CONSENSUS ROUND TABLE MEETING 2018

# USING Ag Oxysalts™

## TO PREVENT & MANAGE WOUND INFECTION

Wounds UK

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# Foreword

Wounds affect large numbers of patients and produce a considerable socioeconomic burden. In 2012/2013, about 2.2 million patients were treated by the NHS in the UK for an acute or chronic wound at a cost of £4.5–5.1 billion (Guest et al, 2015). Timely healing of wounds can help to minimise impact on patients and contain costs. Wound infection or increased wound bioburden can cause or contribute to the delayed healing of wounds. The appropriate management of infection is therefore a key focus for clinicians treating wounds.

A wide range of antimicrobial silver preparations and dressings are used in the management of acute and chronic wounds and have an important role in antimicrobial stewardship. The form of metallic silver or silver compound and the dressing components used in an individual product influence antimicrobial activity and clinical effectiveness. Consequently, clinicians need a clear understanding of the properties of an individual product to ensure effective use.

Ag Oxysalts™ (silver oxynitrate) is a silver compound with unique properties that produce rapid, sustained, broad-spectrum antimicrobial activity. Ag Oxysalts is currently the only silver compound used in dressings to release $Ag^{+}$, $Ag^{2+}$ and $Ag^{3+}$ ions. A group of experts in wound management and microbiology met in November 2017 to:

- Discuss how the chemical properties of Ag Oxysalts relate to its antimicrobial activity and clinical performance
- Explore the potential impact of Ag Oxysalts dressings KerraContact™ Ag and KerraCel™ Ag (Crawford Healthcare) on wound healing
- Devise treatment pathways for the use of KerraContact Ag in a range of acute and chronic wound types.

The discussions at the meeting resulted in this document, which aims to provide clinicians with understanding of the unique chemistry of Ag Oxysalts and the information they need for appropriate use of KerraContact Ag in clinical practice to improve outcomes.


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# Silver, wounds and antimicrobial stewardship

The earliest use of silver for its antimicrobial properties was probably by the Ancient Greeks and Romans who used silver vessels to keep water fresh (Barillo & Marx, 2014). Following the successful topical use of silver in solutions or creams on burns from the 1960s onwards, dressings containing silver have been, and continue to be, developed and used in a wide range of acute and chronic wound types (International Consensus, 2012; Barillo & Marx, 2014).

However, there is uncertainty and confusion among clinicians and microbiologists about the antimicrobial action, safety, role and effectiveness of silver in the prevention and management of infection in wounds. In some instances, this has resulted in restricted availability of silver dressings. This is unfortunate for two main reasons.

Firstly, wounds are a significant problem in the UK: they affect large numbers of patients and result in considerable morbidity, mortality and cost to the NHS (Box 1) (Escandon et al, 2011; Norbury et al, 2016). Infection, considered to be a frequent cause of delayed healing (Guo & DiPietro, 2010; Leaper et al, 2015) (Table 1), further increases costs of acute and chronic wound care (Bennett et al, 2004; Hopkins et al, 2015; Badia et al, 2017). In common with implementation of best practice management of wounds, effective prevention and management of infection has the potential to improve healing rates. Indeed, it has been estimated that an increase of just 1% per annum over the current wound healing rate for all wound types would slow down the predicted increase in wound prevalence (Guest et al, 2017).

Secondly, awareness of increasing antibiotic resistance and the lack of development of new classes of antibiotics has led to calls at national, European and global levels for improved antimicrobial stewardship in an effort to reduce the incidence of antibiotic-resistant infections (NICE, 2015a; O'Neill et al, 2016; Lipsky et al, 2016; WHO, 2017; Baur et al, 2017). The mode of action of agents used in antimicrobial dressings, e.g. silver, is different from antibiotics: these agents usually have multiple sites of action within a microbial cell, unlike antibiotics which usually have one specific target in a bacterial cell. Consequently, they generally have a broader spectrum of activity than antibiotics and are less likely to induce resistance (Percival et al, 2005; Roberts et al, 2017).

As a result, the appropriate use of antimicrobial dressings, such as those containing silver, in the prevention and management of wound infection has the potential to reduce overall use of antibiotics and preserve antibiotics for essential treatment (Roberts et al, 2017). Furthermore, antimicrobial dressings have several potential benefits in comparison with systemic antibiotics: a relatively small amount of the antimicrobial agent can result in high local levels, even in the presence of arterial disease, and systemic side effects are avoided (Lipsky et al, 2016).

**BOX 1:** Examples of the burden of wounds in the UK

- It has been estimated that in 2012/2013 the NHS in the UK managed 2.2 million patients with an acute or chronic wound, at a cost of £4.5–£5.1 billion (Guest et al, 2015)
- In Wales, an analysis of routine data from general practices found the prevalence of chronic wounds to be 6% and that the cost of managing these wounds was £328.8 million (5.5% of total expenditure on the health service in Wales) (Phillips et al, 2016)
- An audit of hospitals in Wales found that 30.3% of hospital inpatients had a wound (Clark et al, 2017)
- 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)

TABLE 1: PROPORTION OF WOUNDS SHOWING SIGNS OF INFECTION IN A WOUND CARE AUDIT OF 1644 PATIENTS (DREW ET AL, 2007)

| Wound type | Showing signs of infection (%) |
|---|---|
| All wounds | 12.80 |
| Pressure ulcer | 10.42 |
| Leg/foot ulcer | 13.33 |
| Surgical/trauma | 14.29 |

# Mode of action of silver

Pure metallic silver is inert and does not have any antimicrobial action. Antimicrobial activity is dependent on the formation of silver ions, which are silver atoms that have lost one or more electrons (Marx & Barillo, 2014).

Atoms comprise positively-charged nuclei surrounded by varying numbers of negatively-charged (-) electrons arranged in layers or 'shells'. When an atom loses an electron, it becomes a positively-charged (+) ion. When ions form, electrons are lost first from the outermost shell of atoms (Ryan & Norris, 2014).

## SILVER ION FORMATION

A silver atom has 47 electrons arranged in five shells around the nucleus (Figure 1) (Bentor, 2017). The outermost (5$^{th}$) shell has only one electron. If the silver atom (chemical symbol: Ag or sometimes $Ag^0$) loses the outer electron it becomes a relatively stable silver ion (denoted: $Ag^+$; the single + sign indicates the loss of one electron). This process is known as oxidation (Ryan & Norris, 2014).

Two further forms (or species/oxidative states) of silver ion can occur:

- **$Ag^{2+}$** – on the removal of a total of two electrons from a silver atom (the electron in the 5$^{th}$ shell and one of the electrons from the 4$^{th}$ shell)
- **$Ag^{3+}$** – on removal of a total of three electrons from a silver atom (the electron in the 5$^{th}$ shell and two of the electrons from the 4$^{th}$ shell) (Lemire et al, 2015; Bentor, 2017).

Removal of electrons from an atom requires energy. $Ag^+$ ions are formed comparatively easily as it requires relatively little energy to remove a single electron from the outer shell of an atom (Ryan & Norris, 2014). However, the formation of $Ag^{2+}$ and $Ag^{3+}$ ions requires more energy than the formation of an $Ag^+$ ion (Kramida et al, 2017). The increased energy required is reflected in the higher reduction potentials for $Ag^{2+}$ and $Ag^{3+}$ (Table 2) (Haynes, 2010). (Reduction is the process by which an ion gains an electron (Ryan & Norris, 2017)). The higher reduction potentials of $Ag^{2+}$ and $Ag^{3+}$ ions mean that they are more reactive than $Ag^+$ ions and more likely to interact with, for example, bacterial cell components, than $Ag^+$.

