Reactive oxygen species treatment in the management of wounds

KEY WORDS
- Anti-Biofilm
- Antibiotic-sparing agent
- Antimicrobial stewardship
- Infection prevention
- Reactive Oxygen Species
- Surgical prophylaxis

Bacterial colonisation and biofilm production with subsequent inflammation and infection is a huge global health problem in wounds especially in diabetes, burn victims, the elderly. In an era of increasing antimicrobial resistance, there are few entirely novel antimicrobial agents in development and antibiotics have limited efficacy in the presence of heavy bacterial bioburden and biofilm. A novel therapy with activity against bacterial load and biofilm is Reactive Oxygen Species (ROS), oxygen radicals, as an antimicrobial mechanism. ROS can be delivered to the site of infection in various formats. ROS is highly antimicrobial against Gram positive and negative bacteria, viruses and fungi. It prevents and breaks down biofilm. These functions make ROS potentially highly suitable for chronic soft tissue inflammation: wounds, ulcers and burns. In addition to its therapeutic role, ROS could play an important part in surgical prophylaxis, infection prevention and antimicrobial stewardship.

Bacterial and fungal biofilms are a significant problem in many clinical settings particularly wounds and soft tissue lesions by virtue of their increased tolerance towards conventionally prescribed antimicrobials (Percival and Bowler, 2004; Davis et al, 2006; Dryden et al, 2017a). Antibiotic use in such conditions (chronic wounds, burns, certain surgical sites, prosthetic devices, chronic respiratory conditions and cystic fibrosis, recurrent cystitis) leads to intense selective pressure often resulting in further antibacterial resistance. Alternative therapeutic strategies that can improve antimicrobial efficacy towards biofilms, thereby limiting antibiotic use and reducing the development of further resistance would be of considerable benefit (Dryden et al, 2017b). One such development may be the use of topical therapy with Reactive Oxygen Species (ROS) in heavily colonised lesions with a host inflammatory response which is often referred to as 'slough.' This will be referred to as 'critical colonisation.' (Dryden et al, 2017a). Therapies involving ROS as a mechanism of action are already available in clinical use for wounds and are being developed for clinical use in other settings (Dunnil et al, 2015; Dryden et al, 2017a; Dryden et al, 2017b).

There is a global antibiotic resistance crisis which may limit therapeutic choices in the future (WHO, 2014; Davies 2013). Governments and professional groups are developing antimicrobial resistance (AMR) strategies that include programs of antimicrobial stewardship (Department of Health and Department for Environment, Food and Rural Affairs, 2013; AMR Review, 2016). Such a program has recently been published specifically for wound care (Lipsky et al, 2016). The more widespread use of ROS in wounds to reduce bacterial bioburden may prevent extension of critical colonisation to deeper infection and reduce the requirements for systemic antimicrobials. The first entirely novel antimicrobial agent to reach early clinical use is one employing reactive oxygen species (ROS) as its mechanism of action and this is specifically for wound treatment (Dryden et al, 2016). Currently available wound ROS therapy is in the form of a honey delivery mechanism — SurgihoneyRO™— not to be confused with other pharmaceutical grade honeys. SurgihoneyRO is engineered honey which delivers therapeutic levels of ROS at constant, steady concentrations over a prolonged period. A synthetic ROS gel is in production.

MATTHEW S DRYDEN
Hampshire Hospitals Foundation NHS Trust, Winchester & University of Southampton Faculty of Medicine, Southampton, UK

THE PROBLEM OF TREATING INFECTION IN WOUNDS

The disease burden of skin and soft tissue care is extensive throughout the world. In the UK alone more than 100,000 new patients per year are estimated to develop leg ulcers at a cost to the UK health service in 2005/6 of up to £198 million. Pressure ulcers were estimated to cost up to £2.64 billion at 2006/6 prices (Posnett and Franks, 2008) and diabetic foot ulcers and amputations up to £662 million in 2010/11 (NHS, 2012).

