A renewed look at silver dressings for wound infections: Ag Oxysalts technology

Abstract

Wound infection is an important complicating factor in the wound healing process, and infections can be even more complex and difficult to manage in the case of wounds with biofilms. Silver has been used to treat infected wounds for a long time now, and the strength of the product depends on the number of Ag ions, where the greater the number of ions, the higher and faster the reactivity is. Ag Oxysalts technology—used in 3M Kerracontact Ag dressing—has three times more ions than standard silver dressings. The technology also does not show the typical disadvantages of silver, such as cytotoxicity and systemic toxicity. This article discusses the use of Ag Oxysalts technology for infected wounds and presents case studies to support the efficacy of this product in promoting wound healing.

■ Wound infection ■ Silver dressings ■ Ag Oxysalts technology ■ Antimicrobial resistance ■ Silver toxicity

Luxmi Dhoonmoon, Hayley Turner-Dobbin, Karen Staines

Luxmi Dhoonmoon, Nurse Consultant Tissue Viability (Goodall), Central and North West London NHS Foundation Trust

Hayley Turner-Dobbin, Clinical Delivery Lead: Wound and R&D, Accelerate CIC

Karen Staines, Director: Education and Research/ Clinical Lead Wound Care, Accelerate CIC

luxmi.dhoonmoon@nhs.net

h.turner-dobbin@nhs.net

karen.staines@nhs.net

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The prevalence of acute and chronic wounds in the UK has been predicted to increase by 9% and 12% per year, respectively (Guest et al, 2017). As suggested previously, wound care should be viewed as a specialised segment of healthcare that requires clinicians with specialist training, because there is potential for better patient management and wound care product selection that would improve outcomes and reduce costs (Guest et al, 2015). Managing infection is one of the main complicating factors for health professionals in wound care. From the time of wounding, all open wounds are contaminated with microbes, but these become harmful to healing if the wound moves from bacterial balance (organisms present but not invasive) to imbalance (local, spreading and systemic infection), where damage to tissue occurs (Sibbald et al, 2003). As wound bacteria multiply, the normal inflammatory response phase is prolonged because harmful enzymes, oxygen free radicals and inflammatory cells are released; these eventually break down tissue in the wound and cause it to deteriorate (Edwards-Jones and Flanagan, 2013). Therefore, it is imperative for health professionals to understand the risk factors, signs and symptoms of wound infection.

A comprehensive wound assessment, where diagnosis of wound infection is primarily based on the clinician's assessment of the individual, the wound and peri-wound tissue and host responses—such as systemic inflammatory response—aids early detection and timely treatment. This article will discuss the use of Ag Oxysalts technology as an antimicrobial to manage and prevent wound infection.

The International Wound Infection Institute (IWII) (2016) defined infection as 'the invasion of a wound by proliferating microorganisms to a level that invokes a local and/or systemic response in the host'. It is well acknowledged that it is more

than just the presence of bacteria that leads to adverse events in wounds. There are several stages described in the IWII document, which guides clinicians on how to respond when conducting a holistic assessment (IWII, 2016).

Signs and symptoms of wound infection

Textbook criteria for any infection are: heat, swelling, pain and redness. However, although some individuals present with classic (overt) signs and symptoms of wound infection, for immunocompromised individuals and those with chronic wounds, early detection of infection relies on identification of more subtle or covert signs of infection. *Table 1* describes the different signs and symptoms of infection.

Effective management of wound infection

In order to manage wound infection effectively, it is important to make an appropriate diagnosis of the infection. There are gold-standard methods to be used when assessing and diagnosing wound infection, including clinical professional judgement and clinical presentation of the wound and/or patient; however, diagnosis depends on both clinical expertise and available methods (Wounds UK, 2020).

Clinicians also need to consider behavioural changes by using the back-to-basics approach to ensure appropriate hand hygiene, aseptic non-touch technique and wound hygiene to minimise any further contamination.

Health professionals also need to be aware of increasing antibiotic resistance and the lack of development of new classes of antibiotics (World Health Organization, 2017). Hence, Percival et al (2005) stated that, unlike antibiotics, which have one specific target in a bacterial cell, antimicrobial dressings that have a broader spectrum of activity are less likely to induce resistance. The IWII reinforced the principle that prompt diagnosis and treatment of infection promotes wound healing and minimises the impact on the individual, their carers and health systems (IWII, 2016). This was also supported by Guest et al (2015), who mentioned that effective diagnosis and wound care management would help to minimise costs and improve patient outcomes. While, generally, thorough wound hygiene technique and wound debridement will facilitate eradication of microbes, topical antimicrobials are also recommended in order to prevent (or at least delay) attachment of planktonic microbes and to kill any organisms in disrupted or dispersed biofilm. It is imperative to optimise and conserve all antimicrobial interventions in wound management. *Table 2* describes all available antimicrobials in practice for wound infection management (IWII, 2016).

