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

India R. Sweeney, Mohsen Miraftab, Graham Collyer

Sweeney IR, Miraftab M, Collyer G. A critical review of modern and emerging absorbent dressings used to treat exuding wounds. Int Wound J 2012; doi: 10.1111/j.1742-481X.2011.00923.x

ABSTRACT

Wound management has progressed significantly over the last five decades. This emanates from a greater understanding of wound healing, technological progression and improved clinical and scientific research. There are currently a plethora of absorbent dressings on the wound care market which claim to have the ability to manage exudates whilst encouraging healing. However, it is becoming clear, from analysing randomised controlled trials, that some of these absorbent dressings are not meeting their expectations when applied in a clinical setting. Many clinicians now feel that there should be more focus, not only on a dressing's ability to manage exudate efficiently, but on a dressing's ability to proactively encourage healing and thus exudate reduction will ensue. This paper proposes to critically review modern and emerging absorbent wound care dressings used to manage exuding wounds and discuses some advances in this area.

Key words: Absorbent dressings • Disadvantages • Exudate • Interactive • Smart

INTRODUCTION

Exuding wounds are notoriously difficult to manage effectively as there are many factors to consider when choosing the appropriate dressing such as; the size of the wound, presence of infection and the total volume of exudate, which can vary during the process of healing. If exuding wounds are not managed effectively this can have a very negative effect on a patient's health and wellbeing. It is increasingly becoming apparent that most modern first-line, absorbent, primary dressings are not meeting the expectations of clinicians, nurses and patients involved (1–3). One review has gone so far as stating that the majority of these types of dressings are comparably no better than any other and perform similarly to traditional saline soaked and paraffin gauze dressings, in relation to healing (4). Most first-line modern, absorbent, primary wound dressings for use on exuding wounds currently aim to absorb excess exudate whilst maintaining a moist wound bed. This has become a necessity since Winter's revolutionary research in the 1960s (5). However, it is progressively becoming clear that these dressings need to evolve further and become increasingly more biologically interactive, to not only manage exudate, but go some way to treating the root cause of exudate production.

Authors: IR Sweeney, MEng, Insitute for Materials Research and Innovation, University of Bolton, Deane Road, Bolton, UK; M Miraftab, PhD, Insitute for Materials Research and Innovation, University of Bolton, Deane Road, Bolton, UK; G Collyer, BSc, Sumed International (UK) Limited, Integrity House, Units 1-2 Graphite Way, Hadfield, Glossop, Derbyshire, UK
Address for correspondence: IR Sweeney, MEng, Insitute for Materials Research and Innovation, University of Bolton, Deane Road, Bolton, UK
E-mail: irs1mpo@bolton.ac.uk

A HISTORY OF ABSORBENT DRESSINGS

Prior to the 19th century, exuding wounds were often dressed with natural materials

Key Points

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- it is increasingly becoming apparent that most modern first-line, absorbent, primary dressings are not meeting the expectations of clinicians,nurses and patients involved
- these dressings need to evolve further and become increasingly more biologically interactive, to not only manage exudate, but go some way to treating the root cause of exudate production

international wound journal

such as oakum, which was a fibrous mass of unpicked rope, and sponges impregnated with active agents such as hemlock and nightshade. These dressings were absorbent but had several disadvantages such as that they could not retain exudates, often caused infection and would adhere to the wound, and so their popularity declined. This paved the way for the development of a new absorbent dressing called 'Gamgee' which was invented by the clinician Joseph Sampson Gamgee in the year 1880. The 'Gamgee' dressing has an absorbent cotton wool core, sandwiched in between two layers of absorbent cotton gauze. Gamgee discovered how to remove wax, found naturally in cotton wool, via a bleaching process, which rendered the cotton more absorbent, as wax is hydrophobic. This dressing was designed to be absorbent, dry, firm and could be kept *in situ* for longer periods of time (6). These dressings are still used in mass today, as an absorbent, as they provide a cheaper alternative to modern absorbent dressings. They are often used as a secondary dressing in conjunction with, for example, an alginate dressing.

Absorbent wound care did not advance further for more than a century until a revolutionary researcher, called George Winter, demonstrated that wounds healed twice or three times as fast if kept moist and the formation of a scab was prevented (5). This led to the production of modern absorbent dressings that had the ability to manage exudates whilst keeping the wound environment moist, such examples include foam and alginate dressings. It is well documented that the provision of a moist healing environment results in increased healing rates via increased re-epithelialisation, macrophage and fibroblast activity, rapid debridement, decreased pain (especially during removal), and reduced dressings changes (7,8). Since this discovery, absorbent wound dressings are transitioning yet again, as they move from being passive and enter a more interactive era.

WHAT IS EXUDATE?

Wound exudate is a generic term used to describe the fluid produced by wounds of all types once haemostasis has been achieved. All wounds will exude at some stage in their healing cycle and the amount of exudates generated by these wounds depends entirely on the nature of the wound, its mode and stage of healing, and whether the wound is subject to complications such as infection. Exudate consists mostly of water but it also contains electrolytes, nutrients, proteins, inflammatory mediators, proteases, growth factors, white blood cells and platelets. Healthy exudate is usually pale amber in colour, odourless and has a watery consistency (9).

Wound exudate forms when an injury is sustained that compromises the integrity of the skin; mostly during the inflammatory stages of healing under the influence of inflammatory mediators such as histamine. It is produced by the body to facilitate wound healing by providing moisture and essential nutrients for cell metabolism, enabling the diffusion of immune and growth factors, assisting the autolytic separation of nonviable cells, and enabling the migration of tissue-repairing cells which promotes new tissue growth (9–11).

When exudate becomes problematic

The presence of exudate becomes problematic when the volumes of exudate become unmanageable, and when the content of the exudate changes. When the quantity of exudate is not being managed effectively, this can lead to problems such as periwound skin maceration, delayed healing, odour, infection and the requirement of increased dressing changes. Excessive exudate production can also cause patients distress and can be financially exhausting on the healthcare system (9,12–14). The content of exudate produced by chronic wounds can also have a detrimental effect on wound healing.

