety of silver dressings are available, including foams, hydrogels, alginates, hydrofiber, hydrocolloids, and polymeric films (Toy and Macera, 2011). These may be classed into four types: nanocrystalline silver dressings that release silver into the wound; dressings that release a silver compound, rather than silver ions; dressings that absorb wound fluid and bacteria into the dressing, where antibacterial action takes place; and dressings that release silver, while simultaneously absorbing wound fluid and bacteria (Drug Therapy Bulletin, 2010).

From a clinical perspective, having confidence in a product’s ability to provide a sustained release of silver, at a therapeutic level, is integral (Parsons et al, 2005). However, it is accepted that not all products are the same, in terms of their composition and silver content. Furthermore, a greater amount of silver released by a dressing does not necessarily result in an enhanced antimicrobial activity (Parsons et al, 2005). This should be borne in mind by clinicians.
when selecting the most appropriate product for use.

1. **Adopt a systematic approach to the assessment of the individual with a wound:** Accurate and ongoing patient and wound assessment is essential to correctly identify the underlying aetiology of the wound and the potentially compounding patient factors that may delay healing (McCluskey and McCarthy, 2012). Once this is established, the plan of care may be developed, implemented, and subsequently evaluated. Use of a specific wound assessment model, such as TIME, is of value as it provides guidance on the specific areas to assess prior to planning a relevant management strategy (Dowsett and Newton, 2005). TIME addresses four components, namely: tissue management, infection/inflammation control, moisture balance, and edge of the wound advancement (Dowsett and Newton, 2005).

2. **Determine the need for a silver dressing:** Once an assessment has taken place, the need to use a silver dressing should be established. Silver dressings are specifically favoured to reduce bioburden in wounds that are infected or are being prevented from healing by microorganisms (International Consensus Group, 2012). They also act as an antimicrobial barrier for wounds at risk of infection or re-infection (International Consensus Group, 2012). Thus, when management of bioburden has been determined as the short-term goal of care, the use of a silver dressing may be appropriate.

3. **Familiarise yourself with the manufacturer’s instructions for use of the silver dressing:** Competency in the selection and use of silver products is essential to ensuring safe use (McCluskey and McCarthy, 2012). Indeed, the EU Commission (2012) warns that compromising patient safety is costly, with between 13% and 16% of all hospital costs being attributable to healthcare-related injuries and ill health.

Not all silver dressings are the same, even though they may display similar physical characteristics, thus it is important to adhere to the manufacturer’s instructions for how to use specific silver dressings (Parsons et al, 2005). These instructions will outline the indications and contraindications for the dressing, including specific guidance on how to use the product.

4. **Select a silver dressing to suit the size and shape of the wound:** It is essential that the dressing comes in contact with the entire wound surface to ensure that all aspects of the wound are exposed to the silver. Indeed, Bowler et al (2010) demonstrated in vitro that lack of conformability of the dressing results in reduced antimicrobial activity. Their study concluded that conformability and silver availability at the wound surface are crucial in maximising the functionality of the dressing.

It is relatively easy to apply dressings to wounds with a uniform shape; however, this task becomes more challenging in wounds that are deep or of irregular shape. The conformability of a silver dressing is, therefore, of importance for all wounds, including those with cavities or irregular contours (Bowler et al, 2010).

5. **Select a silver dressing that has appropriate fluid-handling properties:** It is common in wounds with bioburden to produce substantial amounts of wound fluid. Indeed, Cutting et al (2005) linked an increase in exudate with infection in a variety of wound types. The ability of the dressing to ensure that fluid is not left within pockets of the wound is important, as this increases the risk of further infection (Jones et al, 2004). Thus, the silver dressing selected must also have the ability to manage the specific level of exudate of the wound at hand to ensure moisture balance at the wound–dressing interface (Bowler et al, 2011).

Furthermore, good management of exudate is linked to patient comfort, which is a key consideration in wound management (Gorecki et al, 2009).

6. **Select a silver dressing that is appropriate for the wound tissue type:** In addition to dealing with bioburden, there may be other objectives of wound management that need to be considered. Once again, referring to the TIME model, tissue management is important (Dowsett and Newton, 2005). The presence of nonviable tissue in the wound bed is a focus for infection and also delays wound healing (Dowsett and Newton, 2005).