Until fairly recently, a limited range of antimicrobial products have been available to treat wound infections and reduce bacterial burden (Vermeulen et al, 2010). One of them was iodine—notably Inadine—which was introduced in the 1980s and contains 10% povidone iodine with an equivalent of 1% available iodine (Sibbald et al, 2017). Today, there are several alternative antimicrobial wound products on the market, including silver, honey, enzyme alginogel and polyhexamethylene biguanide (PHMB).

Table 1. Signs and symptoms associated with stages of the wound infection continuum

Contamination	Colonisation	Local infection		Spreading infection	Systemic infection
All wounds may acquire microorganisms. If suitable nutritive and physical conditions are not available for each microbial species, or they are not able to successfully evade host defenses, they will not multiply or persist; their presence is therefore only transient, and wound healing is not delayed	Microbial species successfully grow and divide, but do not cause damage to the host or initiate wound infection	Covert (or subtle) signs of local infection: ■ Hypergranulation (excess 'vascular' tissue) ■ Bleeding, friable granulation tissue ■ Epithelial bridging and pocketing in granulation tissue ■ Wound breakdown and enlargement ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	Overt (classic signs of local infection): ■ Erythema ■ Local warmth ■ Swelling ■ Purulent discharge ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	■ Extending in duration with or without erythema ■ Lymphangitis ■ Crepitus ■ Wound breakdown/ dehiscence with or without satellite lesions ■ Malaise/ lethargy or nonspecific general deterioration ■ Loss of appetite ■ Inflammation, swelling of lymph glands	■ Severe sepsis ■ Septic shock ■ Organ failure ■ Death

Source: International Wound Infection Institute, 2016

Table 2. Antimicrobial agents used to treat wound infections

Antimicrobial agents	Type	Biofilm efficacy	Guidance for us
Enzyme alginogel	Alginate gel with two enzymes: ■ Lactoperoxidase ■ Glucose oxidase	■ Prevents formation of biofilms at concentrations M0.5% (w/v) ■ Inhibits growth of established biofilms at higher concentrations ■ Does not disrupt biofilm biomass	■ Concentrations of alginate of 3% and 5% depending on level of exudate
Iodine (povidone or cadexomer)	■ Solution ■ Impregnated wound dressings ■ Powder and paste	■ Inhibits development of new biofilm ■ Eradicates young biofilm colonies ■ Significantly reduces mature biofilm colonies	■ Contraindicated in individuals sensitive to iodine or with thyroid or renal disorders ■ Contraindicated in those with extensive burns
Honey	■ Medical grade ■ Honey impregnated dressings	■ Inhibits biofilm growth ■ Reduces biofilm colony formation ■ Inhibits quorum sensing of biofilm, therefore ability to proliferate	■ Select products that have been gamma irradiated ■ Leptospermum species is more effective than other types
Silver	■ Salts (e.g. silver sulphadiazine, silver nitrate, silver sulphate, silver CMC) ■ Metallic (e.g. nanocrystalline silver-coated nylon fibres) ■ Impregnated wound dressings	■ Denatures existing bacterial biofilm in concentrations over 5 μg/ml	■ Change more frequently in wounds with heavy exudate ■ Avoid in individuals with silver sensitivities
Ionic silver combined EDTA and BEC (anti-biofilm agents)	■ CMC gelling dressing impregnated with ionic silver enhanced with EDTA and BEC	■ Combines antibiofilm and antimicrobial components that work in synergy to disrupt biofilm and expose associated microorganisms to the broad-spectrum antimicrobial action of ionic silver ■ Eradicates mature biofilm within 5 days ■ Prevents biofilm formation ■ Associated improvement in healing rates	■ Change more frequently in wounds with heavy exudate ■ Avoid in individuals with sensitivities to silver, EDTA or BEC
Surfactant	■ Concentrated surfactant gels with antimicrobial preservatives	■ Prevents biofilm formation ■ Increases antibiotic efficacy ■ Eradicates mature biofilm	■ Can be used between and post-debridement to prevent re-establishment of biofilm ■ May require daily application for the first few days