Chronic wound exudate

A chronic wound is described as: 'a wound that has failed to heal after four or more weeks of treatment and no tendency to heal is apparent' (15). Chronic wounds are immobilised in a prolonged hyper-inflammatory phase of healing. These types of wounds contain higher levels of neutrophils, pro-inflammatory cytokines, biofilm phenotype bacteria and deleterious protein-digesting enzymes (matrix metalloproteinases) (9,16). Matrix metalloproteinases (MMPs) can, in the right balance, aid wound healing by promoting cell migration, remodelling and the breaking down of damaged

extracellular matrix. However, excessive MMP activity can lead to increased degradation of cellular components (17). It has also been indicated that chronic wound exudate is irritating to periwound skin, causing contact dermatitis and allergic reactions (10,18). Some examples of chronic wounds that produce exudate are: leg ulcers, diabetic foot ulcers, pressure ulcers, fungating carcinomas, chronically infected wounds, fistulae, deep wounds, wounds associated with limb oedema and wounds with a sinus oedema (17,19). There are many other factors that also influence the production and nature of exudate. Examples include; if a patient suffers from venous hypertension, if oedema is present, the depth and surface area of the wound and the type of dressing used (20).

How to reduce exudate levels

It is believed that effective exudate management, using the appropriate dressing for the type of wound and its stage of healing, will help to reduce the time to healing of a wound, prevent infection, reduce periwound skin maceration, reduce costs (by reducing number of dressing changes and staffing), and improve the patient's quality of life (21). However, prior to dressing application, it is important that other factors are considered, such as whether the patient needs to elevate their limbs to reduce oedema or to take diuretics to treat heart failure (9).

MODERN FIRST-LINE DRESSINGS USED TO TREAT EXUDING WOUNDS

Exuding wounds are treated using absorbent and moisture vapour transmission dressings. The modern first-line, absorbent, primary dressings that are suitable for exuding wounds are currently alginate, hydrofibre, foam, hydrocolloid and polysaccharide bead dressings (22).

Alginate dressings

Alginates are linear polysaccharides found abundantly in nature as they are the major component of marine brown algae. Alginate is composed of two uronic acid monomers: mannuronic acid (M) and guluronic acid (G). Alginates form hydrophilic gels via a unique ion exchange mechanism by selectively binding divalent cations, e.g. calcium ions, between homo-polymeric G-blocks (23). Therefore high G alginates form much more rigid gels and high M alginates form much softer, flexible gels. The gelling ability of calcium alginate dressings can be improved with the reintroduction of sodium ions which ultimately increases the water solubility of the dressing. Some alginate dressings contain silver/zinc inclusions to improve the dressing's anti-bacterial activity and blood clotting ability, respectively. Alginates are available in nonwoven fabric forms, made from fibres, for superficial wounds and in ribbon/rope forms used for packing deeper wounds and cavities. Currently available alginate dressings include Kaltostat™ (ConvaTec Ltd., Uxbridge, UK), Sorbsan™ (Aspen medical europe Ltd., Worcestershire, UK) and Seasorb™ (Coloplast Ltd., Peterborough, UK) .

Alginates can wick and retain exudate away from the wound bed, thus preventing harmful proteases from disrupting healing, whilst maintaining a moist environment for improved wound healing. Alginate dressings do not adhere to the wound, provided there is enough exudate to form a homogenous gel, and thus dressing changes are said to be relatively pain-free as newly formed granulation tissue is not disturbed. Alginates interact with the wound by donating calcium ions to the bed in exchange for sodium ions present in wound exudate, facilitating blood coagulation, thus assisting haemostasis (24–26). More recently, it has been reported that high M alginate dressings can activate human macrophages causing them to produce cytokines involved in systemic inflammation which can encourage healing (27).

Alginates do, however, have some disadvantages. Some patients experience a burning sensation when alginates are applied to the wound site; this is thought to be because of the rapid movement of fluid from the soft tissue into the dressing matrix. However, this can be overcome by pre-moistening the wound bed with saline. Alginate dressings can sometimes struggle to retain exudates especially when under compression which can lead to the maceration of periwound skin and infection (28). Thus alginates will often have to be used in conjunction with a secondary absorbent, for example, a viscose dressing. A review of alginates dressings against gauze, for application on surgical wounds healing by secondary intention, showed insufficient evidence of a difference in healing rates. This indicates that more research is needed to support alginate's efficacy in relation to accelerated healing times (29).

Key Points

- exuding wounds are treated using absorbent and moisture vapour transmission dressings
- the modern first-line, absorbent, primary dressings that are suitable for exuding wounds are currently alginate, hydrofibre, foam, hydrocolloid and polysaccharide bead dressings

Hydrofibre dressings

Hydrofibres are composed entirely from sodium carboxymethyl cellulose (CMC) which is a water-soluble, anionic derivative of cellulose. These fibres are used to make soft, nonwoven dressings which have the ability to gel upon contact with fluid. There is currently only one manufacturer of CMC fibres (patented as Hydrofibres) and this dressing is called Aquacel™ (ConvaTec Ltd., Uxbridge, UK). They have also released a silver containing dressing, Aquacel-Ag™ (ConvaTec Ltd.). These dressings are available as sheets or ribbons. CMC has also been blended with alginate fibres to improve the dressings wet strength, fluid handling and cohesive properties of the final dressing, for example, Askina Sorb™ (B Braun Medical Ltd., Sheffield, UK).

The carboxyl groups on the surface of the fibre allow the fibres to swell just enough for gel formation (30). They have high fluid absorbency (15–25 g/g) and retention, allowing the user to wear the dressing for longer periods of time. The gel promotes a moist wound healing environment yet it allows the vertical wicking and retention of wound exudates which ensures that periwound tissue is not macerated (31). These dressings are also believed to sequester and bind bacteria within their structure thus reducing the chance of infection.

Hydrofibre dressings do have some disadvantages. For example, in terms of healing, it is well known that wound dressings composed of 100% CMC filaments are physiologically inert as they basically act to absorb and retain exudates. This is unlike dressings such as calcium alginate which have been shown to interact chemically with wound exudate; to assist in the cellular processes involved in wound healing. A publicly funded, blinded, randomised controlled trial (RCT) comparing three dressings: a hydrofibre dressing, an iodine containing dressing and a simple low adherent dressing for the treatment of diabetic foot ulcers concluded that, after 24 weeks of testing, that there was no significant difference between the dressings in relation to mean healing time (32). The hydrofibre dressings were the most expensive dressing of the three tested and it was concluded that the additional costs incurred by this dressing was not justified given no difference in effectiveness between the dressing types (32).