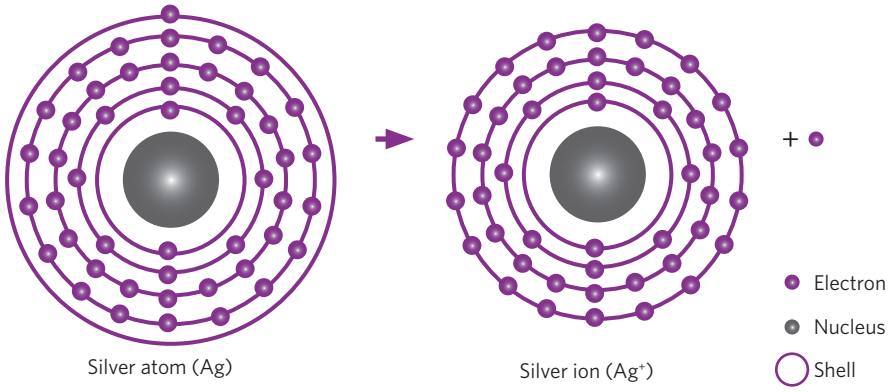



**Figure 1:** A silver atom loses an electron to become a silver ($Ag^+$) ion (adapted from Bentor, 2017)

TABLE 2: REDUCTION POTENTIALS OF SILVER IONS (HAYNES, 2010)

| Reaction | Reduction potential (V) |
|---|---|
| $Ag^{3+}$ + electron$^-$ ⇌ $Ag^{2+}$ | +1.80 |
| $Ag^{2+}$ + electron$^-$ ⇌ $Ag^+$ | +1.98 |
| $Ag^+$ + electron$^-$ ⇌ $Ag^0$ | +0.80 |

## ANTIMICROBIAL EFFECTS OF SILVER IONS

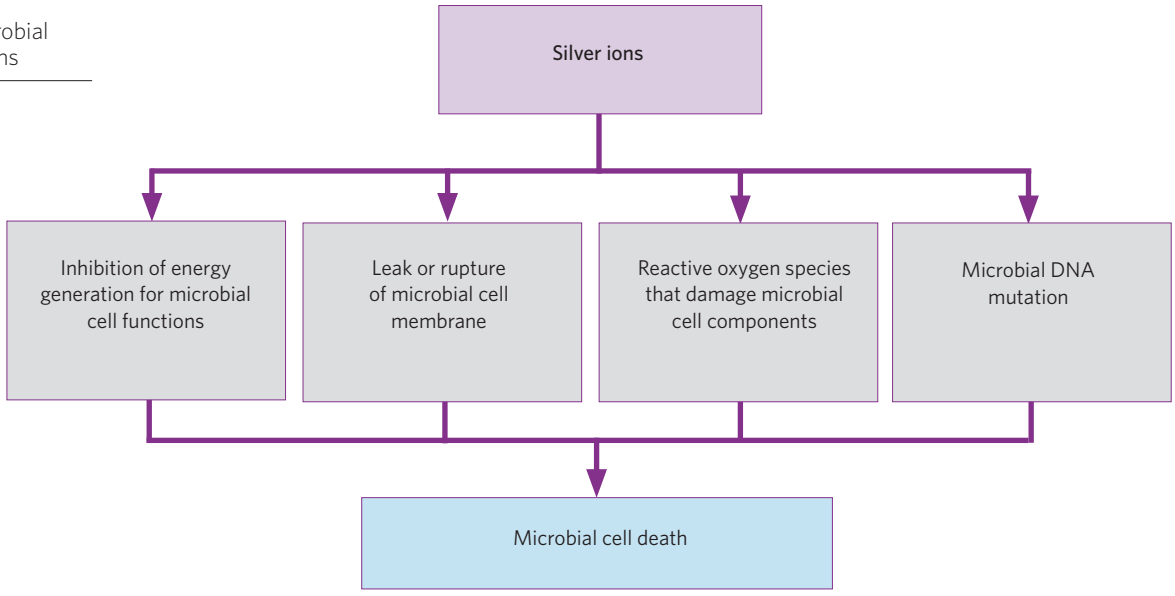
Silver ions are effective antimicrobial agents at very low concentrations (Lemire et al, 2013). They are effective against bacteria (including many antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE)), fungi and viruses (Percival et al, 2005; Li et al, 2016). The antimicrobial actions of silver ions are not fully understood, but there appear to be at least four mechanisms (Figure 2) by which they kill micro-organisms:

- **Inhibition of the molecular mechanism used for generating energy in cells** (i.e. inhibition of the respiratory chain involved in electron transport)
- **Binding to the cell membrane** or wall to cause it to leak or rupture and to prevent the passage of nutrients into the microbial cell
- **Binding to bacterial cell DNA** causing DNA mutation
- **Generation of reactive oxygen species** (free radicals) that damage microbial cell components (Marx & Barillo, 2014; Konop et al, 2016).

## ADDITIONAL EFFECTS OF SILVER

Laboratory studies have indicated that silver may have additional actions beyond its bactericidal effects. For example, dressings containing silver nanoparticles and silver compounds have been found to have anti-inflammatory effects and to inhibit matrix metalloproteinases (elevated levels of which have been associated with delayed healing) (Edwards-Jones, 2009; Nadworny et al, 2010; Bisson et al, 2013; Hebeish et al, 2014). The clinical relevance of this finding remains to be fully elucidated, but is of potential interest in chronic wounds which may be characterised by a heightened and prolonged inflammatory response (Zhao et al, 2016).

**Figure 2:** Antimicrobial effects of silver ions



# Silver in wound dressings

Silver is used in wounds in a number of forms:

- **Elemental silver** – e.g. silver metal, nanocrystalline silver
- **An inorganic compound** – e.g. silver oxide, silver phosphate, silver sulfate, silver-calcium-sodium phosphate, silver zirconium compound, silver sulfadiazine (SSD) and silver oxynitrate
- **An organic complex** – e.g. silver–zinc allantoinate, silver alginate, silver carboxymethylcellulose (Edwards-Jones, 2009; International Consensus, 2012).

The silver component of wound dressings is incorporated as one or more of:

- A coating on one or both external surfaces of the dressing
- Within the body of the dressing:
  - As a coating on the dressing materials
  - Within the spaces of the dressing materials
  - As a compound that forms part of the dressing structure (International Consensus, 2012).

In the context of wound dressings, silver ions are mainly produced on contact of the metal or compound with a solution containing water, e.g. wound exudate (Edwards-Jones, 2009). Most current silver products produce $Ag^{+}$ ions; only silver oxynitrate (Ag Oxysalts) can produce higher oxidative states of silver ($Ag^{2+}$ and $Ag^{3+}$ ions) (Table 3) (Orsted et al, 2013).

Silver ion production by a dressing and the availability of those ions to act on micro-organisms are highly variable, as are the rate, duration and peak level of silver release (Sood et al, 2014). Factors influencing the bioavailability of silver ions include:

- The concentration of silver metal or silver compound in the dressing
- How readily the ions are released from the silver component
- The composition and physical characteristics of the dressing
- The concentration of binding agents, e.g. chloride ions or proteins, in the wound environment that may 'soak up' silver ions and reduce their availability for action against micro-organisms (Melaiye & Youngs, 2005; Marx & Barillo, 2014; Kalan et al, 2017a).

In general, a silver ion release of 10–40 parts per million (ppm) is thought to be necessary for antimicrobial activity in wounds, although higher levels may be required for activity against biofilms (see Appendix 1, page 17 for general information on biofilms) (Marx & Barillo, 2014; Percival & McCarty, 2015). Even so, it is generally unclear how silver content and silver ion availability measured in experimental settings relate to clinical performance (International Consensus, 2012).

