Technological advancements in the fight against antimicrobial resistance

Over-prescription and misuse of antibiotics has contributed to the global crisis of antimicrobial resistance (AMR). In order to manage this growing crisis, it is crucial that new technologies and techniques are developed to deal with infection. Infection in chronic wounds is a common problem, which is often targeted ineffectively by antibiotics. In addition, biofilms in chronic wounds contribute to prolonged morbidity. There are now alternative means of fighting infection and biofilms in chronic wounds with topical antimicrobials rather than systemic antibiotics. Wound irrigation with a topical antimicrobial is an effective technique that should be used to prevent and combat biofilms and potential infection, as well as promote healing, without contributing to the growing AMR crisis.

Antibiotic or antimicrobial resistance (AMR) poses a ‘catastrophic threat’[2]. The Department of Health has issued a UK Antimicrobial Resistance Strategy, which sets out how it will meet this growing challenge[9]. The strategy states: ‘There are few public health issues of greater importance than antimicrobial resistance in terms of impact on society.’

The wide availability of antibiotics has contributed to misuse and overuse, allowing bacteria to develop resistance mechanisms. The UK’s Department of Health (DH)[7] and World Health Organization[5] have both warned of the serious dangers of multi-resistant ‘superbugs’ continuing to develop if interventions are not put into place to combat the rising levels of AMR. There is serious concern that the rising prevalence of multiply-antibiotic resistant bacteria will result in a post-antibiotic era, where previously treatable infections (e.g. infections in chronic wounds) will become untreatable — resulting in dramatically rising death levels. Professor John Watson, deputy chief medical officer at the DH in the UK, said: ‘Antimicrobial resistance is one of the biggest threats to health security facing the world today and everybody must take action[2] — recommendations that are reflected in international policy[3].

Antibiotic-resistant bacteria are responsible for 5,000 deaths per year in the UK, and levels are rising alarmingly — 10 million people will die due to antibiotic resistance by 2050 if no new advancements are made[5]. Furthermore, the Department of Health strategy stated: ‘Coupled to this, the development pipeline for new antibiotics is at an all-time low... The process of developing new antimicrobials and new technologies to allow quicker diagnosis and facilitate targeted treatment must be accelerated[4].

In wound management (whether acute or chronic wounds), it is crucial to assess and diagnose infection correctly, and to use products and techniques that do not contribute to the growing problem of AMR[8]. Therefore, where possible, infection in wounds should be managed locally rather than systemically. In chronic wounds, where there may be large numbers of bacteria in the wound without overt signs of infection (colonisation), it is important that antibiotics are not used and the reduction in colonisation is managed locally, through wound cleansing and debridement regimens.

Chronic wounds and infection

Infection is one of the most common complications in chronic wounds, and also delays healing further[6]. Diagnosing and treating an infection in a chronic wound is often more complex than in an acute wound, as acute wounds are more likely to display classic symptoms of infection (colonisation), it is important that antibiotics are not used and the reduction in colonisation is managed locally, through wound cleansing and debridement regimens.

Wound colonisation and biofilm

When a microbe attaches to the wound bed, biofilm begins to form — a complex structure of microorganisms that forms a thick, slimy barrier to protect bacteria and block the penetration of antibodies and other immune responses[9]. Biofilms may consist of a single or multiple bacterial species, and in chronic wounds where biofilm is present, the likelihood of systemic antibiotics working is very low for several reasons[8], including inability of the antibiotic to penetrate through the biofilm. In one study using electron microscopy, biofilm was identified in 60% of chronic wounds[9]. Bacteria exist in two states within biofilms: those that are firmly attached to the surface or the matrix (sessile state),...
or those that are free floating (not attached) and capable of invading further tissue (planktonic state). As well as protecting bacteria, biofilm presence also delays healing by promoting responses such as inflammation and increased exudate\(^7\). In chronic wounds where biofilm has formed, bacteria play a critical role in the failure of the wound to heal, but the wound may not show obvious signs of infection\(^10\), as the bacteria within the biofilm may not be activating the immune system. In addition, a bacterial species behaves differently within a biofilm, and regulation of bacterial growth and toxin production is greatly affected.