Foam dressings

Foams are made from the synthetic polymers, polyurethane and silicone. They consist of a porous polyurethane foam or polyurethane foam film. Some foam dressings can have an adhesive dressing, an extra layer at the wound surface to prevent adherence or an occlusive polymeric backing layer to prevent excess fluid loss and bacterial contamination (33). Foams are available as flat sheet dressings, of varying thickness, or as fillers for cavity wounds. Foam sheets, for example, PolyMem™ (Aspen medical europe Ltd., Worcestershire, UK) have a hydrophilic underside, provides a low-adherent wound contact layer, and a hydrophobic coating which prevents strike-through. Cavity foams consist of foam chips enclosed in a low-adherent polymeric envelope. Silicone foam dressings such as Cavi-Care™ (Smith & Nephew Healthcare, Ltd., Hull, UK) are foam stents that have to be mixed with a catalyst and poured into the cavity where it takes up the shape of the wound. Foam dressings can be treated with anti-bacterial agents such as polyhexamethylene biguanide (PHMB) and silver.

Foams are absorbent dressings that can be used on a variety of wounds with low to high levels of exudates whilst providing a moist wound environment to help accelerate healing. Foams have an open cell structure which allows for a high moisture vapour transmission rate. They provide good thermal insulation and they can be left in place for up to seven days, if exudate levels remain constant, which can improve cost-effectiveness. Some patient's dressed using foam have also experienced less pain when compared against the traditional gauze dressings (29).

Foams do, however, have some disadvantages as they can cause inflammation either because of an allergic reaction to polyurethane or because of increased blood flow, following thermal insulation of the wound bed. They also have been demonstrated to not have the ability to bind or modulate proteases found in chronic wound exudates which can lead to delayed healing (34). A comparative systematic review of foam dressings against gauze dressings did not produce any clear evidence highlighting the difference between the both dressings in terms of healing (29). This indicates that further unbiased, RCTs are needed to confirm their efficacy.

Hydrocolloids

Hydrocolloid dressings are composed from an elastomeric (polyurethane foam/film) adhesive and gelling ingredient. Common gelling agents are CMC, pectin and gelatine. Hydrocolloids exist in a variety of shapes and sizes (35). Some dressing brands include Tegasorb™ (3M Healthcare Ltd., Loughborough, UK), Comfeel™ (Coloplast Ltd., Peterborough, UK) and DuoDerm™ (ConvaTec Ltd., Uxbridge, UK).

All hydrocolloids are waterproof, impermeable to bacteria, provide thermal insulation, are occlusive; thus providing a moist healing environment and the promotion of autolysis, and cause a reduction in localised pH which enables the body's defence mechanism to function more efficiently. Hydrocolloid dressings gel, when they come into contact with exudate, which swells to fill the wound cavity.

Hydrocolloids do, however, have some disadvantages. They are opaque dressings which prevents the inspection of the wound without removal (35). Constant removal of the dressing can lower the localised wound temperature, which can lead to a reduction in mitotic activity. They can cause maceration of surrounding skin and can leak excessive tissue exudate as their absorption abilities are now a subject of debate. Although hydrocolloid dressings are advertised as highly absorptive, in reality they are not quite so and are more suited to wounds that produce light to moderate levels of exudate (36). There have been recent claims that hydrocolloids are not suitable for diabetic foot ulcers as they can lead to infection as occlusive dressings can encourage the growth of anaerobic bacteria (37). There is yet to be any conclusive evidence supporting the efficacy and safety of hydrocolloid dressings especially for application on diabetic foot ulcers, and any evidence that does exist is largely contradictory (38). After the removal of hydrocolloids, there is often residual gel material (which can resemble pus) and a distinctive malodour, an inexperienced practitioner could mistake this for infection (36). Hydrocolloids can cause over-granulation due to the lack of oxygen present at the wound bed and can cause contact dermatitis; inflammation of the skin (39). If this dressing were to be applied to an unsuitable wound this could have detrimental effects therefore the contraindications should be closely noted prior to application. However, if these dressings are applied to the appropriate wounds, after a thorough patient assessment, they may encourage healing (38).

There is contradicting evidence supporting the efficacy of hydrocolloids for the treatment of chronic wounds. A selection of recent randomised controlled trials (RCTs) found hydrocolloids to be more effective against gauze dressings for the healing of pressure ulcers (40,41). However, more recently published trials have indicated that hydrocolloids are no more beneficial than simple low adherent dressings in ulcer healing when used under compression. Overall there is inadequate evidence to draw conclusions about the efficacy of hydrocolloids against other absorbent advanced dressings and conventional gauze (42). These dressings need to be assessed further to confirm their efficacy.

Polysaccharide beads

Polysaccharide bead dressings, are produced from hydrophilic, biodegradable sterile dextranomer beads, 0·1–0·3 mm in diameter, mixed with glycol and water to form a paste. The paste is contained within a low-adherent nylon bag or is available as a foil-wrapped paste. These dressings can come in a pad or paste form which can be removed via saline irrigation and can contain antiseptic materials such as iodine, for example, Iodosorb™ (3M Healthcare Ltd., Loughborough, UK). The original non biodegradable beads, Debrisan™ (Pharmacia & Upjohn Ltd., Milton Keynes, UK), were marketed as desloughing agents but were eclipsed by hydrogel dressings which have the same effect but at a reduced cost. Hydrogel dressings, however, do not act as absorbents but rather as moisture donors for dry, necrotic wounds. The Debrisan™ beads were reinvented as biodegradable beads containing the anti-bacterial agent iodine.

Bead dressings can absorb large amounts of liquid, up to seven times their weight, via a capillary action which helps to remove and trap slough and hold bacteria away from the wound bed. They also provide a moist wound environment for healing. The beads absorb solutes depending on their molecular size and any material left on the wound bed can be irrigated away. As the beads swell they slowly release iodine which acts as an anti-bacterial agent (43).