### TESTING FOR ANTIMICROBIAL ACTIVITY

A wide range of *in vitro* and *in vivo* tests is available to establish the impact of silver dressings on levels of micro-organisms (Nadworny & Burrell, 2008a; Nadworny & Burrell, 2008b). However, comparisons of antimicrobial activity between silver dressings are difficult because, even when apparently the same

**TABLE 3: SILVER ION PRODUCTION BY METALLIC SILVER OR SILVER COMPOUNDS USED IN WOUND DRESSINGS (RODIJK ET AL, 2011; ORSTED ET AL, 2013)**

| Type of silver | Chemical formula | Silver ions |
|---|---|---|
| Silver oxynitrate (Ag Oxysalts) | $Ag_7NO_{11}$ | $Ag^{+}$, $Ag^{2+}$, $Ag^{3+}$ (in the ratio 1:2:4) |
| Metallic/nanocrystalline silver | Ag | $Ag^{0}$, $Ag^{+}$ |
| Silver chloride | AgCl | $Ag^{+}$ |
| Silver oxide | $Ag_2O$ | $Ag^{+}$ |
| Silver sodium hydrogen zirconium phosphate | $AgNaO_8P_2Zr$ | $Ag^{+}$ |
| Silver sulfadiazine | $AgC_{10}H_9N_4O_2S$ | $Ag^{+}$ |
| Silver sulfate | $Ag_2SO_4$ | $Ag^{+}$ |

**BOX 2:** Definitions (International Consensus, 2012; Smith et al, 2015; Finley et al, 2015; Brauner et al, 2016)

- **Bacteriostatic agent** – an antimicrobial agent that prevents bacteria from growing or reproducing
- **Bactericidal agent** – an antimicrobial agent that kills bacteria
- **Antimicrobial resistance** – genes in bacteria can reduce or remove the ability of an antimicrobial to act, e.g. the *sil* family of genes is associated with silver resistance, but even when present, bacteria may be susceptible to silver
- **Antimicrobial tolerance** – the ability of bacteria to survive antimicrobial exposure by temporarily slowing or stopping their growth; if the antimicrobial is withdrawn, the bacteria may be susceptible to it on re-exposure

test has been performed, the method employed may have involved variables, such as different media or incubations times, that influence the outcome (International Consensus, 2012).

#### Log reductions

A test often reported in the assessment of silver dressings is the log (logarithmic) reduction in numbers of viable bacteria (Nadworny & Burrell, 2008a). An antimicrobial agent is usually considered to be bactericidal (Box 2) when it produces at least a 3-log reduction in the bacterial count (Pankey & Sabath, 2004). A 3-log reduction equates to a 99.9% reduction in the bacterial count. However, the complexity of the wound environment means that such *in vitro* tests of antimicrobial efficacy may not relate directly to clinical performance (International Consensus, 2012). In addition, regulatory bodies such as the Food and Drug Administration (FDA) in the USA may require greater log-reductions, e.g. ≥4-logs, to consider an agent to be an effective antimicrobial (FDA, 2009).

## SILVER RESISTANCE

There have been occasional reports of silver resistance and a range of bacterial genetic changes that may confer resistance have been discovered (Box 2) (Finley et al, 2015). However, it is considered that silver resistance is probably of no clinical significance (Marx & Barillo, 2014). The likelihood of silver resistance can be reduced if silver ions are released from dressings at high levels and produce a rapid bactericidal effect (Chopra, 2007).

## SILVER TOXICITY

There have been reports that silver may cause *in vitro* cytotoxicity and delay healing *in vivo*. But there are also reports that silver accelerates re-epithelialisation and, overall, silver is thought to have low toxicity (Lansdown, 2010; Wilkinson et al, 2011; Percival & McCarty, 2015; Konop et al, 2016).

In general, only small amounts of silver are absorbed systemically from the topical application of silver-containing dressings (Lansdown, 2010). There have been reports of raised systemic levels of silver when silver-containing dressings have been used on large burns or in paediatric patients with epidermolysis bullosa (Denyer, 2009; Moiemen et al, 2011). In these cases, silver levels reduced on discontinuation of the dressing (Denyer, 2009; Moiemen et al, 2011).

Adverse effects from silver, including allergy, are unusual. Silver dressings sometimes cause localised skin staining, but this is usually harmless and reversible (International Consensus, 2012). Argyria (a generalised blue-grey discolouration of the skin and eyes) is usually related to oral ingestion of colloidal silver, and while unsightly, is not life-threatening (Wilksinson et al, 2011; Barillo & Marx, 2014).

## ROLE OF SILVER DRESSINGS IN WOUND MANAGEMENT

The main roles of antimicrobial dressings, such as silver-containing dressings, in the management of acute and chronic wounds are:

- Local management of wound infection
- Local management of wounds with delayed healing that is suspected to be due to biofilm
- Prevention of infection in wounds at high risk of infection (WUWHS, 2008; International Consensus, 2012; IWII, 2016; Wounds UK, 2017).

#### Selecting a silver dressing for clinical use

Many factors are involved in dressing selection. When it has been decided that a silver dressing is indicated, clinicians may refine their choice of dressing by considering issues such as:

- Evidence of broad-spectrum bactericidal activity
- Evidence of rapid-onset and sustained antimicrobial activity
- Evidence of clinical effectiveness
- Other characteristics of the dressing – e.g. absorptive capacity, conformability, need for a secondary dressing, recommended dressing change frequency
- Patient preference (International Consensus, 2012).

# Ag Oxysalts

**BOX 3:** Broad-spectrum antimicrobial activity of Ag Oxysalts (White & Parker, 2015; Kalan et al, 2017a)

**Gram-negative bacteria**
- *Acinetobacter baumanii*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*

**Gram-positive bacteria**
- *Corynebacterium striatum*
- *Enterococcus faecalis*
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*

**Antibiotic-resistant bacteria**
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococci* (VRE)
- Carbapenem-resistant *Enterobacteriaceae* (CRE)

**Fungi**
- *Candida albicans*
- *Aspergillus niger*

Ag Oxysalts is the trademarked name for the unique silver compound silver oxynitrate ($Ag_7NO_{11}$). Ag Oxysalts can release $Ag^+$, $Ag^{2+}$ and $Ag^{3+}$ ions and has chemical properties that result in enhanced antimicrobial action (White & Parker, 2015).

## UNIQUE CHEMISTRY OF Ag OXYSALTS

Until the development of Ag Oxysalts, the higher oxidative states of silver were not considered as suitable for development as antimicrobial agents because their reactivity made them unstable (Lemire et al, 2015). However, the chemical structure of Ag Oxysalts keeps $Ag^+$, $Ag^{2+}$ and $Ag^{3+}$ ions in a stable condition at room temperature (Lemire et al, 2015). The ratio of silver ions in Ag Oxysalts is one $Ag^+$: two $Ag^{2+}$: four $Ag^{3+}$ (Rodijk et al, 2011) (Table 3, page 5). When in contact with an aqueous solution, e.g. wound exudate, Ag Oxysalts releases the three types of silver ion (Figure 3). As described on page 5, $Ag^{2+}$ and $Ag^{3+}$ ions are more reactive than $Ag^+$ ions and so Ag Oxysalts is able to produce a powerful antimicrobial effect (Thomason & Beasley, 2016).

The higher reactivity of the $Ag^{2+}$ and $Ag^{3+}$ silver ions produced by Ag Oxysalts means that a dressing containing the compound can have a lower overall silver content than other commercially available silver dressings, but maintain effective antimicrobial activity (Orsted et al, 2013; Kalan et al, 2017a).

## SUSTAINED SILVER ION RELEASE

From a clinical perspective, ongoing release of silver ions for the recommended maximum duration of dressing wear is important to maintain antimicrobial efficacy. Laboratory tests have shown that the release of silver ions from a dressing containing Ag Oxysalts into simulated wound fluid continues for 7 days (Kalan et al, 2017a). In addition, Ag Oxysalts has been found to be non-toxic for cytotoxicity, systemic toxicity, irritation and sensitisation (Kalan et al, 2017a).

## RAPID, BROAD-SPECTRUM AND SUSTAINED ANTIMICROBIAL ACTIVITY OF Ag OXYSALTS DRESSINGS

Ag Oxysalts dressings have been shown to have broad bactericidal activity against a wide range of gram-negative and gram-positive bacteria and fungi, and a number of antibiotic-resistant bacteria (Box 3) (White & Parker, 2015; Kalan et al, 2017a).