Although early identification and treatment of a biofilm in a wound can increase healing rates and improve patient wellbeing, they are microscopic structures and difficult to identify with the naked eye\(^11\). However, biofilm presence may be indicated by factors including the following\(^12\):

- Failure to close or progress to healing despite appropriate therapy
- Exudate and malodour
- Shiny, slimy wound surface
- Persistent necrotic tissue
- Persistent slough.

Biofilms start to form quickly (within two to four hours) and evolve into a fully mature community within two to four days; they recover rapidly from mechanical disruption and reform within 24 hours\(^13\). Therefore, chronic wounds that fail to heal and become static, or those that become infected, need to be treated using multiple approaches to promote healing and manage infection. Treatments include:

- Wound cleansing/irrigation
- Debridement
- Antimicrobial soaks/washes
- Topical antimicrobials.

### The role of wound cleansing/irrigation

Biofilm-based wound care involves breaking up the biofilm and preventing its redevelopment; targeting biofilms through wound cleansing is an important method in managing chronic wounds and preventing infection\(^15\).

Wound cleansing is defined as the removal of surface contaminants, loose debris, slough, softened necrosis, microbes and/or remnants of previous dressings from the wound surface and its surrounding skin\(^14\). Wound cleansing assists wound bed preparation by removing loose material to create optimum conditions for healing.

Cleansing and preparing the wound bed is one of the key steps in assessing the wound and selecting appropriate treatment [Figure 1] for a best practice decision-making algorithm, using the TIME principle. The TIME principle in wound healing involves: tissue management (T); reducing infection and inflammation (I); maintaining moisture levels (M); encouraging epithelialisation of the wound edge (E)\(^15\). The preferred method of wound cleansing is irrigation, which clears the wound of debris and microbes, while avoiding wound bed trauma\(^14\).

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<th>Box 1. Tips for wound irrigation.</th>
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<td>- The choice of solution should be based on both examination of the wound and a holistic assessment of the patient</td>
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<td>- When delivering irrigation, consider the patient’s needs and the wound itself, taking into account factors such as levels of pain experienced and general skin fragility</td>
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<td>- Irrigation solution volumes of 50–100ml per centimetre of wound length is the standard rule</td>
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<td>- To prevent cross-contamination, the clinician should wear personal protective equipment and make sure not to use solution that has been opened for longer than 24 hours</td>
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<td>- For the patient’s comfort, make sure that irrigation is at room temperature or slightly warmer. Use analgesia for painful wounds</td>
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<td>- Position the patient so that the solution runs from the upper end of the wound downward (unless the upper end is heavily infected and the lower end is cleaner), into a clean basin or irrigating pouch</td>
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<tr>
<td>- Record all aspects of wound cleansing, including full assessment, date, skin care performed, dressings applied and notes on the patient’s adherence to treatment</td>
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When choosing a wound irrigation solution, it is vital that the irrigation agent does not impair the wound healing process. The broad categories of solutions that can be used for wound irrigation are: water, saline, highly reactive solutions and antimicrobial solutions.

### Water and saline

Water and saline are not cytotoxic and have not been found to be harmful to wounds; however, neither do they actively promote wound healing or contain antimicrobial properties of any significance\(^16\). Water and saline can remove planktonic bacteria and other wound debris, but this cleansing may not remove some of the harmful molecules that may be present, which delays healing.
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Woundox® Irrigation Solution is a powerful, rapidly acting, broad spectrum, topical antimicrobial solution that will not allow the formation of bacterial resistance.

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**Products & technology**

**Figure 1: Best practice decision-making algorithm**[^5].

The Cochrane review on water and saline as irrigation agents[^14] found no evidence that using water and saline to cleanse wounds increases infection; however, the review also found that there is no strong evidence to indicate that cleansing with water and saline is better than not cleansing, and concluded that more research was needed. It was also noted that even ‘safe’ tap water can become colonised with microbes, which may in turn infect wounds irrigated in this way[^17].

**Highly reactive solutions**

The highly reactive solution options such as peroxide and povidone iodine, as well as some commercially available products (e.g. foams, soaps, wipes and solutions with surfactants), can be cytotoxic[^18,14]. The Cochrane review[^17] found that highly reactive solutions have little effect on controlling wound bacteria; in fact, they may interfere with healing mechanisms.