Bead dressings do have some disadvantages. The dextranomer beads can cause discomfort when applied to clean, granulating wounds. This primary dressing must be used in conjunction with a secondary dressing to maintain its position on the wound, which can reduce cost-effectiveness. The beads containing iodine can cause an allergic response as the iodine becomes systemically absorbed. There have been some instances of iodine-induced hyperthyroidism especially in elderly patients; it is believed that this is caused by mutational events in thyroid cells that lead to autonomy of function (44). This is a rare occurrence but it does require further investigation. Iodine cadexomer dressings have been indicated only suitable for the early stages of the healing cycle for cleansing and removal of infected material.

A review comparing bead dressings against traditional Eusol soaked gauze dressings for use on wounds healing by secondary intention showed that there is insufficient evidence, from one trial, supporting the efficacy of the beads (29). There have been various trials supporting the efficacy of polysaccharide beads for improved healing times but a critical review has indicated that these trials are outdated and further more formal studies were required to strengthen the evidence base in support of the use of bead dressings (45). There have also been a lack of good quality studies indicating the efficacy of iodine as an anti-bacterial agent; it is still not evident if iodine dressings are any better than un-medicated dressings for the prevention or treatment of wound infection. There is evidence supporting the use of cadexomer beads used in conjunction with compression for the healing of venous leg ulcers, however the evidence is not robust and further RCTs are needed to strengthen the evidence (2).

Summary of critical review of absorbent dressings

It is evident that there are distinct lack of RCTs evaluating the clinical efficacy of modern absorbent dressings against each other. The majority of good quality trials have focused on the comparison of modern absorbent dressings against conventional gauze dressings, which is a flawed method, since gauze is not classified as modern (46). Of the RCTs that have been submitted it is apparent that there is no consistent evidence that any one modern absorbent dressing is better than any other for the healing of ulcerated wounds (1). It is also clear that most studies aimed at supporting the effectiveness of these modern dressings often have poor assessor blinding, poor randomisation methods and baseline characteristics, and where conclusions could be drawn, bias could not be ruled out (2). This has led to the publication, by the EWMA Patient Outcome Group, describing recommendations for the design of clinical studies in wound management to meet the demand for more high quality evidence to strengthen the efficacy of modern absorbent dressings used to treat exuding wounds (2,47). These absorbent dressings are still being employed even in spite of abundant evidence supporting their poor effectiveness (3).

NEXT GENERATION DRESSINGS

It is imperative that modern absorbent dressings undergo another revolution during the 21st century with the view of becoming more interactive and smart in nature, whereby they not only absorb exudates, but also interact with the wound to encourage healing and thus a reduction in exudate will ensue. This could be achieved by many means such as by reducing the activity of harmful proteases, applying growth factors to the wound bed, by the use of effective antimicrobials, or by applying smart dressings with inbuilt biosensory mechanisms.

Protease inhibition

Many researchers are now investigating ways of managing the protease activity of chronic wound exudate. As stated previously, chronic wound exudate differs greatly from acute wound exudate and has been described as being 'corrosive' in nature (48) If there is an imbalance between protease activity and inhibition then wound healing is impaired, as excessive MMP activity can lead to increased degradation of cellular components. This contributes to wound chronicity, thus the topical use of protease inhibitors might influence wound healing and promote the transition from a chronic to acute wound which would effectively decrease exudate production (49).

Researchers have produced a protease inactivator modulating matrix Promogran™ (Systagenix Wound Management, West Sussex, UK), composed of oxidised regenerated cellulose (ORC) and collagen (50) which can reduce elastase, plasmin and MMP activity in chronic

wound fluids of diabetic patients. This dressing forms a gel on contact with wound exudate and is reported to bind and inhibit MMPs without affecting the beneficial activity of the growth factors (51). This is believed to help reduce the prolonged inflammatory phase as seen in chronic wounds leading to reduced exudate production. These dressings may have to be used in conjunction with a secondary absorbent dressing to mop up excess exudate.

However, it has been reported that both material components of this dressing, collagen and ORC, only act to physically bind MMPs in a non selective manner and hold them away from the wound bed (52). Research shows that cheaper, standard dressings, such as alginates, have this ability too (53). Another notable disadvantage of these newer dressings is that they have yet to be assessed in large, well-designed trials (54). At this moment in time there is no concrete evidence to indicate that these 'smart' dressings rise to their claims. The efficacy of this dressing on wounds that have been present for six months or longer has also been queried (51). Over time subsequent trials and testing may reveal the true potential of these dressings.

Growth factors

An exuding wound will often exude less after the wound starts to heal and the wound surface area is subsequently reduced (55). To help the wound healing processes and thus subsequent reduction of exudate levels, researchers are trying to deliver transdermal and topically bioactive molecules, such as growth factors, for example, epidermal growth factors (EGFs), to the wound bed. EGFs are believed to stimulate the growth of keratinocytes *in vivo*, and therefore play an important role in the process of wound healing that depends on the mitosis and migration of keratinocytes (56,57).

Presently, growth factors are normally applied topically by the clinician. The only available topical growth factor approved by the US Food and Drug Administration is Platelet Derived growth Factor isoform-BB (PDGF-BB) (Regranex™; Ethicon, Livingston, UK) and it is believed to promote the chemotactic recruitment and proliferation of cells involved in wound repair (58). Researchers are now working on the delivery of growth factors to a wound via a dressing. For example, Ulbayram *et al*. have designed a biocompatible, absorptive gelatin-based sponge dressing containing EGF which was shown to provide a higher degree of reduction in the wound areas (57).

Growth factor application can have some potential disadvantages. Chronic wounds have raised levels of protease activity (MMPs) and any growth factors that are applied to the wound are often subjected to proteolytic degradation, which renders them inactive. They have a low bioavailability and very high manufacturing costs. It is also becoming clear that the application of a single growth factor to a wound may have limited effect on healing processes as effective wound healing requires a complex mixture of growth factors (they work symbiotically to achieve wound closure). For these reasons, it is often the case that the therapeutic application of isolated and purified growth factors, can lead to disheartening results (59). Growth factor application has not yet been proven to be efficacious and the efficiency of growth factor application for the management of chronic/recalcitrant wounds is still under much debate. This therapy which is licensed for use in diabetic foot ulcers has yet to report any significant benefits from growth factor application, alone (60). There still may be hope as growth factors undergo further modifications and clinical trials (61).