Although skin and soft tissue infections are among the most common for which antibiotics are prescribed, there is little published guidance for prudent antimicrobial therapy practice for these patients. A recent position statement has reviewed the issues around antibiotic prescribing in this area (Lipsky et al, 2016). The main problem is the diagnosis of infection, particularly in chronic wounds. All breaks in the skin get colonized with bacteria. It is not possible to rely on the results of microbiology swabs to determine infection. The difficulty is in knowing when there is a pathogenic combination of bacterial invasion and inflammation requiring systemic antibiotics (Lipsky, 2012). Colonised wounds and infected chronic wounds are frequently polymicrobial, and most wounds take many weeks (or even months) to heal. Some clinicians think that they should continue broad spectrum antibiotic therapy until healing occurs, but no evidence supports this belief (Abbas et al, 2015). Furthermore, because wounds are frequently recurrently infected, these patients are often exposed to repeated courses of therapy. Additionally, while some wounds that show evidence of inflammation may not be infected, there is currently no universally accepted criterion standard for diagnosing infection. These factors frequently lead to antibiotic misuse among patients with both infected and uninfected wounds, ultimately leading to antibiotic-resistant infections (Howell-Jones et al, 2006).

A study in Sweden, where the consensus is to restrict antibiotic therapy of wounds, found that 27% of patients being treated via hospital care were receiving systemic antibiotic therapy, a rate of antibiotic therapy over 10 times higher than that for the whole population of the study region (Tammelin et al, 1998). Another report from Sweden, where a mandatory national registry of ulcer treatment was subsequently established (Oien and Forsell, 2013), documented widespread unnecessary use of systemic antibiotics in the management of chronic wounds. Introduction of the registry led to a dramatic 40% reduction in patients receiving antibiotic (Oien and Forsell, 2013).

THE USE OF TOPICAL ANTIMICROBIALS IN WOUNDS

The use of topical antimicrobials in wounds is controversial. While systemic antibiotic therapy is appropriate for most clinically infected acute wounds, topical antimicrobial (antibiotic and non-antibiotic) agents may have several potential benefits for superficial, mild infections (Lipsky and Hoey, 2009). A small amount of topical agent can achieve high levels directly at the site of infection; it avoids systemic adverse effects; and allows use of agents that cannot be administered systemically. There is much regional and geographical variation in the use of topical antibiotics, and in resistance rates of pathogens to these agents. There is limited evidence of the effectiveness of topical antibiotics and they often select for resistant colonizing bacteria. Furthermore, topical treatment may cause peri-wound skin irritation, rash, eczema or impairment of wound healing (Gottrup et al, 2013). Concerns also remain about possible cytotoxic effect of topical antimicrobials on the wound bed, especially with long-term treatment (Wilkinson, 1998; Holder and Boyce, 1999). A few topical antibiotics, e.g. fusidic acid, mupirocin, neomycin, have been used to treat localized acute superficial skin infections, such as impetigo and folliculitis, but almost all other clinically infected wounds require systemic antibiotic therapy (Holder and Boyce, 1999; Wilkinson, 1998). Topical metronidazole may be beneficial in reducing wound odour, but the evidence is weak (Castro and Santos, 2015). Generally, topical antibiotic use should be discouraged because it is poorly effective and encourages the selection of resistance (Lipsky et al, 2016).

Non-antibiotic antimicrobials are widely used in wound care, notwithstanding the limited data supporting their usefulness. These include antiseptics, e.g. chlorhexidine, povidone or iodine; heavy metals, e.g. silver, mercury (mercurochrome);

Table 1. Potential benefits and limitations of topical agents and dressings in wounds