Source: IWII, 2016. CMC=carboxymethyl cellulose; EDTA=ethylenediaminetetraacetic acid; BEC=benzyloxyethyl cellulose

All antimicrobial wound products should be used based on regular individual assessment. Considerable research recommends the use of a 2-week challenge with a topical antiseptic, as this allows sufficient time for the topical agent to exert a beneficial activity (Percival et al, 2005; IWII, 2016). A wound that does not progress despite the use of an antimicrobial agent and remains chronic could be indicative of the presence of biofilm (IWII, 2016). It is now widely accepted that biofilm is present in 70–100% of chronic wounds (Malone et al, 2017). Biofilms are not visible to the naked eye and can be difficult to confirm unless a biopsy is taken (Wounds UK, 2020). This will involve regular physical debridement and cleansing to remove debris as part of standard care. However, it will also require the use of an antimicrobial with proven effect against mature biofilms in clinical practice. Hence, the use of a highly effective

antimicrobial is required for shorter-duration treatments to kill bacteria, thereby minimising the risk of inducing microbial resistance (Ayello et al, 2012).

Role of silver in managing wound infection

Silver is unreactive and does not kill bacteria in its metallic form. It is only effective at killing bacteria when it is missing electrons and in its ionic state. The more electrons that are missing, the more reactive it becomes and the greater is its ability to disrupt the normal function of bacteria. Several silver dressings are available on the market to reduce bioburden and combat wound infection. The proven advantages of silver dressings are numerous, with one being localised antimicrobial wound therapy, as opposed to whole-body systemic exposure, and immediate access to the wound bed in bactericidal concentration, which would reduce the overall use of antibiotics (Lipsky and Hoey, 2009).

Unfortunately, a lack of understanding about the mode of action of silver dressings may have led to their inappropriate use, for example, continued use after the infection has cleared or as prophylaxis against infection, thereby increasing local wound dressing costs (Young et al, 2016). Silver resistance and toxicity are also among the reported disadvantages, where raised systemic levels of silver are noted, although they reduce once silver is discontinued, for example, with use of silver over prolonged periods for large burn wounds. Other mild adverse effects of silver include allergy or skin staining.

Choosing the right silver dressing

The main criteria a silver dressing will need to meet are to:

- Provide sustained broad-spectrum antibacterial action
- Be efficacious against biofilm
- Be efficacious in the presence of exudate
- Have adequate absorptive capacity and conformability; need for a secondary dressing and recommended dressing change frequency also must be considered
- Be safe.

Ag Oxysalts Technology

3M™ Kerracontact™ Ag, a ground-breaking, patented silver wound dressing using Ag oxysalts technology is the first dressing to use silver in its most active state (Lemire et al, 2015). It is a unique silver wound dressing that acts quickly (within 1 week) against bacteria and destroys biofilms (Warde, 2018). This swiftness of response means that, instead of targeting for a '2-week challenge', clinicians can reassess wounds for reduction in the signs and symptoms of infection after just 1 week.

The AG Oxysalts technology used in 3M Kerracontact Ag is a unique silver technology that facilitates fast and effective bactericidal activity and an ability to disrupt biofilms and prevent reformation within 24 hours of application (Thomason and Beasley, 2015), while also being cost effective and patient friendly (Crawford Healthcare, 2015).

Ag Oxysalts is designed with three missing electrons (Ag3+), while other silver dressings are only missing one electron (Ag1+). Thus, it offers enhanced reactivity, which underlies its fast and powerful antimicrobial activity (Thomason et al, 2018). Oxygen is vital for wound healing, and adequate wound tissue oxygenation can trigger healing responses. AG Oxysalts technology produces oxygen for wound healing in two ways: from the natural breakdown of Ag Oxysalts technology and the breakdown of hydrogen peroxide (Thomason et al, 2018).

Effectiveness of AG Oxysalts

When in contact with an aqueous solution, for example, wound exudate, Ag Oxysalts release three types of silver ions, which provides a sustained silver ion release for the duration of dressing wear while maintaining the antimicrobial activity (Wounds UK, 2018). This is a recommended point of clinical practice to ensure continuous antimicrobial effect during the treatment and minimise wound disturbance. In addition, Ag Oxysalts has also been found to be non-toxic, showing no cytotoxicity, systemic toxicity, irritation and sensitisation in laboratory tests (Kalan et al, 2017), indicating that it is safe for application in clinical practice.