Antimicrobial agents

It is becoming more apparent that silver dressings are not rising to meet their claims but they are still very popular even without an evidence-base to support their increasing use (2). One RCT comparing the use of silver dressings and non-silver dressings for application on venous leg ulcers found that there was no statistical significance between the two in relation to healing times (62). A Cochrane review of silver dressings for the treatment of infected wounds from 2007 came to the conclusion that there was insufficient evidence to recommend the use of silver containing dressings for treatment of infected wounds (63). It is now important to investigate and research new and effective antimicrobial agents that can be incorporated or applied to infected wounds to help reduce infection. A subsequent benefit of this will be a reduction in the level of wound exudate, as wounds that are infected will often exude more, as the body tries to fight infection (10). To follow are a selection of two antimicrobials, chitosan and honey, which are currently under intense research.

Key Points

- growth factor application has not yet been proven to be efficacious and the efficiency of growth factor application for the management of chronic/recalcitrant wounds is still under much debate
- it is becoming more apparent that silver dressings are not rising to meet their claims but they are still very popular even without an evidence base to support their increasing use

Key Points

- chitosan or chitosan containing dressings have yet to be launched commercially on the UK market despite the anticipated advantages associated with this marine polysaccharide, even though the current dominating fibrous polysaccharide dressings such as those containing CMC and alginate, are believed to perform inertly as absorbents
- recent research claims that honey is an effective anti-biofilm agent (88), is a deodorant,as bacteria prefer sugar to protein and the metabolic product of sugar is lactic acid which is not malodorous can promote autolytic debridement and is anti-inflammatory
- there is ongoing research into the development of a more efficient method for the application of honey via a dressing

Chitosan

Researchers have started to investigate the antimicrobial effectiveness of an abundantly available, natural, positively charged polysaccharide called chitosan and its derivatives. Chitosan is the partially N-deacetylated derivative of chitin which is an extract from the exoskeletons of animals of the *Phylum Arthropoda*, primarily from the shells of crustaceans, for example, crabs, shrimp and lobsters (64). This biopolymer was discovered by Rouget in 1859 when he discovered that boiling chitin in potassium hydroxide rendered chitin soluble in organic acids (65).

Chitosan, and its derivatives, have excellent antimicrobial properties. This polymer has been shown to inhibit the growth of gram-positive and gram-negative bacteria, whilst showing low toxicity towards mammalian cells. Most encouragingly, chitosan has been shown to be effective in depressing the growth of MRSA under both wet and dry conditions (66). The exact mechanism of this activity is still under interpretation and there have been many propositions. The most accepted model for chitosans' anti-bacterial activity is the interaction between the positively charged amino groups and negatively charged moieties on the microbial outer cell membranes causing cell damage and leakage of intracellular constituents (67,68). There have also been several studies on the bactericidal activity of low molecular weight chitosans (chitooligomers). Chitooligomers have shown greater bactericidal efficiency against *E. coli* in comparison to their higher molecular weight counterparts (69). Chitooligomers have also been shown to inhibit the activation and expression of MMP2 in primary human dermal fibroblasts. Inhibition is at its highest when the molecular weight of chitosan is as low as 3–5 kDa. Increased levels of MMP2 in the wound bed can hinder wound healing, as this protease can hydrolyse the basement membrane collagen 1V (70). The antimicrobial nature of chitosan is considered to be its most important attribute, but this natural polymer can also act as a haemostat (71), have an analgesic effect on inflammatory pain (72,73), show antitumor activity (74), and have the ability to activate immunocytes and inflammatory cells such as macrophage, fibroblasts and angioendothelial cells and therefore aid healing (75).

As chitosan is positively charged it can bond with other negatively charged materials, for example, alginate. Chitosan has so far been incorporated into fibres (76–78), sponges (79,80), hydrogels (81) and membranes (82). Chitosan or chitosan containing dressings have yet to be launched commercially on the UK market despite the anticipated advantages associated with this marine polysaccharide, even though the current dominating fibrous polysaccharide dressings such as those containing CMC and alginate, are believed to perform inertly as absorbents (28).

Honey

Current research has indicated that honey is a valuable anti-bacterial topical agent in modern wound management with growing concerns of the increase of antibiotic-resistant bacteria. Not all honeys behave similarly and the properties, such as antimicrobial activity, of each honey can vary depending on its source. Mannuka honey has been suggested as: 'the best antibiotic in the world' (83). Honey can be applied topically or carried via a dressing such as alginates or gauze. Honey used on wounds should be of a medical grade and thus must be filtered, gamma-irradiated and be produced under controlled standards of hygiene to ensure standardisation (83).

Honey can attack a broad spectrum of bacteria and can be applied to a variety of wounds ranging from the infected, to acute and chronic (84). The effect of honey can be clearly seen on wounds that have failed to become healthy using conventional antibiotics or antisceptics (85). Honey's anti-bacterial activity arises from its high sugar content, its acidic nature (pH 3·2–4·2) and its ability to produce hydrogen peroxide (86,87).

Recent research claims that honey is an effective anti-biofilm agent (88), is a deodorant, as bacteria prefer sugar to protein and the metabolic product of sugar is lactic acid which is not malodorous can promote autolytic debridement and is anti-inflammatory (89). Venous leg ulcers have been treated with honey alginate dressing with promising results. The honey appeared to act as an effective antibacterial, anti-inflammatory and deodorising agent, and total wound healing was achieved (88). Honey is now used as a standard treatment in chronic wounds. However, there

are still some practical problems that remain in relation to the application of honey. Currently honey is either poured onto the wound bed or applied via a honey-saturated substrate. These application techniques are cumbersome, wasteful and, given the viscous nature of honey, can be very messy and glutinous. Other disadvantages include:

- The viscosity of honey increases with increase in temperature which may cause the honey to liquefy at body temperature, rendering the dressing unusable.
- Honey cannot be applied to large wounds of diabetic patients as their blood glucose levels may rise to dangerous levels.
- Some patients experience a 'drawing' sensation which can be discomforting (87).

There is ongoing research into the development of a more efficient method for the application of honey via a dressing.

Sensory smart wound dressings

Smart wound dressings are being developed that have the ability to detect and report pathogenic bacterial colonisation and sense when a wound has become infected. Wound infection can lead to biofilm formation which are notoriously difficult to treat (90). The prevention of biofilm formation will greatly reduce the amount of exudate expressed by the wound, as biofilms stimulate inflammation, which in turn increases vascular permeability and production of wound exudate (91). The following are two such dressings, with differing mechanics, currently undergoing research in this area.