If surgical debridement is not an option, dressings that facilitate autolysis (the body’s own ability to eliminate the dead tissue) should be considered. This is achieved by ensuring that a moist wound–dressing interface is maintained (Thomas, 1997). Thus, when infection and tissue management are

### References


Canadian Agency for Drugs and Technologies in Health (2010) *Silver Dressings For The Treatment of Patients With Infected Wounds: A Review of Clinical And Cost-Effectiveness.* CADTH, Toronto, Ontario


Askina® Calgitrol® Paste

A soft paste wound dressing containing 100% ionic silver:
More intimate contact between the wound and active antimicrobial silver ions, particularly valuable in difficult to manage wounds.

- Easy to apply on deep wounds and sinuses
- No activation needed
- Sustained controlled delivery of silver ions
- Antimicrobial efficacy against a broad spectrum of microorganisms, including MRSA
- Safe for use
- Non staining
the goals, the choice of silver dressing should facilitate this combined approach.

7 Select a silver dressing that matches the frequency of dressing change: For many people with wounds, daily dressing changes are not possible. Furthermore, such an approach often increases the discomfort of the patient and adds to the healthcare expenditure. Nonetheless, Bowler et al. (2010) note the importance of continued antimicrobial activity of the dressing in order to ensure maximum control of bioburden. Thus, the sustained release of silver at therapeutic levels is necessary for the dressing to be effective (Leaper, 2006). When choosing a silver dressing, consideration should be given to the dressing change frequency and ability to achieve a sustained release of silver during use. This information will be available in the manufacturer’s instructions for use of the specific dressing.

8 Consider patient-related factors in the choice of silver dressing: As with all treatment modalities, placing the patient at the centre of decision making is fundamental. Pain is often under-recognised by clinicians, yet is of major concern to the patient (Briggs and Closs, 2006). Walker et al. (2011) found that pain and infection management are the most challenging for patients and clinicians alike. Therefore, it is important to consider specific factors, such as ease of application and removal, contribution to the pain experience, and overall acceptability to the patient, when choosing a silver dressing.

9 Know how long to use the silver dressing for: It has been recommended that antimicrobial dressings should be used for 2 weeks initially – seen as a 2-week “challenge” period – during which the efficacy of the silver dressing can be assessed (International Consensus Group, 2012). If, after 2 weeks, there is improvement in the wound, but there are continuing signs of infection, it may be clinically justifiable to continue use of the silver dressing with further regular reviews (International Consensus Group, 2012). If the signs and symptoms of wound infection are no longer present, the silver dressing should be discontinued (International Consensus Group, 2012). If there is no improvement, the silver dressing should be discontinued and the treatment regimen reassessed (International Consensus Group, 2012). Once the bioburden is under control and the wound is improving, a traditional dressing should be used (International Consensus Group, 2012).

10 Re-evaluate the patient and the wound to ensure that treatment goals remain consistent: As with all wound management strategies, it is important to regularly re-evaluate the patient and wound to determine the requirement for continuing with the current treatment plan (Gray et al., 2010). The TIME model is valuable at this juncture as it facilitates an assessment of whether there is improvement, or otherwise, in the wound (Dowsett and Newton, 2005). In order to provide a justification for decision making, use of a systematic approach to assessment and re-evaluation is essential. Thus, assessment planning, implementation, and evaluation is a cyclical process that should continue throughout the patient’s care (Gray et al., 2010).

CONCLUSION
Silver dressings play an integral role in the management of wound bioburden. A variety of silver dressings are currently available, thus it is important that clinicians using these products are aware of their indications and contraindications. A systematic assessment of the individual and their wound is central in the selection of an effective treatment strategy, including dressings.

The patient should be at the centre of care, and consideration of the impact of the wound and the chosen treatment strategies is closely aligned to quality of care. Not all silver products are the same, thus, having a clear understanding of the properties of the dressing and matching them to the needs of the wound and the patient is central to achieving success. Ongoing assessment and re-evaluation will provide guidance on the need to continue, alter, or discontinue the use of a silver dressing, thereby providing a clear rationale for treatment choices.

References
This issue features Carmen Alba who is Nurse Manager, Functional Unit of Wounds, Hospital Clínico Universitario, Valencia, Spain.