An in vitro study conducted by Lemire et al (2015) found that Ag2+ and Ag3+ ions effectively eradicate organisms growing planktonically or in a mature biofilm state and prevent biofilm reformation at low concentrations, which reduces the risk of toxicity, as well as the overall exposure to silver. Evidence from several in vitro and in vivo studies has demonstrated that Ag Oxysalts technology is proven to quickly kill 99.999% of a broad spectrum of bacteria (Crawford Healthcare, 2015), as described in *Box 1*.

In a 50-centre study by Motta et al (2012), a dramatic response in terms of bacterial elimination and biofilm disruption was seen within 7 days, which indicates that the wear time of the dressing was up to 7 days. This was further supported by an in vitro study by Miller et al (2013), who found that mature biofilms of *Pseudomonas aeruginosa* and *Staphylococcus aureus* showed a log 4 reduction in 4 hours or less (in a simulated wound fluid), with a sustained bactericidal effect over 7 days. No viable bacteria were retrieved after 24 hours, and the biofilms were disrupted, allowing the bacteria to be killed quickly and effectively.

Indications for use

3M Kerracontact Ag can be used for acute and chronic wounds that are locally infected or at high risk of infection, including burns, leg ulcers, pressure ulcers, diabetic foot ulcers and surgical wounds (Crawford Healthcare, 2015). From a clinician point of view, following the IWII (2016) document, 3M Kerracontact Ag can be used in the stage between colonisation and local infection to reduce the overt and covert signs of infection. It can also be used immediately following debridement if a biofilm is suspected due to its effectiveness in rapid disruption of biofilm and prevention of reformation (Miller et al, 2013).

Following holistic assessment and where standard care has failed, 3M Kerracontact Ag can be applied directly to the wound bed, wet or dry. Since the silver does not need to be activated

Box 1. Organisms against which Ag Oxysalts technology is effective

Gram negative
- *Acinetobacter baumannii*
- *Escherichia coli*
- *Pseudomonas aeruginosa*

Gram positive
- *Corynebacterium striatum*
- *Enterococcus faecalis*
- *Enterococcus faecalis VRE*
- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- Methicillin-resistant *Staphylococcus aureus*

Fungus
- *Candida albicans*
- *Aspergillus niger*

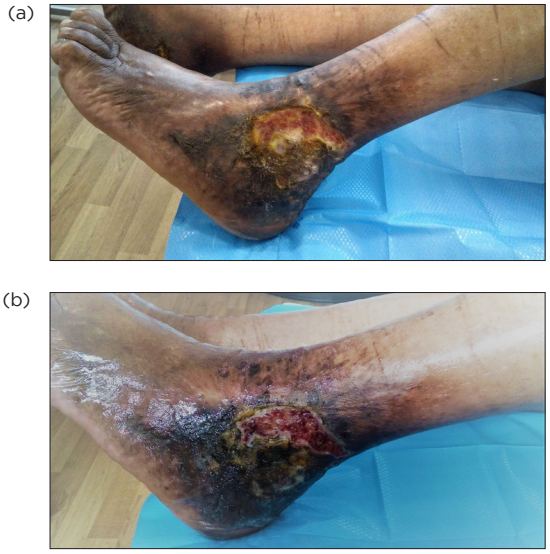

Figure 1. Case 1. (a) Wound over the left malleolus at presentation. (b) Wound at 4 weeks after treatment with Kerracontact Ag

in any way, the dressing does not need to be moistened. It can be cut to wound size and shape, and a secondary dressing will be required in most cases. Depending on clinical assessment, the secondary dressing may require changing more often, but the Kerracontact Ag dressing can be left in situ for up to 7 days. There is no evidence of skin staining or toxicity reported from use of Kerracontact Ag to date and no patient discomfort mentioned in any studies or case reports (Motta et al, 2012).

Case studies

Case 1

A 56-year-old woman with sickle cell disease presented with multiple ulcerations to the medial and lateral malleolus. The size of the wound over the lateral left malleolus at presentation was 6.6 x 2 cm, and the patient-reported pain score was 6/10 (*Figure 1a*). The appearance of the wound bed was poor, with 60% granulation tissue and 40% slough.