**Antimicrobial solutions**

Common cleansing agents in this category have been found to be effective while having a minimally toxic effect when used in low concentrations[^14]. Because they are antiseptic rather than antibiotic, antimicrobial solutions also have the advantage of being widely usable in chronic wounds without resulting in AMR issues. They also have the ability to

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[^5]: Best practice decision-making algorithm. The wound has not improved, and signs of infection continue. Discontinue treatment and reassess underlying conditions to determine what factors might have changed or need to be considered.
reduce bioburden, and disrupt and/or prevent biofilm, effectively\(^{[14]}\).

**New advances**

Hypochlorous acid (HOCI) is a powerful antimicrobial agent. It is highly active against all bacterial, viral and fungal human pathogens\(^{[15]}\), while preventing the creation of resistant strains by attacking bacteria at multiple sites\(^{[20,21]}\). HOCI has been shown to have specific anti-biofilm activity, and is able to rapidly penetrate through biofilm, in order to kill the microorganisms within the biofilm\(^{[19]}\). This is effective at low concentrations, while also being non-cytotoxic and non-irritating\(^{[22]}\).

HOCI is naturally produced by the body as a fundamental immune response against infection — when white blood cells engulf pathogens, HOCI is generated, which neutralises bacteria as part of the oxidative burst process\(^{[22]}\). HOCI demonstrates antimicrobial properties by targeting DNA synthesis within bacteria cells, which not only kills the bacteria but inhibits further bacterial growth or mutation — crucially, helping to prevent the development of resistant bacterial strains\(^{[20]}\).

HOCI is also commercially available as an antimicrobial wound cleansing solution (e.g., Woundox\textsuperscript{R} Irrigation Solution, Martindale Pharma). Woundox Irrigation Solution was specifically designed with the aim of preventing the development of resistant bacteria.

**In vitro studies** showed that Woundox Irrigation Solution has rapid, broad-spectrum antimicrobial action against the bacterial species commonly found in chronic wounds. Application of Woundox Irrigation Solution to microbes known to inhibit wound healing successfully reduced 25 of the 27 microbes tested by 99.99% (4-log) or more, within 15 seconds of exposure\(^{[23,24]}\). Of the two organisms that were not reduced by 99.99% or more, *Aspergillus brasiliensis* (a fungus) was reduced by 99.3% (2-log) and *K. pneumoniae* by 93.3% (1.2-log). In *in vitro* studies for longer exposure time (30 seconds/1 minute/3 minutes) are currently ongoing.

It was also demonstrated that Woundox Irrigation Solution is effective in destroying biofilms — following 3-minute treatment with Woundox Irrigation Solution on 72-hour pre-formed biofilms, a biofilm assay showed that no viable bacteria were recovered\(^{[23,24]}\). Woundox Irrigation Solution demonstrated clinical efficacy within 3 minutes, compared to 10–15 minutes for comparable solutions. Clinical studies have reported generally improved wound-healing outcomes with HOCl-based products such as Woundox Irrigation Solution\(^{[23,24]}\). New approaches to wound cleansing should include an agent that contains a tolerable and efficacious antimicrobial that reduces microbial bioburden within the wound bed, promotes an optimal healing environment and the development of healthy tissue, making Woundox Irrigation Solution an ideal option in current clinical practice, while fitting in with important new strategies for combating the crisis of antimicrobial resistance.

**Conclusion**

Inappropriate prescription and overuse of antibiotics in managing chronic wounds, together with their inability to easily penetrate and act within biofilms, have contributed to the increasing development of resistant microbial strains\(^{[25]}\). To combat this, irrigation with an antimicrobial solution should be used as standard practice for chronic wounds. Healthcare professionals can now harness the natural, concentrated power of HOCI for the effective management of chronic wounds and wound bed preparation. Treating infection with a HOCl-based topical antimicrobial, such as Woundox Irrigation Solution, rather than systemic antibiotics, will reduce bacterial bioburden without contributing to the development of resistant microbial strains, while promoting an optimal healing environment\(^{[26]}\).

**Acknowledgment**

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References:

23. Martindale Pharma, Clinical evaluation report. Data on file
24. Martindale Pharma, Biological evaluation report. Data on file