Can you outline where you practise?
I work at the Hospital Clínico Universitario in Valencia, Spain, which is the referral hospital for the Health Department of Valencia-Clínico-Malvarrosa, treating a population of more than 334 000 citizens, divided into 16 primary healthcare (PHC) areas. Our wound care unit is a recently established nurse-based unit. I coordinate patients with complex wounds.

Consultations come from the different departments in the hospital, along with referrals from within any of the centres in the 16 PHC areas. My job involves evaluating patients and putting in place protocols for specific wound care, and, where necessary, contacting the different specialists at the hospital, acting as a liaison between the PHC areas and specialised care.

What is the make-up of your team?
Currently, I am the only nurse and have one assistant nurse and one administrative assistant. Our work is carried out in conjunction with other specialists, mainly the vascular surgery department, internal medicine department, infectious diseases unit, as well as endocrinology, traumatology, plastic surgery and dermatology departments, and with the clinicians at the PHC centres.

What types of wounds do you regularly see?
We treat all kind of wounds with diverse aetiologies at our clinic. The vast majority of them have a vascular origin (ischaemic, venous, and neuroischaemic ulcers), neuropathic or post-surgical coming from a variety of specialities, including paediatrics and, on occasion, oncological.

What are the main types of equipment, dressings, and techniques that you use on a day-to-day basis?
We believe that success in the cicatrisation process comes from the early diagnosis of infection and trying to characterise it using biopsy cultures, quantitative cultures, or comprehensive blood tests. Our target is to reach an aetiological diagnosis, at the same time trying to avoid invasive techniques. If other diagnostic procedures are required, such as MRI, ultrasound, or angiography, we cooperate with the relevant departments.

In cases of venolymphatic pathology, it is mandatory to treat oedema immediately to speed up the healing process. All processes involving decongestion are made with low elasticity bandages during the initial stages of treatment and later we provide patients with high compression socks. If the patient is older and unable to put on the compression socks by themselves, we switch to double layer socks, which combine the different levels of pressure available (8, 19, 21 mmHg, for instance) and/or round or flat knitted garments.

We are well stocked in terms of therapeutical material in moist wound care and we can provide negative pressure therapy if needed, as well as cadexomer iodine, protease modulators, collagen dressings with gentamicyn or ionic (colloidal) silver.

What is the most unusual wound you have seen recently and how did you manage it?
It was not so much the rarity as the complexity in the case that comes to mind. It related to a 70-year-old person with diabetes, hypertension and lymphomatoid papilloma that had been operated on some 4 years ago in the thigh. The patient’s ankle brachial index (ABI) was 1.3. At first consultation, two lesions were discovered, both having been present for 1 year. The lesions affected two-thirds of the patient’s left leg, one on the calf (30 × 10 cm) and the other on the ankle (7 × 7 cm). The pain experienced by the patient was recorded at 6–8 on a visual analogue scale.

There were clinical signs of infection by methicillin resistant Staphylococcus aureus, but the antibiotic therapy was empirical at that time. We then adapted the antibiotic regimen based on the results of antibiogram of the biopsy culture. The wound had irregular edges, with some granulation tissue, but other necrotic areas, slough, and some residual lymphorrhagia. The periumler area had been damaged by the exudate, with erythema, and other lesions with haematoma aspect covered almost the rest of the leg. The abundant exudate had a fetid odour, resulting in the patient’s family having to change dressings often.

Symptoms of the wounds were controlled through coordination with the input of an oncologist, who was responsible for drug prescription, adjustment of chemotherapy levels, and controlling protein supply. A weekly evaluation of the patient was also conducted by a PHC-based nurse. Wound care consisted of cleaning the wound with a chlorhexidine sponge, while periumler protection was provided using zinc foam. Activated carbon/coal dressings with silver, alginates, and absorbent dressings were all used.

The patient’s ankle wound healed completely, while the calf wound reduced in size by 60%, with all satellite lesions healing fully. I believe that the low elasticity bandages were instrumental in the healing process and oedema control in this case.

Do you feel your service/practice has any unique obstacles that hamper your work?
The workload is too much for one person alone. It would be wonderful to have more people, but this is just how it is right now.