The patient was started on Kerracontact Ag and short-stretch compression bandaging, and she attended for twice weekly dressing changes. After 4 weeks of treatment with Kerracontact Ag, the size of the wound reduced to 4.4 x 2 cm (*Figure 1b*), and the pain score was 7/10. This increase in the pain score was not uncommon for this patient, as she experienced pain all over her body during this visit and subsequently attended the haematology unit for management of sickle cell crisis. The wound bed appeared much healthier, with 90% granulation tissue and only 10% slough.

Although this patient was not followed up until her wounds had healed completely, the clinicians noted that the wound had shown considerable progress towards healing.

Case 2

A 51-year-old man presented with long-standing ulceration that had been non-healing for 4 years; the wounds would improve but then recur. The patient had a past medical history of sickle cell disease. At presentation, the pain score was 9/10, and the main wound measured 11.5 x 5.5 cm, with a depth of 0.2 mm (*Figure 2a*). The wound bed appeared poor with 100% slough. The patient was treated with Kerracontact Ag dressing, for which he was seen three times a week. After 4 weeks, the wound bed showed significant improvement in appearance; the slough was lifting, and small areas of granulation were now visible (*Figure 2b*). Further, the bridge between the main wound and the smaller one adjacent to it had widened. The size of the wound in week 4 was 10 x 4 cm, but it had insignificant depth. After 15 weeks of treatment with Kerracontact Ag, the main wound had improved significantly, and the smaller one adjacent to it had closed.

Case 3

A 56-year-old man presented to the complex wound clinic with a 6-year history of bilateral venous leg ulcers (VLUs). Both legs were ulcerated to the gaiter area, but the left wound was worse than the right leg, with a high level of thick, green exudate, pain reported to be worse during dressing change and malodour (*Figure 3a*). The wounds were found to be locally infected (methycillin-resistant *S. aureus* detected on a swab test and presence of *P. aeruginosa* indicated by the green exudate), and the patient had a past medical history of hypertension, hypercholesterolaemia and type 2 diabetes mellitus.

The patient was treated with several courses of oral antibiotics before being referred to the complex wound clinic. On assessment in the clinic, he was started on an antimicrobial dressing (which was changed three times a week), with the aim of decolonising the wound, reducing bioburden and reducing malodour. After 2 weeks, the wound bed had remained stagnant, and the pain level not reduced despite all standard care and compression bandages. Kerracontact Ag was

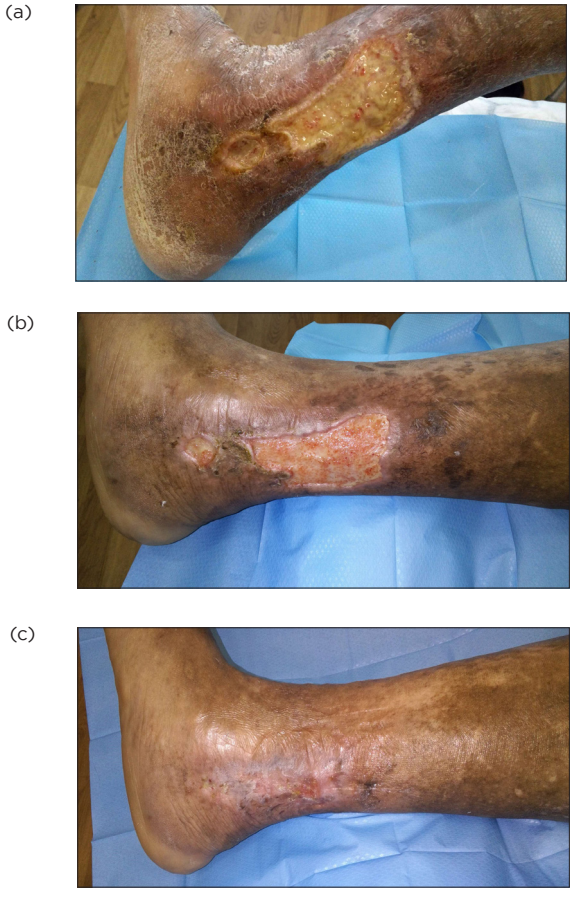

Figure 2. Case 2. (a) Wound on the left leg at presentation. (b) Wound at 4 weeks after treatment. (c) Wound at 15 weeks after treatment; the main wound is almost completely healed, and the lower wound has closed