The onset of bactericidal activity of Ag Oxysalts dressings is rapid and has been shown to produce at least a 4-log reduction in bacterial numbers of a wide range of bacterial species within 4 hours (Kalan et al, 2017a). Figure 4 shows that for some bacterial species, Ag Oxysalts dressings have very rapid bactericidal activity, e.g. for *P. aeruginosa* a >5-log reduction within 30 minutes (Data on file). Ag Oxysalts dressings also maintain bactericidal activity over 7 days (Data on file).

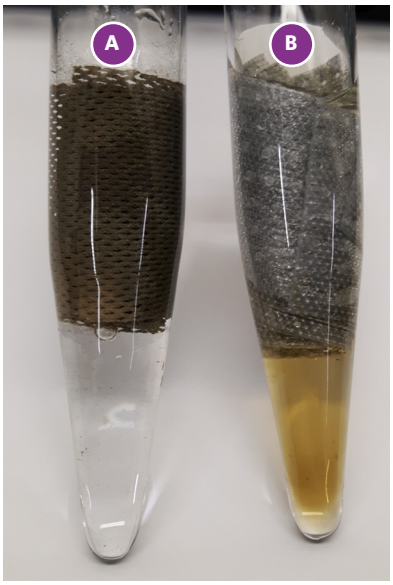



**Figure 3 (left):** Release of silver ions from an Ag Oxysalts dressing

The presence of $Ag^{2+}$ and $Ag^{3+}$ ions in a solution can be demonstrated in the laboratory by the production of a brown/yellow colour on the addition of nitric acid solution to the dressing. Although nitric acid will react with $Ag^+$, the resulting chemical reaction does not change the colour of the solution
**(A) Dressing containing nanocrystalline silver:** there is no discolouration on addition of nitric acid, i.e. no $Ag^{2+}$ or $Ag^{3+}$ ions are produced
**(B) Dressing containing Ag Oxysalts:** the solution becomes discoloured on addition of nitric acid, i.e. $Ag^{2+}$ and $Ag^{3+}$ ions are released

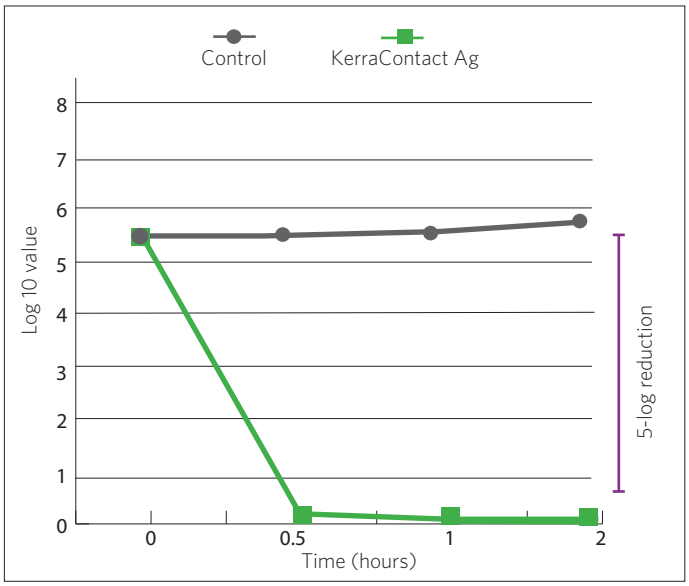



**Figure 4 (right):** Rapid onset of bactericidal activity of an Ag Oxysalts dressing against *P. aeruginosa* (Data on file)

### Activity against antibiotic and silver-resistant bacteria

In addition, *in vitro* tests have shown that the antimicrobial activity of Ag Oxysalts dressings to be sustained over the course of 7 days for a variety of antibiotic-resistant bacterial species, including MRSA, VRE and CRE, despite daily re-inoculation with bacteria (Kalan et al, 2017a).

Ag Oxysalts dressings have also been shown to be effective against clinical isolates of bacteria which carry silver-resistance genes (*sil*) when some other silver dressings were ineffective (Finley et al, 2015).

## PREVENTION AND DISRUPTION OF BIOFILM BY Ag OXYSALTS

There is growing awareness of the potential role of biofilm in delayed wound healing. *In vitro* tests on established single-species biofilms of *P. aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae* or *Escherichia coli* have found that Ag Oxysalts:

- Inhibits biofilm formation
- Eradicates planktonic and biofilm microbial populations (Lemire et al, 2015; Thomason et al, 2017a; Kalan et al, 2017a).

Furthermore, the concentration of silver ions required to eradicate established biofilms was found to be 10x lower for Ag Oxysalts ($Ag^{+}$, $Ag^{2+}$, $Ag^{3+}$) than for silver nitrate ($Ag^{+}$) (Lemire et al, 2015).

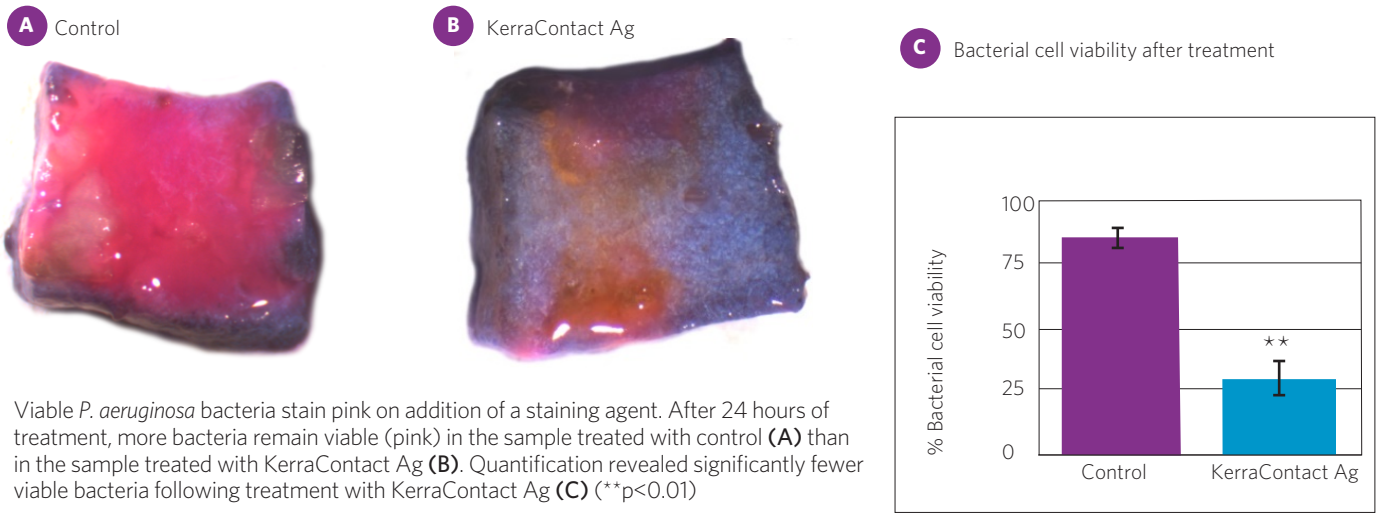
Similarly, an Ag Oxysalts dressing applied to an *ex vivo* porcine wound model and to an *in vivo* mouse wound model, both of which contained a mature (72 hour-old) *P. aeruginosa* biofilm, has been shown to reduce numbers of viable bacteria (Thomason et al, 2017a). Figure 5 illustrates the effect of 24 hours of treatment with an Ag Oxysalts dressing on a *P. aeruginosa* biofilm.

### *In vitro* effects of Ag Oxysalts on dual-species biofilms

In clinical situations, biofilms in wounds are likely to contain several species of micro-organism (Sun et al, 2009; Lemire et al, 2017). However, most evaluations of the effects of antimicrobial agents on biofilm are conducted in studies that use single-species biofilms and there are questions about the applicability of these studies to clinical practice in wound care.

As a result, the effects of Ag Oxysalts on dual-species biofilms have been investigated (Lemire et al, 2017). Biofilms containing *P. aeruginosa* plus *S. aureus*, *P. aeruginosa* plus *E. coli*, and *S. aureus* plus *E. coli* were studied. The investigation found that, although higher concentrations of Ag Oxysalts were required than in single-species biofilm models, Ag Oxysalts effectively inhibited biofilm formation and eradicated established biofilm (Lemire et al, 2017).