What equipment/resource/education would make the most difference to your everyday work?
I would really like to implement the use of autologous growth factors in complex wound care. I would also like to be able to work with the rehabilitation department to deliver lymphatic drainage therapy or ultrasound therapy to fragment proteins, thus enhancing lymphatic transportation. This is my dream.
Honey is a topical antimicrobial agent that has been used for millennia in wound care. Licensed wound care products containing medical-grade honey first became available in 1999 and are now widely used. Honey’s therapeutic properties are largely attributed to its antimicrobial and anti-inflammatory activities. This review provides an insight into the laboratory evidence published in the past 5 years that illustrate how the mechanisms by which honey impacts on wounds are beginning to be understood.

Although honey has been used for centuries in wound care, it is now being integrated into modern medical practice. The first modern wound care product to gain regulatory acceptance by the Australian Therapeutic Goods Administration was an irradiated tube of blended honeys. Currently, a range of products are available from several manufacturers (Table 1) and honey is being used to treat many types of wound, including: traumatic wounds, surgical incision sites, burns, sloughy wounds, and pressure ulcers.

The number of publications reporting the use of honey has increased, yet systematic reviews have been critical of the design of some of those studies (Moore et al, 2001; Bardy et al, 2008; Jull et al, 2008). Moore et al (2001) concluded that clinical evidence to support the use of honey in the treatment of superficial wounds and burns was of low quality. By contrast, a review of 19 randomised controlled trials (RCTs) with a total of 2554 participants suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings (Jull et al, 2008). Moore et al (2001) concluded that clinical evidence to support the use of honey in the treatment of superficial wounds and burns was of low quality.

By contrast, a review of 19 randomised controlled trials (RCTs) with a total of 2554 participants suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings (Jull et al, 2008). This was supported by a meta-analysis of systematic reviews of topical and systemic antimicrobial interventions for wounds. A total of 44 Cochrane reviews out of 149, which had been graded into five categories based on their size, homogeneity, and the effect size of outcome, were selected. Of 109 evidence-based conclusions, robust evidence was found to support the use of topical honey to reduce healing times in burns (Bröllmann et al, 2012).

Another recent review (Molan, 2011) of 33 RCTs noted that participants using honey had increased from 1965 in 2006 to 3556 in 2011, with a broadening in the range of wound types included, the choice of dressings available to clinicians, and the types of honey employed. With such variations, it is difficult to make generalised deductions about clinical efficacy.

Characterisation of the various bioactivities of honey is required if sound comparisons between products are to be made. To date, no RCT has randomised similar wounds to receive different types of honey to assess their relative efficacy.

**THERAPEUTIC PROPERTIES OF HONEY**

Much has been written about the bioactivities of honey (Molan, 1999; 2011), which can best be summarised thus: antimicrobial activity, deodorising action, debriding action and osmotic effect, anti-inflammatory activity, antioxidant activity, and enhanced rate of healing. Essentially, honey can be regarded as an antimicrobial agent with the ability to promote wound healing.

In chemical terms, honey is a complex substance whose antimicrobial components have been well established (Molan, 1992). However, all honeys are not equal (Allen et al, 1991; Cooper and Jenkins, 2009; Kwakman et al, 2011) and new bioactive components are still being discovered.

Methylglyoxal was shown to contribute to the antibacterial activity of manuka honey (Adams et al, 2008; Mavric et al, 2008), as well as leptosin (Kato et al, 2012). An antimicrobial...
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“In 2009, a study into the effects of honey on planktonic and biofilm-embedded bacteria suggested that honey has a bactericidal effect against the wound pathogens grown in the laboratory as biofilms.”

Inhibition of planktonic bacteria

Honey has a broad spectrum of activity against bacteria and fungi (Molan, 1992; Blair and Carter, 2005). A variety of bacteria capable of causing wound infection have now been tested under laboratory conditions for their susceptibility to honey.

Gram-positive bacteria are often involved in wound infection. *Staphylococcus aureus* – the most common cause of wound infection – has been shown to be inhibited by relatively low concentrations of honey (Cooper et al, 2002; Blair et al, 2009; Henriques et al, 2010), as have antibiotic resistant strains, such as methicillin-resistant *S. aureus* (MRSA), vancomycin-sensitive and vancomycin-resistant Enterococci (VSE and VRE, respectively) (Cooper et al, 2002; George and Cutting, 2007; Sherlock et al, 2010; Jenkins, et al, 2011), and coagulase negative *Staphylococci* (French et al, 2005). A recent study showed that the growth of 15 cultures of *Streptococcus* species isolated from wounds were inhibited by honey (Cooper et al, 2011a).