Zhou *et al*. have produced a prototype dressing composed from stabilised lipid vesicles containing a quenched carboxyfluorescein dye. The discussed lipid vesicles are sensitive to the presence of bacterial toxins in particular toxins produced by the two pathogenic microorganisms *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The lipid vesicles are lysed by secreted toxins which subsequently releases the dye indicating pathogenic colonisation. In the future, the lipid vesicles could also be impregnated with a suitable antimicrobial agent that is therefore only released when it is required (92).

Researchers from the University of Cranfield are investigating ways of attenuating bacterial biofilm formation, in particular the opportunistic human pathogen *P. aeruginosa*, via specific sequestration of its signal molecule using a molecular imprinted polymer (MIP) specifically designed to interact with and sequester the signal molecule produced by *P. aeruginosa*. They quantified the biofilm formation using a crystal violet dye and they found a significant reduction in the biofilm growth when the presence of MIP >80%. This process of sensing bacterial numbers through signal molecule concentration is termed quorum sensing (93). The aim is to one day apply this system to a wound dressing, creating a smart, sensory dressing that has the ability to detect an increase in bacterial number and prevent the formation of biofilms, by sequestering associated biofilm signal molecules.

These smart dressings are still, however, in their infancy and it may be some time before commercialisation is attained. The inevitable costs of these dressings could also cause further retardation in this area.

CONCLUSION

Effective management of large volumes of exudates from wide variety of wounds continues to be an ongoing challenge for the researchers as well as wound dressing manufacturers. Modern dressings have come a long way since their humble beginning and this is largely due to the greater understanding of the physiological characteristics of wounds and the availability of a broad range of suitable materials used for wound dressing applications. Claims and counter claims aside, modern dressings have, by and large, served their purpose and have reached the limits of their functionality in terms of both wound management and treatment. Next generation wound dressings intend to push these boundaries to new heights by interacting at the cellular level of the exuding wound to treat underlying causes. These works are still in their infancy and have many clinical and biological hurdles to cross before they are accepted within the main stream healthcare arena. However, given the interdisciplinary nature of science and the professionals engaged in these areas today, progress in this newly found paradigm will continue and before long, multifaceted dressings with superior properties, will become widely available.

Key Points

- smart wound dressings are being developed that have the ability to detect and report pathogenic bacterial colonisation sense when a wound has become infected which can lead to biofilm formations which are notoriously difficult to treat
- modern dressings have, by and large, served their purpose and have reached the limits of their functionality in terms of both wound management and treatment
- next generation wound dressings intend to push these boundaries to new heights by interacting at the cellular level of the exuding wound to treat underlying causes
- given the interdisciplinary nature of science and the professionals engaged in these areas today, progress in this newly found paradigm will continue and before long, multifaceted dressings with superior properties, will become widely available

REFERENCES

1 Polak F, Clift M, Bower L, Sprange K. Buyers' guide: advanced wound dressings (CEP08038).

London: NHS Purchasing and Supply Agency, 2008:90.
2 MeReC Bulletin. Evidence-based prescribing of advanced wound dressings for chronic wounds in primary care. MeReC Bull 2010;21.
3 Horken L, Stansfield G, Miller M. An analysis of systematic reviews undertaken on standard advanced wound dressings in the last 10 years. J Wound Care 2009;18:298–304.
4 Chaby G, Senet P, Vaneau M, Martel P, Guillaume JC, Meaume S, Teot L, Debure C, Dompmartin A, Bachelet H, Carsin H, Matz V, Richard JL, Rochet JM, Sales-Aussia N, Zagnoli A, Denis C, Guillot B, Chosidow O. Dressings for acute and chronic wounds. Arch Dermatol 2007;143:1297–304.
5 Winter GD. Formation of the scab and the rate of epithelisation of superficial wounds in the skin of the young domestic pig. Nature 1962;193:293–4.
6 Gamgee J. Absorbent and medicated surgical dressings. Lancet 1880;1:127.
7 Hinman CD, Maibach H. Effects of air exposure and occlusion on experimental human skin wounds. Nature 1963;200:377–8.
8 Field CK, Kerstein MD. Overview of wound healing in a moist environment. The American Journal of Surgery 1994;167 Suppl 1:2–6.
9 Thomas S. Wound exudate. In: Thomas S, editor. Surgical dressings and wound management. Cardiff, South Wales: Medetec, 2010:39–42.
10 White R. Managing exudate. Nurs Times 2001;97: 11–13.
11 Cutting KF. Wound exudate. In: White RJ, editor. Trends in wound care. Vol. 3. Dinton Salisbury: Quay Books, 2004.
12 Beldon P. Versiva® XC™ gelling foam dressing and the control of moderate to high exudate. Wounds UK 2008;4:74–7.
13 Woodall RD. Tissue viability. Living with leg ulcers: a patient's personal experience. Nurs Stand 1996;10:52.
14 Anderson I. Practical issues in the management of highly exuding wounds. Prof Nurse 2002;18:145–8.
15 Kujath P, Michelsen A. Wounds – from physiology to wound dressing. Dtsch Arztebl Int 2008;105:239–48.
16 Wolcott RD, Rhoads DD, Bennett ME, Wolcott BM, Gogokhia L, Costerton JW, Dowd SE. Chronic wounds and the medical biofilm paradigm. J Wound Care 2010;19:52–3.
17 Adderley U. Wound exudate: what it is and how to manage it. Wound Essent 2008;3:8–13.
18 Cameron J. Dermatological changes associated with venous leg ulcers. Wounds Essent 2007;2:60–6.
19 Dealey C. The physiology of wound healing. In: Dealey C, editor. The care of wounds: a guide for nurses. 2nd edn. Oxford: Blackwell, 1999:1–9.
20 Thomas S. Assessment and management of wound exudate. J Wound Care 1997;6:327–330.
21 Dowsett C. Moisture in wound healing: exudate management. Brit J Commun Nurs 2011;16:6–12.
22 Dealey C. Wound management products. In: Dealey C, editor. The care of wounds: a guide for nurses. 2nd edn. Oxford: Blackwell, 1999:68–95.
23 Grant GT, Morris ER, Rees DA, Smith PJC, Thom D. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Lett 1973;32:195–8.
24 Stashak TS, Farstvedt E, Othic A. Update on wound dressings: indications and best use. Clin Tech Equine Pract 2004;3:148–63.
25 Blair SD, Jarvis P, Salmon M, McCollum C. Clinical trial of calcium alginate haemostatic swabs. Br J Surg 1990;77:568–70.
26 Timmons J. Alginates as haemostatic agents: worth revisiting? Wounds UK 2009;5:122–5.
27 Thomas A, Harding KG, Moore K. Alginates from wound dressings activate human macrophages to secrete tumour necrosis factor-α. Biomaterials 2000;21:1797–802.
28 Thomas S. Polysaccharide fibre dressings. In: Thomas S, editor. Surgical dressings and wound management. Cardiff, South Wales: Medetec, 2010:237–70.
29 Vermeulen HH, Ubbink DT, Goossens A, de Vos R, Legemate DA. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. Br J Surg 2005;6:665–72.
30 Qin Y. Advanced wound dressings. J Text Inst 2001;92:127–38.
31 Barnea Y, Weiss J, Gur E. A review of the applications of the hydrofiber dressing with silver (Aquacel Ag®) in wound care. Ther Clin Risk Manag 2010;6:21–7.
32 Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, Amery CM, Edmonds ME, Gibby OM, Johnson AB, Jones GR, Masson E, Patmore JE, Price D, Rayman G, Harding KG. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technol Assess 2009;13.
33 Hampton S. Dressing for the occasion. Nurs Times 1999;95:58–60.
34 Trengove NJ, Stacey MC, MacAuley S, Bennett N, Gibson J, Burslem F, Murphy G, Schultz G. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Rep Regen 1999;7:442–52.
35 Thomas S. Hydrocolloids: a guide to the composition, properties and uses of hydrocolloid dressings and the commercial presentations available. J Wound Care 1992;1:27–30.
36 Pudner R. Hydrocolloid dressings in wound management. J Commun Nurs 2001;15:44–8.
37 Foster AVM, Spencer S, Edmonds ME. Deterioration of diabetic foot lesions under hydrocolloid dressings. Pract Diabetes Int 1997;14:m62–4.
38 Mcintosh C. Are hydrocolloid dressings suitable for diabetic foot ulcers? Wound Essent 2007;2:170–2.
39 Seheiz M, Rauterberg A, Weib J. Allergic contact dermatitis from hydrocolloid dressings. Contact Dermat 1996;34:146.
40 Singh A, Halder S, Chumber S, Misra MC, Sharma LK, Srivastava A, Menon GR. Meta-analysis of randomized controlled trials on hydrocolloid occlusive dressing versus conventional gauze dressing in the healing of chronic wounds. Asian J Surg 2004;27:326–32.