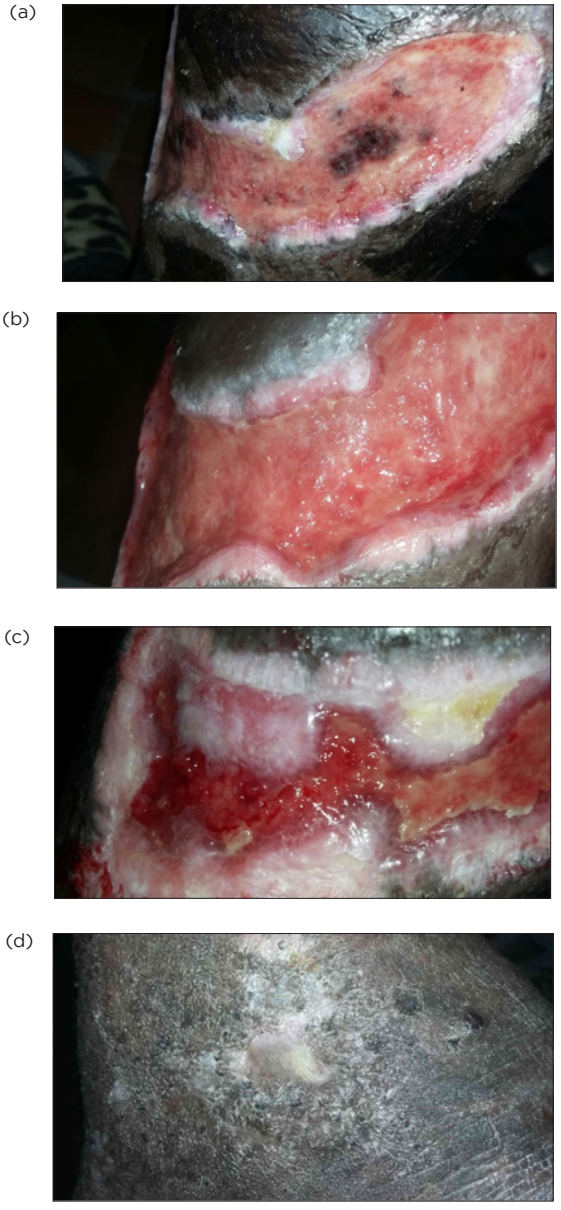

Figure 3. Case 3. (a) Wound at presentation. (b) Wound at 1 week after treatment with Kerracontact Ag. (c) Week 2 of Kerracontact Ag treatment. (d) Wound in week 8 of treatment

then started for 7 days, with the aim of treating the infection, and Kerramax Care was used as a secondary dressing for absorption under the compression.

At week 1 after starting Kerracontact Ag, pain was reported to be 6/10, and no analgesia was required when the dressing was changed (*Figure 3b*). The patient's mobility had improved, and he was eating and drinking better as the malodour was less. The Kerracontact Ag dressing was changed twice in the first week of use. Thereafter, it was left in situ, and only the secondary dressing was changed.

In week 2 of Kerracontact Ag use, the wound edges were contracting, and new epithelial tissue was present in the wound bed (*Figure 3c*). At that point, the patient did not experience any pain during dressing change and reported better sleep at night, as there was no pain or malodour. The patient arrived at the clinic wearing normal trousers instead of jogging trousers, as he felt more comfortable to dress up with no exudate or malodour. His quality of life had improved with the new dressing, and the impact was noticeable in just 1 week. After 2 weeks of Kerracontact Ag use, the dressing was discontinued, as no signs of infection was present, and treatment was stepped down to another formulary product suitable for the wound bed (*Figure 3d*).

Case 4

A 61-year-old women was admitted to care after abdominal surgery following trauma. She had a past medical history of hypertension, high cholesterol, rheumatoid arthritis and recent washout following an infected abdominal wound in the hospital.

On discharge to the community, she had negative pressure (VAC) in situ for exudate management and to speed up wound healing. The VAC therapy was discontinued, as the