Of Gram-negative bacteria commonly implicated in wound infection, *Pseudomonas aeruginosa* (Cooper et al, 2002; Blair et al, 2009; Sherlock et al, 2010), enteric bacteria (Lin et al, 2011), *Stenotrophomonas* species (Majtan et al, 2011), and *Acinetobacter baumannii* (George and Cutting, 2007; Blair et al, 2009) have been shown to be susceptible to honey.

Many honeys generate hydrogen peroxide on dilution (Allen et al, 1991), but manuka honey does not produce detectable levels and, as such, has been called a non-peroxide honey (Kwakman et al, 2011).

In recent years, laboratory studies have been designed to investigate the mode of action of manuka honey at cellular and molecular levels, and have demonstrated that cell division in *S. aureus* (Henriques et al, 2010) and in MRSA (Jenkins et al, 2011) is interrupted by exposure to honey. Cells exposed to manuka honey accumulated at the end of the cell cycle with fully formed cross walls, but did not separate into daughter cells. Without completing cell division, bacteria cannot establish a colony. Multiple changes in cellular proteins have also been observed in *S. aureus* exposed to manuka honey (Packer et al, 2012).

Analysis of changes in *Escherichia coli* following exposure to manuka honey demonstrated multiple effects on the expression of genes (Blair et al, 2009). In *P aeruginosa*, manuka honey caused changes in the bacterial cell wall that led to instabilities, resulting in cell lysis (Henriques et al, 2011; Roberts et al, 2012). Hence, manuka honey has been shown to induce distinct cellular effects in Gram-positive bacteria, compared with Gram negatives.

Buckwheat honey has been shown to inhibit MRSA, VRE, *E. coli* and *Bacillus subtilis* by extensive degradation of DNA elicited by the generation of hydrogen peroxide on exposure (Brudzynski et al, 2012).

Patients with infected or highly exuding wounds may experience wound malodour. Honey has been shown to have a deodorising effect in patients with malodorous wounds, which is probably due to the inhibition of bacteria. This trait is most notable within 24 hours of the application of honey to the wounds (Molan and Betts, 2004; Gethin et al, 2008; Segovia, 2010).

Table 1: Honey dressing modalities (from Hewish [2012], with permission).

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honey gel or ointment</td>
<td>Packaged in tubes and useful for sinus or cavity wounds with low exudate levels. Generally, more effective in wounds with low exudate levels.</td>
</tr>
<tr>
<td>Honey-impregnated tulle</td>
<td>A synthetic, fine-weave, non-adherent dressing; low absorbency, for use on superficial wounds with low to moderate exudate levels.</td>
</tr>
<tr>
<td>Honey gel sheet</td>
<td>Consists of a mix of honey and sodium alginate; conforms well to uneven wound surfaces and cavity wounds; generally effective at managing low-exudating wounds.</td>
</tr>
<tr>
<td>Honey-impregnated calcium alginate</td>
<td>Alginate dressing impregnated with honey; useful for cavity wounds with moderate- to high-exudate levels.</td>
</tr>
</tbody>
</table>

Inhibition of biofilms

Following reports that link the presence of biofilms in a wound to chronicity (Mercoll et al, 2009), interest in the control of biofilms has increased. Unsurprisingly, research indicates that higher concentrations of honey are required to disrupt established biofilms than to prevent biofilm formation, and they also indicate that planktonic bacteria are more susceptible to honey than are biofilms. The adherence of bacteria to a wound is an important step in establishing initiation of infection and biofilm formation.

In 2009, a study into the effects of honey on planktonic and biofilm-embedded bacteria suggested that honey has a bactericidal
effect against the wound pathogens grown in the laboratory as biofilms (MERCkoll et al, 2009). Similarly, biofilms of S. aureus and P. aeruginosa exposed to honey were inhibited in vitro (Alandejani et al, 2009). Methylglyoxal has been implicated in the inhibition of biofilms (Jervis-Bardy et al, 2011). Biofilms of methicillin-sensitive S. aureus (MSSA), MRSA, and VRE can be prevented from forming – and established biofilms can be inhibited – in vitro with varying concentrations of manuka honey (Cooper et al, 2011b). Honey has been shown to be effective in inhibiting six isolates of P. aeruginosa forming biofilms in vitro (Okhiria et al, 2009) and one reference strain of Streptococcus pyogenes (Maddocks et al, 2012).