**Figure 5:** Ag Oxysalts reduces the number of viable bacteria in a *P. aeruginosa* biofilm wound model (Data on file)




Viable *P. aeruginosa* bacteria stain pink on addition of a staining agent. After 24 hours of treatment, more bacteria remain viable (pink) in the sample treated with control **(A)** than in the sample treated with KerraContact Ag **(B)**. Quantification revealed significantly fewer viable bacteria following treatment with KerraContact Ag **(C)** (**p<0.01)

### *In vitro* and *in vivo* effects of Ag Oxysalts on wound healing and inflammation

Use of Ag Oxysalts in *in vitro* and *in vivo* wound models was associated with enhanced wound closure and the presence of fewer inflammatory cells in the wound in comparison with control (Thomason et al, 2017b).

### Effects of Ag Oxysalts on wound microbiome

Intact skin and wounds contain a wide range of micro-organisms. Even after treatment with antimicrobials, whether with a systemic antibiotic or a topical agent, wounds are not sterile and can progress to healing in the presence of bacteria (WUWHS, 2008).

A study of the bacterial communities in a range of non-healing chronic wound types found considerable variation in the types of bacteria resident in each wound. When the wounds were treated with an Ag Oxysalts dressing, the diversity of bacterial species in the wound decreased substantially within 24 hours of initiation of treatment (Kalan et al, 2017b). As healing progressed, diversity increased again, although the balance between different species was different from before treatment. The clinical significance of these findings is not clear and research is ongoing.

## EFFECT OF Ag OXYSALTS ON pH

Some metallic silver dressings may be associated with stinging on application to a wound. This is thought to be due to the hydrolysis of water occurring when silver oxide that has formed on the surface of the metal comes into contact with wound exudate. The consequent sudden rise in pH, i.e. increase in alkalinity, is thought to cause stinging (Parsons, 2005). Ag Oxysalts dressings have been shown to produce a relatively small change in pH in comparison with other silver dressings and so are likely to have a reduced risk of stinging (Kalan et al, 2017a).

## ADDITIONAL EFFECT OF Ag OXYSALTS

Chronic wounds are often thought to be held in a cycle of perpetuated chronic inflammation in which an imbalance of reactive oxygen species, such as hydrogen peroxide, contributes to ongoing tissue damage (Zhu et al, 2017). As a result, it has been suggested that hydrogen peroxide may be a therapeutic target in the management of chronic wounds (Zhu et al, 2017).

The ability of dressings containing Ag Oxysalts and other silver compounds to break down hydrogen peroxide (into water and oxygen) has been investigated (Thomason et al, 2017b). Only dressings containing Ag Oxysalts were found to produce water and oxygen from hydrogen peroxide (Figure 6). These effects may be of interest in wound healing (Kimmel et al, 2016).

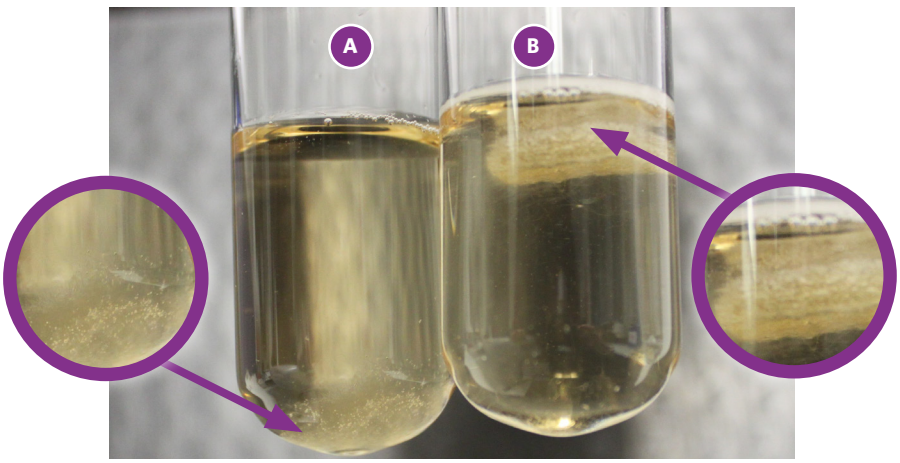



**Figure 6:** Ag Oxysalts can breakdown hydrogen peroxide into water and oxygen

On addition of hydrogen peroxide solution, a dressing containing silver chloride **(A)** sinks to the bottom of the test tube. Whereas, KerraCel Ag (an Ag Oxysalts-containing carboxymethylcellulose dressing) **(B)** breaks down hydrogen peroxide to produce water and bubbles of oxygen. The dressing floats because oxygen bubbles are trapped in the dressing

# Ag Oxysalts dressing: KerraContact Ag

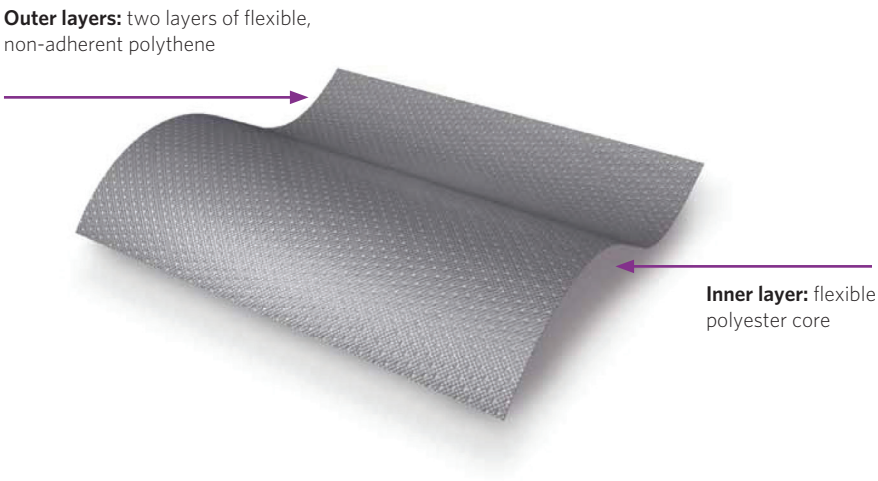
KerraContact Ag dressings are comprised of three layers: two non-adherent polyethylene mesh wound contact layers and a polyester core. All three layers are coated with Ag Oxysalts. The dressing has a silver concentration of approximately 0.4mg/cm$^2$ (Figure 7) (KerraContact Ag IFU, 2017).

KerraContact Ag can be used on a wide range of partial and full thickness acute and chronic wounds that are infected or at high risk of infection, e.g. pressure ulcers (PUs), venous leg ulcers (VLUs), diabetic foot ulcers (DFUs), superficial and partial-thickness burns, surgical wounds, skin grafts and donor sites (White & Parker, 2015; KerraContact Ag IFU, 2017). Box 4 summarises the characteristics of KerraContact Ag.