41 Bouza C, Saz Z, Munoz A, Amate JM. Efficacy of advanced dressings in the treatment of pressure ulcers: a systematic review. J Wound Care 2005;14:193–9.
42 Palfreyman S, Nelson EA, Michaels JA. Dressings for venous leg ulcers: systematic review and meta-analysis. BMJ 2007;335:244–8.
43 Lawrence JC. The use of iodine as an antiseptic agent. J Wound Care 1998;7:421–5.
44 Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, Vidor G, Braverman LE, Medeiros-Neto G. Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid 1998;8:83–100.
45 Bianchi J. Cadexomer-iodine in the treatment of venous leg ulcers: what is the evidence? J Wound Care 2001;10:225–9.
46 Archbold PG, Fitzpatrick JJ, Stewart BJ. Annual review of nursing research. Geriatric Nurs Res 2002;20:49.
47 Gottrup F, Apelqvist J. The challenge of using randomised trials in wound healing. Br J Surgery 2010;97:303–4.
48 Walker M, Lam S, Pritchard D. Biophysical properties of a Hydrofiber® cover dressing. Wounds UK 2010;6.
49 Brantigan CO. The history of understanding the role of growth factors in wound healing. Wounds 1996;8:78–90.
50 Lobmann R, Zemlin C, Motzkau M, Reschke K, Lehnert H. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Compl 2006;20:329–35.
51 Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg 2002;137:822–7.
52 Cullen B, Watt PW, Lundqvist C, Silcock D, Schmidt RJ, Bogan D, Light ND. The role of oxidised regenerated cellulose/collagen in chronic wound repair and its potential mechanism of action. Int J Biochem Cell Biol 2002;34:1544–56.
53 Wiegand C, Heinze T, Hipler UC. Comparative in vitro study on cytotoxicity, antimicrobial activity, and binding capacity for pathophysiological factors in chronic wounds of alginate and silver-containing alginate. Wound Repair Regen 2009;17:511–21.
54 Mason J, O'Keeffe C, Hutchinson A, McIntosh A, Young R, Booth A. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. II: treatment. Diabetic Med 1999;16:889–909.
55 Waldrop J, Doughty D. Wound healing physiology. In: Bryant RA, editor. Acute & chronic wounds: nursing management. 2nd edn. Missouri: Mosby, 2000:17–39.
56 Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger LJ, Holtzin L, Schultz GS, Jurkiewicz MJ, Lynch JB. Enhancement of wound healing by topical treatment with epidermal growth factor. New Engl J Med 1989;321:76–9.
57 Ulubayram K, Cakar AN, Korkusuz P, Ertan C, Hasirci N. EGF containing gelatin-based wound dressings. Biomaterials 2001;22:1345–56.
58 Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: a practical approach to the care of non-healing wounds and wound care dressings. J Am Acad Dermatol 2008;58:185–206.
59 Badylak SF. Extracellular matrix as scaffolds for tissue engineering in veterinary medicine: applications to soft tissue healing. Clin Tech Equine Pract 2004;3:173–81.
60 Hardwicke J, Schmaljohann D, Boyce D, Thomas D. Epidermal growth factor therapy and wound healing – past, present and future perspectives. Surgeon 2008;6:172–7.
61 Baxter H. Surgical wounds and their care. Maxwell DH, editor. Surgical techniques in obstetrics and gynaecology. London: Churchill Livingstone, 2003:27–40.
62 Michaels JA, Campbell B, King B, Palfreyman SJ, Shackley P, Stevenson M. Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). Br J Surg 2009;96:1147–56.
63 Vermeulen H, van Hattem JM, Storm-Versloot MH, Ubbink DT, Westerbos SJ. Topical silver for treating infected wounds. Cochrane Database Syst Rev 2007;1:CD005486.
64 Pallai CKS, Paul W, Sharma CP. Chitin and chitosan polymers: chemistry, solubility and fibre formation. Prog Polym Sci 2009;34:641–78.
65 Rouget C. Des substances amylacees dans le tissue des animaux, specialement les Atricules (Chitine). Comp Rend 1859;48:792–5.
66 Lee DS, Jeong SY, Kim YM, Lee MS, Ahn CB, Je JY. Anti-bacterial activity of amino derivatized chitosan against methicillin Resistant *Staphylococcus Aureus* (MRSA). Bioorg Med Chem 2009;17:7108–12.
67 Liu H, Du Y, Wang X, Sun L. Chitosan kills bacteria through cell membrane damage. Int J Food Microbiol 2004;95:147–55.
68 Vallapa N, Wiarachai O, Thongchul N, Pan J, Tangpasuthadol V, Kiatkamjornwong S, Hoven VP. Enhancing antibacterial activity of chitosan surface by heterogeneous quaternization. Carbohyd Polym 2011;83:868–75.
69 Kong M, Chen XG, Xing K, Park HJ. Antimicrobial properties of chitosan and mode of action: a state of the art review. Int J Food Microbiol 2010;144:51–63.
70 Muzzarelli RAA. Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone. Carbohyd Polym 2009;76:167–82.
71 Park PJ, Je JY, Jung WK, Ahn CB, Kim SK. Anticoagulant activity of heterochitosans and their oligosaccharide sulphates. Eur Food Res Technol 2004;219:529–33.
72 Ohshima Y, Nishino K, Yonekura Y, Kishimoto S, Wakabayashi S. Clinical application of chitin non-woven fabric as wound dressing. Eur J Plast Surg 1987;10:66–9.