The downregulation of two genes coding for surface-binding proteins in S. pyogenes following exposure to manuka honey was found to contribute to the prevention of biofilm formation (Maddocks et al, 2012).

These findings need to be validated by clinical studies once a reliable test for the presence of a biofilm has been developed.

**Antimicrobial resistance to honey**

With the introduction of new antimicrobials into clinical practice, the emergence of resistant strains of bacteria normally follows at some point. Resistant species tend to dominate in environments where antimicrobial agents are in common use. For example, in healthcare settings where many patients are vulnerable to infection.

Antibiotic-resistant bacteria have become a worrying global public health issue. Antimicrobial resistance not only threatens to increase the cost of health care and jeopardise healthcare gains to society, but it may even damage trade and impact the economy (WHO, 2012). Experiments in which bacteria were exposed to low concentrations of manuka honey failed to select for honey-resistant strains (Blair et al, 2009; Cooper et al, 2010). While these findings do not preclude the emergence of bacterial strains resistant to honey in the future, they do suggest that the possibility is slight.

**Debriding action of honey and osmotic effect**

The role of honey in wound debridement has been described by Molan (2009). In one RCT, Manuka honey was demonstrated to promote improved debridement, compared to a hydrogel (Gethin and Cowman, 2009).

In chronic wounds, the increased level of proteases lead to the degradation of growth factors, cytokines, and extracellular matrix components and thereby contribute to the deposition of nonviable tissue (Tarnuzzer and Schultz, 1996). Proteases work optimally at an alkaline pH and manuka honey has been shown to reduce pH (Gethin et al, 2008); this is likely to modulate protease activity in chronic wounds.

The osmotic effect of honey has been thought to encourage lymphatic flow to devitalised tissue (Molan 2009), while reducing bacterial load (Gethin and Cowman, 2009). This promotes autolytic debridement by bringing plasminogen into the wound environment, which is normally activated into active plasmin by plasminogen activator. In chronic wounds, the production of plasminogen activator inhibitor (PAI) by macrophages inactivates plasminogen activator and results in low levels of active plasmin. By inactivating PAI, honey allows plasminogen to become plasmin and, in turn, digest fibrin and so lower the quantity of nonviable tissue (Molan, 2009).

**Antioxidant and anti-inflammatory activity of honey**

Wounds that do not progress through the usual phases of healing persist in a chronic inflammatory state that is characterised by excessive neutrophil infiltration (Menke et al, 2007). Release of reactive oxygen species by neutrophils leads to damaging oxidation reactions within the wound, as well as the recruiting of more neutrophils to the wound. One way to interrupt this chronic inflammatory cycle is to remove free radicals with antioxidants and honey is known to contain antioxidants that scavenge free radicals (Henriques et al, 2006; van den Berg et al, 2008).

The antioxidant potential of honey has been attributed to its phenolic content (van den Berg et al, 2008; Kassim et al, 2010; Leong et al, 2012). Although the anti-inflammatory effects of antioxidants in honey have been demonstrated in animal models, clinical studies are scarce (Subrahmanyam et al, 2003), but it may be that these effects explain the benefits seen in treating burns with honey (Jull et al, 2008).

**THE FUTURE**

The use of honey in modern wound care is still met with some scepticism. Since the advent of evidence-based medicine, changing clinical practice depends on providing clinicians with appropriate levels of evidence of clinical efficacy.

Although honey has become a first-line intervention in some wound care clinics, larger and better designed RCTs are needed to cement the role of honey in modern wound care.
Medical devices (such as wound dressings) are not required to demonstrate the same level of evidence in order to become licensed for use, but high levels of evidence should be aimed for, and will widen use. However, carrying out meaningful RCTs is difficult in complex and chronic wounds.