KerraContact Ag has been used in a wide range of chronic and acute wound types for the treatment or prevention of infection. The dressing has been reported to have beneficial effects on (Table 4, page 11):

- **Signs and symptoms of infection**, including reductions in pain, exudate levels and odour, and improvements in periwound skin condition
- **Overgranulation**
- **Progression towards healing.**

Figure 7: KerraContact Ag




**BOX 4:** Characteristics of KerraContact Ag* (KerraContact Ag IFU, 2017)

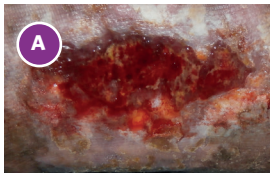
KerraContact Ag:

- Is a primary dressing and should be applied to have direct contact with the wound bed
- Requires a secondary dressing to aid retention and to manage excess exudate
- Can be applied wet or dry to a wound; does not need to be pre-moistened
- Can be used on wounds that have been cleansed with saline
- Can be cut to shape
- Antimicrobial activity is maintained for 7 days; the dressing can be left in place for up to 7 days if there are no other indications for more frequent dressing change
- Is not compatible with oil-based products, such as petrolatum

*Clinicians considering application of KerraContact Ag should consult the product Information for Use before applying the dressing.

| TABLE 4: CLINICAL EVIDENCE FOR KERRACONTACT Ag | | | |
|---|---|---|---|
| **Reference** | **Wound type(s)** | **Study details** | **Key points** |
| Stephenson, 2017 | Infected leg ulcers (venous, arterial or mixed) | Non-comparative evaluation by UK clinicians (n=31); 80% VLUs | ■ At the end of the evaluation:<br>- **Pain** levels were reduced by 67% (n=25)<br>- **Exudate** levels were reduced by 83% (n=31)<br>- **Wound odour** was reduced by 77% (n=27)<br>- **Swelling/heat/redness** was reduced by 75% (n=24)<br>■ More patients had dressing changes every 5–7 days during the evaluation than before (12 vs 7); KerraContact Ag dressings were left in place for longer than previous dressings<br>■ 87% of clinicians reported the wound to be 'improved' or 'significantly improved' and 90% stated they would use the dressing again |
| Young et al, 2016 | VLUs with a clinical diagnosis of infection or suspected of being infected | Case series (n=17 wounds in 15 patients); 4-week study | ■ Mean age was 73 years (range 39 to 92 years)<br>■ Baseline wound area ranged from 1cm$^2$ to 20cm$^2$<br>■ **Wound area**: mean reduction in wound area at week 4 was 52%<br>■ **Exudate:** at week 0, 94% of wound had moderate or high exudate levels; at week 4, 53%, 41% and 6% respectively had low, moderate or high exudate levels<br>■ **Odour**: at week 0 only 6% of wounds had no odour; at week 4, 82% of wounds had no odour<br>■ **Pain**: mean pain score reduced from week 0 to week 4<br>■ **Periwound skin condition**: all measures (maceration, erythema, oedema and other) had improved by week 4; at weeks 0 and 4 periwound skin was reported as healthy in 18% and 71% of patients respectively |
| Stephenson, 2016 | Wounds that were infected or at risk of infection, including VLUs, burns, PUs, surgical wounds, DFUs and arterial ulcers | Non-comparative evaluation by UK clinicians (n=48); duration of dressing use was <1 week in 65% of cases | ■ The dressing was used to treat wound infection in 78% of cases and to prevent infection in the remainder<br>■ **Pain**: 51% of clinicians reported that there was a reduction in pain during use of the dressing<br>■ **Exudate**: 78% of clinicians reported a reduction in exudate; 20% stated that the reduction was significant<br>■ **Odour**: 86% of clinicians reported that there was a reduction in odour; 26% stated that the reduction was significant<br>■ **Signs of infection**: 67% of clinicians reported a reduction in swelling, heat and redness<br>■ 98% of clinicians stated that they would use the dressing again |
| Motta et al, 2012 | Infected chronic and non-chronic wounds: VLUs, DFUs, PUs, arterial ulcers, surgical wounds, skin tears, trauma and other wounds | Multicentre case series (n=50); 4-week study | ■ Median age 67 years (range 33 to 95 years)<br>■ Median wound duration 3.5 months (range 2 days to 24 months)<br>■ **Healing**: 45% of wounds healed within an average of 2.9 weeks<br>■ **Signs of infection**: remission of clinical infection indicators was observed in >60% of patients within 6 weeks<br>■ **Pain**: 93% of patients perceived a reduction in pain over the course of treatment and for many patients, pain dropped to zero within one week; no pain was reported on application or removal of the dressing<br>■ Clinicians observed little or no staining and no stinging, and reported increased granulation tissue, reduced inflammation, odour and pain |
| Coutts et al, 2012 | Chronic leg and foot ulcers with signs of superficial critical colonisation | Case series (n=20); 8-week study | ■ **Wound size**: By week 8, wound size had reduced in 16/20 patients; 7/20 wounds had decreased in size by 50%<br>■ **Pain**: The total of the pain scores reported on an 11-point verbal rating scale by 17/20 patients who had pain at baseline was 44.5 at week 0 and 33 at week 8 |
| Chadwick & Haycocks, 2017 | Overgranulated DFUs | Case series (n=2) | ■ Patient 1: Following surgical debridement, a patient receiving i.v. antibiotics for osteomyelitis and a large DFU developed overgranulation; KerraContact Ag was commenced and i.v. antibiotics continued<br>■ Patient 2: An overgranulated DFU had been treated unsuccessfully for 1 week with a silver hydrofibre dressing; KerraContact Ag was commenced<br>■ At the end of 4 weeks, there was a significant reduction in wound size, slough and overgranulation tissue for both patients; patient 2 showed an improvement after one week of treatment and the DFU eventually healed |
| Weaving, 2017 | Overgranulated DFU | Case study (n=1) | ■ An overgranulated DFU of more than 3 months' duration was 'almost healed' after 3 weeks of treatment with KerraContact Ag; the wound was fully healed after a total of 4 weeks<br>■ KerraContact Ag was reported as easy to apply and remained intact during use in conjunction with off-loading (a non-removable cast) |
| Parker et al, 2017 | Delayed healing of spinal wound in a paediatric patient | Case study (n=1) | ■ Ongoing skin breakdown of unknown duration over the patient's mid-spine was suspected to be due to a combination of pressure damage, chronic infection, biofilm and hypergranulation<br>■ KerraContact Ag was applied for a total of 14 days; treatment was continued thereafter with a silicone foam dressing<br>■ By day 14, the wound had reduced considerably in size and the hypergranulation was resolved |
| **Abbreviations**: DFUs – diabetic foot ulcers; i.v. – intravenous; PUs – pressure ulcers; VLUs – venous leg ulcers | | | |

# Indications for the use of KerraContact Ag



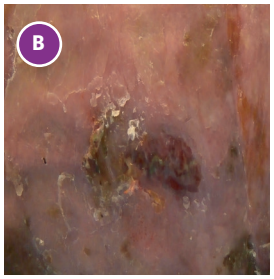




**Figure 8:** Infected VLU before **(A)** and after **(B)** treatment with KerraContact Ag for 4 weeks

The Expert Working Group agreed that the enhanced antimicrobial activity of Ag Oxysalts means that KerraContact Ag has roles in the management of acute and chronic wounds that have:

- Infection (see Figure 8 for an example)
- Delayed healing in the absence of overt infection and despite optimal standard care, e.g. delayed healing that is likely to be due to biofilm or is due to overgranulation considered to result from increased bioburden
- Increased risk of infection.

Figure 9, page 14, provides an overview of the potential roles of KerraContact Ag in wound management.

## COMPREHENSIVE PATIENT AND WOUND ASSESSMENT

Comprehensive assessment underpins management. As well as indicating the need for further investigation and determining wound aetiology/type, it will aid setting of appropriate treatment goals and management strategies and indicate whether the wound is suitable for treatment with KerraContact Ag. Wound assessment will also provide a baseline from which to monitor progress. The results of the assessments should be documented (Ousey & Cook, 2012).

Comprehensive assessment should include (Coleman et al, 2017):

- **Patient**:
  - Medical history, surgical history, allergies and sensitivities
  - Current health and lifestyle, including medication and smoking, factors that may be causing/contributing to the wound (e.g. diabetes, arterial disease, venous disease) and risk factors for delayed healing and infection (Box 5)
  - Psychosocial status
- **Wound**:
  - Duration
  - Location
  - Type/classification
  - Size/area/depth/volume
  - Wound bed tissue types and proportions of each
  - Level and nature of exudate
  - Presence, nature and level of odour
  - Wound edge condition, tunnelling, undermining, and condition of the periwound skin
  - Signs and symptoms of local or systemic infection (Table 5, page 13)
- **Pain**: presence, frequency and severity of wound-related or non-wound-related pain
- **Further investigations**: to establish wound aetiology or suitability for adjunctive treatment such as compression therapy.