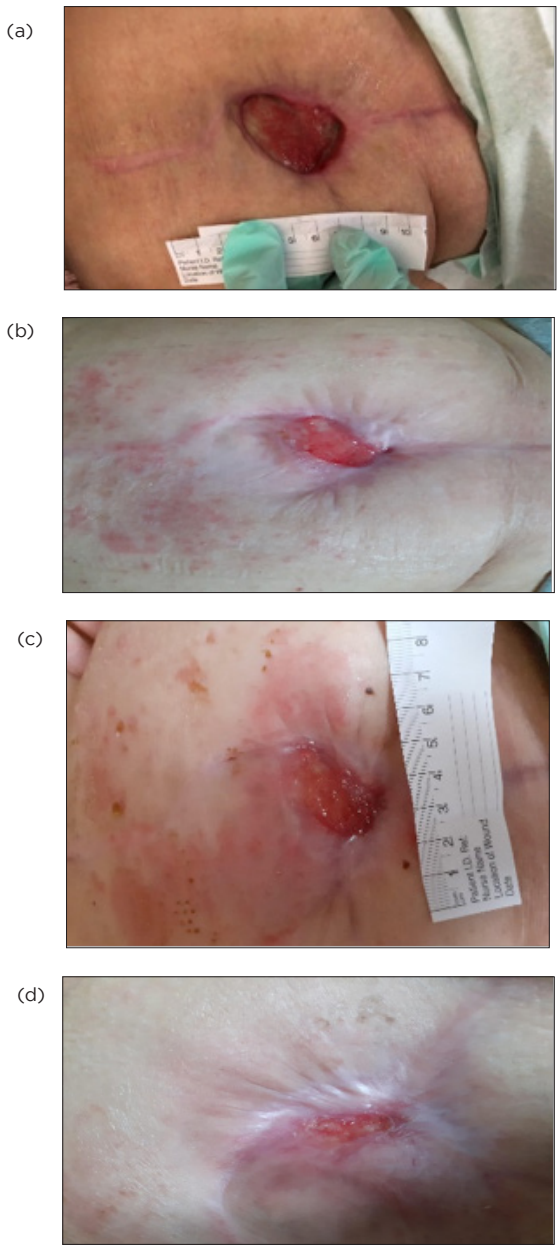

Figure 4. Case 4. (a) Wound at presentation. (b) Wound at 1 week after treatment with Kerracontact Ag. (c) Week 2 of Kerracontact Ag treatment. (d) Wound at 1 week after stopping Kerracontact Ag treatment

exudate level was low and the wound bed appeared stagnant (*Figure 4a*). On assessment by a tissue viability nurse, the wound bed was found to be dry and shiny, with no malodour or pain reported on dressing change. In order to disrupt the biofilm suspected in the wound bed, the wound was curetted using a Derma Curette, and Kerracontact Ag was started.

After 1 week of using Kerracontact Ag, healthy granulation tissue was present on the wound bed on assessment, and the edges were advancing (*Figure 4b*). No curetting was done, and Kerracontact Ag was re-applied for week 2 of treatment (*Figure 4c*). In week 3, despite stopping the Kerracontact Ag dressing, the wound bed progressed to healing, with all edges contracted and new epithelial tissue present (*Figure 4d*). This supports the findings of studies which demonstrated that Kerracontact Ag disrupts biofilm rapidly and prevents its reformation, thus improving the healing rate (Lemire et al, 2015). The patient was discharged from care with skin care advised.

KEY POINTS

- Silver dressings have been in use for infected wounds for a long time, but are associated with silver toxicity
- Considering global concerns around antimicrobial resistance, silver shows potential as it does not produce resistance in microorganisms
- Ag Oxysalt technology, which produces three silver ions instead of two, is more reactive and effective than regular silver dressings and shows no silver toxicity
- Since Ag Oxysalts technology allows for faster healing, it can contribute considerably to improving patients' quality of life and reducing the cost of infected wound treatment

Conclusion

The IWII document (IWII, 2016) is an excellent tool for clinicians to effectively diagnose and manage infection appropriately, although following national and local guidance is the priority. Clinical evidence of the effectiveness of Kerracontact Ag dressing continues to grow in practice, and many clinicians have opted to use Kerracontact Ag because of its fast and effective action in killing bacteria within just 7 days and its sustained bactericidal effect within these 7 days, hence reducing the 2-week challenge to 1 week only in some cases. The effectiveness of Kerracontact Ag on biofilm has also demonstrated its importance in the wound care world, as delayed healing and infection are often attributed to biofilm formation. The Kerracontact Ag should help overcome some of the problems encountered in clinical practice and achieve better health outcomes, thereby reducing the unnecessary use of antibiotics and corresponding costs, and improving patient's outcomes. **CWC**

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CPD REFLECTIVE QUESTIONS

- What are the overt and covert signs of local wound infection?
- What are the advantages and disadvantages of the use of silver for treating infected wounds?
- What important criteria must silver dressings meet before they can be used for an infected wound?