73 Okamoto Y, Kawakami K, Miyatake K, Morimoto M, Shigemasa Y, Minami S. Analgesic effects of chitin and chitosan. Carbohyd Polym 2002;49:249–52.
74 Jeon YJ, Kim SK. Antitumor activity of chitosan oligosaccharides produced in ultrafiltration membrane reactor system. J Microbiol Biotechnol 2002;12:503–7.
75 Aranaz I, Megibar M, Harris R, Paños I, Miralles B, Acosta N, Galed G, Hera A. Functional characterization of chitin and chitosan. Curr Chem Biol 2009;3:203–30.
76 Knill CJ, Kennedy JF, Mistry J, Miraftab M, Smart G, Groocock MR, Williams HJ. Alginate fibres modified with unhydrolysed and hydrolysed chitosans for wound dressings. Carbohyd Polym 2004;55:65–76.
77 Tamura H, Tsuruta Y, Tokura S. Preparation of chitosan-coated alginate filament. Mater Sci Eng C 2002;20:143–7.
78 Fan L, Du Y, Zhang B, Yang J, Zhou J, Kennedy JF. Preparation and properties of alginate/carboxymethyl chitosan blend fibres. Carbohyd Polym 2006;65:447–52.
79 Kucharska M, Niekraszewicz A, Wiśniewska-Wrona M, Brzoza-Malczewska K. Dressing sponges made of chitosan and chitosan-alginate fibrids. Fibres Textiles East Eur 2008;16: 109–13.
80 Dai M, Zheng X, Xu X, Kong X, Li X, Guo G, Luo F, Zhao X, Wei YQ, Qian Z. Chitosan-alginate sponge: preparation and application in curcumin delivery for dermal wound healing in rat. J Biomed Biotechnol 2009;2009:595126.
81 Murakami K, Aoki H, Nakamura S, Nakamura SI, Takikawa M, Hanzawa M, Kishmoto S, Hattori H, Tanaka Y, Kiyosawa T, Sato Y, Ishihara M. Hydrogel blends of chitin/chitosan, fucoidan and alginate as healing-impaired wound dressings. Biomaterials 2010;31:83–90.
82 Dong Y, Liu HZ, Xu L, Li G, Ma ZN, Han F, Yao HM, Sun YH, Li SM. A novel CHS/ALG bi-layer composite membrane with sustained antimicrobial efficacy used as wound dressing. Chin Chem Lett 2010;21:1011–14.
83 Cowan T. Wound care handbook. London: Mark Allen Healthcare, 2010–1.
84 Visavadia BG, Honeysett J, Danford MH. An effective treatment for chronic wound infections. Br J Oral and Maxillofac Surg 2008;46:55–6.
85 Molan PC. Re-introducing honey in the management of wounds and ulcers: theory and practice. Ostomy Wound Manage 2002;48:28–40.
86 Dunford C, Cooper MP. Using honey as a dressing for infected skin lesions. Nursing Times 2000;96(14 Suppl):7–9.
87 Lusby PE, Coombes A, Wilkinson JM. Honey: a potent agent for wound healing? J Wound Ostomy Cont Nurs 2002;29:295–300.
88 Okhiria O, Henriques A, Burton N, Peters A, Cooper RA. The potential of Manuka honey for the disruption of biofilms produced by strains of Pseudomonas aeruginosa isolated from wounds. Dublin, Ireland: September 6–9, Poster presentation at the 155th Meeting of the Society for General Microbiology, 2004.
89 Haynes JS. Properties of honey: its mode of action and clinical outcomes. Wounds UK 2011;7:50–7.
90 Olson ME, Ceri H, Morck DW, Buret AG, Read RR. Biofilm bacteria: formation and comparative susceptibility to antibiotics. Can J Vet Res 2002;66:86–92.
91 Philips PL, Wolcott RD, Fletcher J, Schultx GS. Biofilms made easy. Wounds Int 2010;1:1–6.
92 Zhou J, Tun TN, Hong SH, Mercer-Chalmers JD, Laabej M, Young AE, Jenkins AT. Development of a prototype wound dressing technology which can detect and report colonization by pathogenic bacteria. Biosens Bioelectron 2011;30:67–72.
93 Piletska EV, Stavroulakist G, Larcombet LD, Whitcombet MJ, Sharma A, Primroset S, Robinson GK, Piletskyt SA. Passive control of Quorum Sensing: Prevention of *Pseudomonas aeruginosa* Biofilm Formation by Imprinted Polymers. Biomacromolecules 2011;12:1067–71.