**BOX 5:** Examples of risk factors for wound infection (WUWHS, 2008; Siddiqui & Bernstein, 2010; PHE, 2013; IWII, 2016)

- Diabetes
- Multiple and/or poorly controlled comorbidities
- Immunocompromise or autoimmune disease
- History of poor wound healing/infection
- Malnourishment or obesity
- Smoking; alcohol/drug abuse
- Hypoxia or local ischaemia
- Advanced age
- Surgical factors: surgery classified as 'clean-contaminated', 'contaminated' or 'dirty', long operative duration, hypothermia, blood transfusion
- Complex or large wound
- Wound in a high risk anatomical location, e.g. burns of the perineum, axillae or feet
- Poor wound bed condition, e.g. contains necrotic tissue, contaminants or foreign bodies

| TABLE 5: SIGNS AND SYMPTOMS OF WOUND INFECTION (WUWHS, 2008; IWII, 2016) | |
|---|---|
| **Local symptoms of wound infection** | |
| Acute wounds | Chronic wounds |
| ■ New or increasing pain<br>■ Erythema and local warmth<br>■ Swelling<br>■ Purulent discharge<br>■ Abscess<br>■ Malodour<br>■ Wound breakdown/dehiscence<br>■ Lymphangitis<br>■ Soft tissue crepitus<br>■ Skin graft rejection | ■ New, increased or altered pain<br>■ Wound breakdown and enlargement<br>■ Delayed or stalled healing<br>■ Periwound oedema<br>■ Bleeding or friable granulation tissue/hypergranulation<br>■ Increased and/or altered/purulent exudate<br>■ Induration<br>■ Bridging and pocketing<br>■ Lymphangitis |
| Systemic symptoms of wound infection in acute and chronic wounds | |
| ■ Malaise<br>■ Lethargy<br>■ Loss of appetite<br>■ Non-specific general deterioration<br>■ Pyrexia/hypothermia | ■ Tachypnoea<br>■ Elevated C-reactive protein (CRP)<br>■ Elevated or suppressed white blood cell count<br>■ Sepsis<br>■ Septic shock |

## STANDARD CARE

KerraContact Ag should be used in the context of appropriate standard care for the wound. Standard care will depend on wound aetiology and condition, and will include wound bed preparation, i.e. cleansing and debridement, treatment of infection/inflammation, exudate management and periwound skin care, and management of aetiology and comorbidities (Schultz et al, 2003; Harries et al, 2016).

Patients under consideration for compression therapy, e.g. patients with VLUs, should undergo vascular assessment, such as determining ABPI (ankle–brachial pressure index) (SIGN, 2010; Wounds UK, 2016). Patients with PUs will require implementation of measures to redistribute pressure (NICE, 2014; NPUAP, EPUAP, PPPIA, 2014) and patients with DFUs should be assessed for offloading devices (McIntosh & Halford, 2014; NICE, 2015b).

### Importance of debridement

The presence of slough and devitalised or necrotic tissue in a wound can provide a focus for infection and a barrier to the action of antimicrobial dressings (Schultz et al, 2003; Sood et al, 2014). Debridement is used to remove slough, devitalised tissue and biofilm and to reduce bacterial burden (Vowden & Vowden, 2011) and will enable the activity of antimicrobial dressings, such as KerraContact Ag, to focus on the areas of the wound bed where reducing microbial levels will benefit healing most.

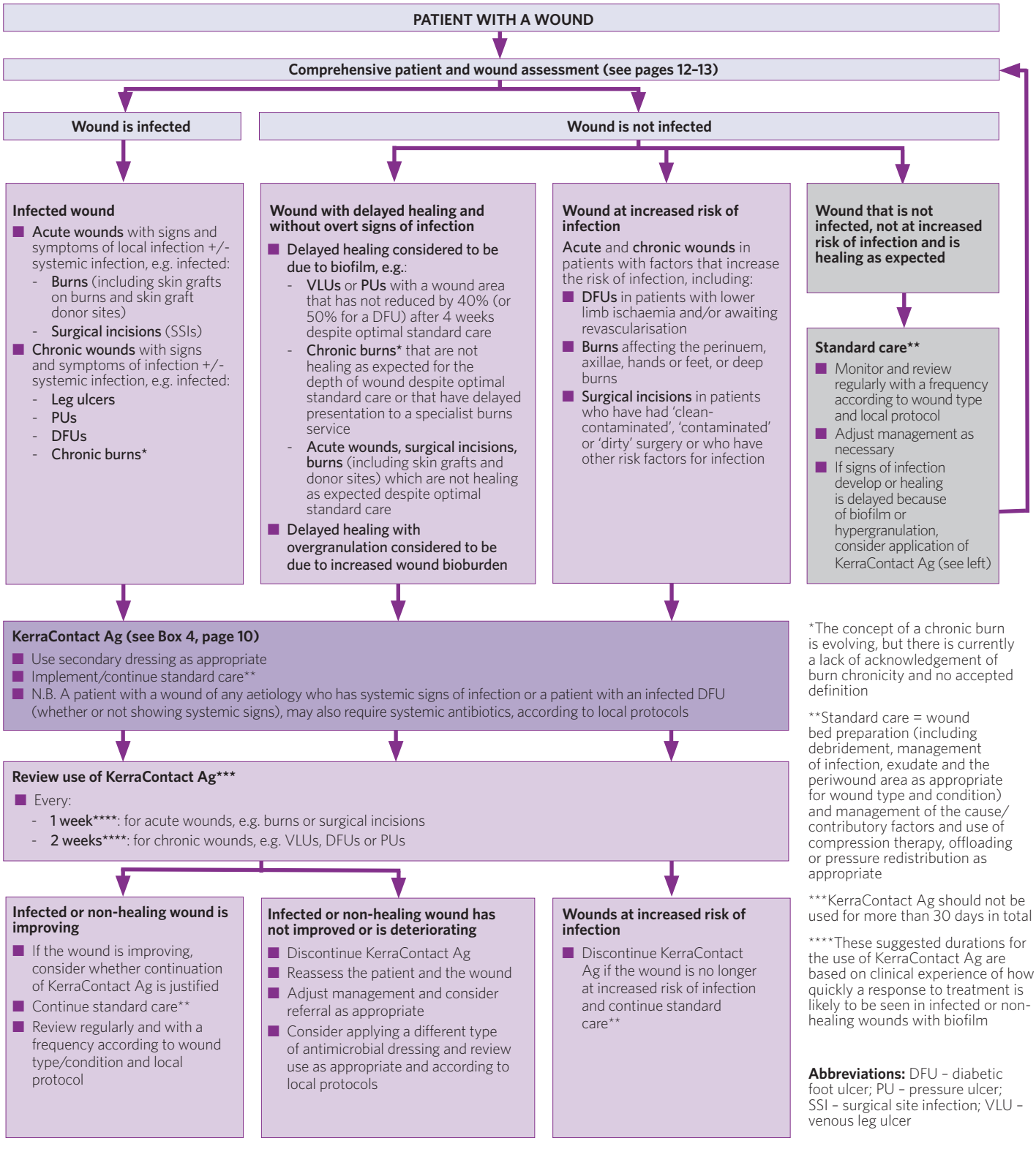
The method of debridement used will depend on the condition and type of wound (Wounds UK, 2013a). If the most appropriate method is outside the skill set of the clinician, referral may be necessary (Vowden & Vowden, 2011).

## INFECTED WOUNDS

Antimicrobial dressings, such as KerraContact Ag, are used for the treatment of local wound infection (Figure 9, page 14) (IWII, 2016). A diagnosis of wound infection is usually made on the basis of clinical signs and symptoms (Table 5).