CONCLUSION
In the context of the continued emergence of antibiotic-resistant pathogens, some alternative or “traditional” topical antimicrobials have been reintroduced into modern wound care, one such example being honey. While a range of evidence is available for the use of honey in wound management, definitive RCTs remain to be undertaken.

References
Brudzynski K et al (2012) Powerful killing by buckwheat honeys is concentration-dependent, involves complete DNA degradation and requires hydrogen peroxide. Front Microb 3: 242
On reading this article by Seckam and Cooper, we are reminded of both the traditional uses of honey in wound care over the past 2000 years, and the renewed interest in honey over the past two decades. This renewed interest has been prompted primarily by concerns around antibiotic resistance and the need for antimicrobial agents that inhibit planktonic and biofilm organisms in wounds. We note that the literature reflects increasing evidence to explain the broad-spectrum antimicrobial efficacy and cytocompatibility of honey, as well as its other bioactive properties that facilitate debridement and control malodour and inflammation. Such a combination of properties in one product makes one wonder why honey is not used more frequently and by more clinicians?

The authors suggest “some scepticism in some quarters” exists with regard to the use of honey and perhaps this is related more to practicalities in clinical practice than demands for high-level evidence. The amorphous honey formulations usually require twice-daily applications to ensure sustained efficacy. This frequency of application is not practical in most situations and comes with additional resource costs that can be inhibitive. However, the expanded range of honey formulations listed in Table 1 may not be widely appreciated or used by some clinicians. Not only do these honey-impregnated formulations afford greater clinical choice for more wound types, but they also provide more sustainable effects (up to 3 days in wounds with low to moderate amounts of exudate).

Clinicians’ experiential knowledge can offer additional practical insights in regards to the selection of honey dressings. Recently, a patient presented at the community clinic at which I work with an iatrogenic, deep partial thickness burn on his abdomen, extending into his umbilicus.

The burn had occurred during the surgical repair of an umbilical hernia but the causative agent was not known. Clinical indications suggested it was a chemical burn. Surgical debridement and skin grafting had been offered to the patient, but he declined; his preference was to be discharged from hospital and receive wound care from a community clinic. Prior to hospital discharge, a silver alginate dressing had been applied to the burn, which was covered in thick, white eschar. However, the dressing had adhered, causing the patient significant pain.

Following comprehensive assessment, the short-term goals of care in our clinic were debridement, infection control, and pain management. Iodine- and chlorhexidine-based products were not used due to concern that the skin preparation agent used prior to surgery – although unknown – was likely one of these agents and may have been the cause of the burn. The wound was too dry for a silver fibre or fabric product. Thus, a honey-impregnated alginate dressing was applied and found to conform well to the wound and umbilical undulations and was comfortable for the patient. Medical-tape sensitivity was also suspected, so a secondary absorbent pad was held in situ with an abdominal binder. Autolysis of the eschar was efficient and over the next 4 weeks the wound progressed to healing. Even the surgeon was impressed.

This scenario suggests that perhaps clinicians need to reconsider the use of honey, not only in light of new and expanding evidence, but from a pragmatic perspective when sensitivities or concerns exist in relation to other antimicrobials.
This digest summarises recent key papers published in the areas of pressure ulcers, skin integrity, venous leg ulcers, and diabetic foot ulcers.

**SELECTED PAPERS OF INTEREST**

1. **MRSA infections of the foot: cost savings using linezolid**

2. **A critical review of modern and emerging absorbent dressings used to treat exuding wounds**

3. **Observations of periwound skin protection in venous ulcers: a comparison of treatments**

4. **Efficacy of two compression systems in the management of venous leg ulcers: results of a European randomised control trial**

To compile the digest, a MEDLINE search was performed for the three months ending in February 2013 using the search terms "diabetic foot ulcers," "pressure ulcers," "skin integrity," and "leg ulcers." Papers have been chosen on the basis of their potential interest to practitioners involved in day-to-day wound care. The papers were rated according to readability, applicability to daily practice, and novelty factor.

**Diabetic foot ulcers**

1. **MRSA infections of the foot: cost savings using linezolid**

- **Readability**: ✗ ✗ ✗ ✗ ✗
- **Relevance to daily practice**: ✗ ✗ ✗ ✗ ✗
- **Novelty factor**: ✗ ✗ ✗ ✗ ✗

- Management of diabetic foot ulcers can be significantly complicated by infection with methicillin-resistant *Staphylococcus aureus* (MRSA). Linezolid is not a first-line antibiotic treatment for diabetic foot infections, but can be used to minimise inpatient admissions.