In general, routine microbiological investigations, e.g. using swab or biopsy samples, of infected wounds are not justified (Cooper, 2010) unless specified in local protocols or required for

Figure 9: KerraContact Ag clinical pathway




*The concept of a chronic burn is evolving, but there is currently a lack of acknowledgement of burn chronicity and no accepted definition

**Standard care = wound bed preparation (including debridement, management of infection, exudate and the periwound area as appropriate for wound type and condition) and management of the cause/ contributory factors and use of compression therapy, offloading or pressure redistribution as appropriate

***KerraContact Ag should not be used for more than 30 days in total

****These suggested durations for the use of KerraContact Ag are based on clinical experience of how quickly a response to treatment is likely to be seen in infected or non-healing wounds with biofilm

**Abbreviations:** DFU – diabetic foot ulcer; PU – pressure ulcer; SSI – surgical site infection; VLU – venous leg ulcer

surveillance purposes. Microbiological reports should generally also not be acted upon in isolation, but considered in the context of the patient and the wound.

A patient with a wound of any aetiology who has systemic signs of infection or a patient with an infected DFU (whether or not showing systemic signs), may also require systemic antibiotics, according to local protocols.

### WOUNDS WITH DELAYED HEALING DESPITE OPTIMAL STANDARD CARE

One of the many factors that can disrupt wound healing is the presence of biofilm (Wounds UK, 2017). However, although biofilm is now thought to be ubiquitous in chronic wounds, some wounds do heal without anti-biofilm management (Percival et al, 2015). There are difficulties in determining when biofilm may be causing a problem with wound healing. There is no readily available test for biofilm and the signs and symptoms thought to indicate biofilm may be subtle (Wounds UK, 2017).

Consequently, it has been suggested that biofilm should be suspected as the cause of delayed healing in wounds that have received optimal standard care and that do not have any other explanation for the delay (Wounds UK, 2017). For some types of chronic wounds, research into the likelihood of healing can be used to provide a more objective measure of delayed healing. VLUs and PUs that have not reduced in area by 40% (or by 50% for DFUs) after 4 weeks of optimal standard care for the wound type are unlikely to heal (Phillips et al, 2000; Kantor & Margolis, 2000; Flanagan, 2003; Günes, 2009; Sheehan et al, 2003; Coerper et al, 2009; Snyder et al, 2010).

Once biofilm is suspected of being the cause of delayed healing and other causes have been excluded, management strategies include debridement to physically disrupt the biofilm and the use of antimicrobial dressings, such as KerraContact Ag, to further reduce wound bioburden and prevent biofilm reformation (Figure 9, page 14) (Wounds UK, 2017).

Another cause of non-healing is overgranulation (hypergranulation) – excessive growth of granulation tissue from the wound bed to above the plane of the wound edges that prevents epithelialisation and delays healing (Widgerow et al, 2010). The mechanism for the development of hypergranulation is not clear, but repeated minor trauma, physical irritation or friction, excessive inflammation, and infection or raised bioburden may contribute (Vuolo, 2010). If infection or raised bioburden are suspected causes, management of overgranulation may include an antimicrobial dressing. Improvements have been observed in overgranulated wounds treated with KerraContact Ag (Table 4, page 11).

### WOUNDS AT INCREASED RISK OF INFECTION

Antimicrobial dressings have been recommended for the prevention of wound infection in individuals who are considered to be at increased risk (IWII, 2016).

The Expert Working Group identified the following as at increased risk of infection and as candidates for consideration of the use of KerraContact Ag:

- **Acute and chronic wounds** in patients with factors that increase the risk of infection
- **DFUs** in patients with lower limb ischaemia and/or awaiting revascularisation
- **Burns** affecting the perinuem, axillae, hands or feet, or deep burns
- **Surgical incisions** in patients who have had surgery classified as 'clean-contaminated', 'contaminated' or 'dirty' or who have other risk factors for infection.

Patients with DFUs can descend into infection and deteriorate rapidly, and some patients with recurrence of DFUs exhibit a repeated pattern of infection and osteomyelitis. As a result, the Group considered that the threshold for using KerraContact Ag for prevention of infection in patients with DFUs is lower than for patients with other types of wound.

### REVIEWING USE OF KERRACONTACT Ag

As a general principle, it has been recommended that the use of an antimicrobial dressing is reviewed after 2 weeks (the '2-week challenge'). The dressing should be discontinued if the wound has improved. It should also be discontinued, and the patient and wound fully reassessed, if the wound has deteriorated (International Consensus, 2012; Wounds UK, 2013b). These recommendations were designed to prevent prolonged use of antimicrobial dressings in chronic wounds and to encourage review and use of a different antimicrobial if the initial selection was not effective in reducing wound bioburden.

Clinical experience has suggested that the effect of KerraContact Ag may become apparent quickly. This has led the Expert Working Group to suggest modifying the '2-week challenge' to one week for infected or non-healing acute wounds treated with KerraContact Ag (Figure 9, page 14). The Group considered that a review after 2 weeks continues to be appropriate for infected or non-healing chronic wounds. In both situations, wounds should continue to be monitored during treatment and management adjusted as necessary.

When KerraContact Ag is used on wounds at increased risk of infection, the same frequencies of review are recommended, i.e. one week for acute wounds and 2 weeks for chronic wounds. The dressings should be discontinued when the wound is considered no longer to be at increased risk of infection.

# Summary

Ag Oxysalts is an important development that will aid antimicrobial stewardship in this era of escalating antibiotic resistance. The production of highly reactive $Ag^{2+}$ and $Ag^{3+}$ ions, in addition to $Ag^{+}$ ions, by Ag Oxysalts gives this silver compound unique chemical properties. The resulting rapid, broad-spectrum and sustained antimicrobial action means that Ag Oxysalts dressings are effective at lower concentrations of silver than are other silver dressings that produce $Ag^{+}$ ions alone.

Clinical evidence of the effectiveness of KerraContact Ag continues to accumulate. In addition to roles in the management of infection in acute and chronic wounds, the Expert Working Group considers KerraContact Ag to have roles in the management of wounds considered to be non-healing because of biofilm or hypergranulation due to increased bioburden and wounds that are at high-risk of infection. Further research (Box 6) and the development of further formulations of Ag Oxysalts dressings beyond the currently available KerraContact Ag will broaden clinical applicability of this unique silver compound.

**BOX 6:** Areas for further research into Ag Oxysalts

- To investigate further the details and clinical significance of:
  - The effects of Ag Oxysalts dressings on the wound microbiome
  - The ability of Ag Oxysalts dressings to degrade hydrogen peroxide and produce oxygen
  - The potential of Ag Oxysalts dressings to promote healing independently of its antimicrobial activity
- To conduct adequately powered randomised controlled trials of Ag Oxysalts dressings versus other silver dressings in the management of acute and chronic wound infection
- To develop cohort studies and registries that record the effects of Ag Oxysalts dressings in multiple wound types and provide data that can inform cost-effectiveness studies

**Key points**

- Ag Oxysalts has unique chemical properties
- Ag Oxysalts releases $Ag^{+}$, $Ag^{2+}$ and $Ag^{3+}$ ions on contact with water, e.g. wound exudate
- Ag Oxysalts has rapid, broad-spectrum and sustained antimicrobial activity
- KerraContact Ag has roles in:
  - The prevention and management of wound infection
  - The management of wounds that are not healing despite optimal standard care and in which non-healing is considered to be due to biofilm
  - The management of wounds not healing as a result of overgranulation thought to be due to increased bioburden

## APPENDIX 1: BIOFILM – AN OVERVIEW

- Biofilm is formed by free-floating (planktonic) microbial cells that adhere to a surface, e.g. a wound bed, and produce a protective coating (extrapolymeric substance; EPS). The EPS protects the embedded microbes from the patient's immune system and from antimicrobials (Wounds UK, 2017)
- There is currently no straightforward/bedside test for the presence of biofilm in wounds (Phillips et al,2010)
- A recent meta-analysis reported the prevalence of biofilm in chronic wounds to be 78.2%, and that it is likely that all chronic wounds contain biofilm (Malone et al, 2017)
- Biofilm is thought to delay healing by causing a heightened inflammatory state that results in further tissue damage (Schultz et al, 2016)
- Where biofilm is considered to be the cause of delayed healing, management involves physically removing biofilm (debridement), and the use of topical antimicrobials, e.g. silver, to disrupt the biofilm, reduce the number of planktonic bacteria in the wound and prevent biofilm reformation (Wounds UK, 2017)

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