- The authors audited outpatient linezolid usage in 704 people attending the Diabetes Foot clinic at the Royal Infirmary of Edinburgh, Scotland, from 2005 to 2010. Admissions (defined as a length of inpatient hospital stay), antibiotic usage, and microbiological culture results were recorded.

- Clinical effectiveness of linezolid was defined as resolution of MRSA infection (downgrading of ulcer to Infectious Disease Society of America grade 1 or 2 infection) and avoidance of admission for further treatment.

- MRSA infection was diagnosed in 17% (n=119) of the cohort, of whom 28% (n=33) were prescribed linezolid. In 94% of people, linezolid was prescribed for up to a maximum of 14 days. No one took linezolid for more than 28 days.

- Admission for further treatment was avoided, or early discharge facilitated, and infection resolved in 91% (n=30) of people taking linezolid. The total cost of linezolid was £58 000.

- Linezolid treatment of MRSA diabetic foot infections avoided 420 bed-days (at a cost of £500/day), and yielded a total saving of £210 000 on inpatient costs. The authors concluded that linezolid treatment is cost-effective in clinical use for treatment of diabetic foot infections.


**Pressure ulcers**

2. **A critical review of modern and emerging absorbent dressings used to treat exuding wounds**

- **Readability**: ✗ ✗ ✗
- **Relevance to daily practice**: ✗ ✗ ✗ ✗ ✗
- **Novelty factor**: ✗ ✗ ✗ ✗ ✗

- This study was conducted to review randomised controlled trials (RCTs) on absorbent dressings and their ability to manage exudate, while also discussing advances in exudate management dressings.

- There is a lack of RCTs comparing modern first-line (primary) dressings, such as alginate, hydrofiber, foam, hydrocolloid, and polysaccharide bead dressings, against each other. Of the trials that have been conducted, methods have been mixed and bias could not be ruled out. None of the dressings trialled proved more effective than the others.

- The authors suggest that modern absorbent dressings must interact with the wound by stimulating healing while also absorbing exudate.

- Next generation methods of achieving more effective absorbent dressings are being developed. These involve protease inhibitors, growth factors, antimicrobial agents, and sensory smart wound dressings.

- Although there is a lack of evidence for the use of modern first-line dressings in ulcers, they still serve a...
Wound digest

Skin integrity

3 Observations of periwound skin protection in venous ulcers: a comparison of treatments

Remedy Nutrashield reduced the size of the periwound area 3-times faster than Cavilon Moisturising Lotion.

The authors suggested that the integrity of periwound skin may be a determinant of potential treatments, strategies for protecting fragile skin, and reducing ulcer healing time.


Leg ulcers

4 Efficacy of two compression systems in the management of venous leg ulcers (VLUs): results of a European randomised control trial

The objective of this randomised controlled trial was to access the use of a two-layer bandaging system (K Two®; URGO) against a four-layer bandage system (Profore™; Smith & Nephew) in the management of venous leg ulceration. The study involved 187 patients at 37 investigation centres in France, the UK, and Germany.

Patients with a venous or mixed aetiology leg ulcers, and an ankle brachial pressure index of 0.8–1.3 in both legs, were recruited. Compression bandaging was used for 12 weeks or until the wound was completely healed. Clinicians documented each dressing change and took wound area tracings and digital photographs. Patients were assessed every 2 weeks.

The endpoint was the percentage of ulcers healed at 12 weeks as calculated by the relative wound area reduction (RWAR) (the percentage of wounds with a RWAR >40%, and the absolute wound area reduction [AWARI]).

Results were analysed by an independent company approved by all parties. By trial end, 44% of wounds managed with K Two two-layer bandaging system had healed, and 39% of those using the Profore four-layer bandaging system. The AWARI was 6.6 cm² in the K Two group and the RWAR was 47%. The AWARI in the group using Profore was 4.9 cm² and the RWAR was 44%.

The authors concluded that the K Two two-layer bandaging system was considered easier to apply, had a good local pain tolerance, and is an acceptable alternative to the Profore four-layer bandaging system.