	Topical antibiotics	Hydrocolloid alginate	Silver agents /dressings	Antiseptics (iodine, chlorhexidine)	Reactive oxygen agents
Reduction in bacterial load	+	-	+	+	+
Reduces/prevents biofilm	-	-	+	-	+
AVOIDS selection of antibiotic resistance	-	+	+	+	+
Non-toxic	-	+	-	-	+
Promotes wound healing at cellular level	-	-	-	-	+
Wound barrier	-	+	+	-	+
Wound nutrition	-	-	-	-	+
Odour control	+	-	-	+	+
Pain suppression	-	+	-	-	+
Desloughing agent	-	-	-	-/+	+

natural products, e.g. honey, charcoal. Topical antimicrobials may be helpful where there is limited localised infection of chronic wounds (Gottrup et al, 2013), although some antiseptics may delay healing (Holder and Boyce, 1999; Lipsky and Hoey, 2009). For wounds with secondary clinical signs of localised infection (Cutting and White, 2005; Leaper et al, 2015) applying topical non-antibiotic agents after adequate debridement may be useful, perhaps by suppressing biofilm formation (Leaper et al, 2015). ROS could deliver all these functions and replace all topical antibiotics and antiseptics (*Table 1*).

WHAT IS ROS?

The term 'ROS' applies to reactive oxygen radicals including superoxide anion $^{\bullet}O_2^-$, peroxide $^{\bullet}O_2^{-2}$, hydrogen peroxide H_2O_2, hydroxyl radicals $^{\bullet}OH$, hydroxyl OH^- ions (Dunnill et al, 2015). ROS are directly antimicrobial. H_2O_2 appears to elicit its antimicrobial action by a reaction with thiol groups in enzymes and proteins, DNA and bacterial cell membranes. It possesses concentration-dependent activity and toxicity. H_2O_2 is unstable, rapidly breaking down to H_2O and O^-. While H_2O_2 can be used as a cleansing, antiseptic agent, the duration of its activity is too short to be of use as a therapeutic agent. However, ROS gels have been manufactured to slowly release ROS over a prolonged period of time, to a target site (Cooke et al, 2015).

In addition to their antimicrobial activity, ROS are pivotal in the normal wound-healing response. They act as secondary messengers to many immunocytes and non-lymphoid cells, regulation of angiogenesis and perfusion into the wound area (Dunnill et al, 2015). ROS act in early host defence against infection through phagocytes and ROS burst. These immunomodulating roles could be exploited in clinical practice in addition to the direct antimicrobial activity to treat wounds and other sites of chronic inflammation, particularly when there is stalled healing, e.g. in chronic leg ulcers, pressure injury and infected/dehisced surgical wounds and burns and deeper structures of the respiratory tract, uroepithelium, peritoneum and prosthetic devices. Emerging concepts associated with ROS modulation and delivery mechanisms have the potential to introduce novel strategies into clinical practice (Dunnill et al, 2015).

ROS has potent antimicrobial activity against bacteria, fungi and viruses. ROS is rapidly active in vitro against all Gram positive and Gram negative bacteria tested including multidrug resistant (MDR) strains that are causing such infection control and therapeutic concern (Dryden et al, 2014a). Even against those organisms that produce catalase such as Staphylococcus aureus, ROS is very effective presumably because the persistent production of ROS overwhelms the catalase (Dunnill et al, 2015). Minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) are consistent amongst isolates of the same bacterial species whether the isolates were MDR or highly sensitive. MICs and MBCs are well below concentrations that can be achieved with topical

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delivery. Cidal activity is very swift with 3-fold log reduction in colony forming units in 30 minutes of exposure and complete eradication in 2 hours when the lowest potency of ROS gel was used against *Staphylococcus aureus*.

The first ROS therapeutic agent was in the form of a pharmaceutical honey wound gel, SurgihoneyRO. SurgihoneyRO is a modified honey that has been engineered to provide a constant level of ROS over a prolonged period of time when applied to a wound (Cooke, 2014). The availability of ROS from SurgihoneyRO, or indeed an alternative synthetic delivery system, can be enhanced and is scalable depending on the level of the engineered process (Halstead et al, 2016). Other ROS, antibiotic agents and delivery systems, such as gels, sprays, nebulizers and infusions, employing this mechanism are being developed and may be particularly useful for delivery of ROS to other clinical sites.

ROS ACTIVITY *IN VITRO* AND IN CLINICAL PRACTICE

SurgihoneyRO and ROS prototypes of increased antimicrobial activity were compared to five antimicrobial dressings (AMDs) containing pharmaceutical grade honeys, in their ability to prevent and disrupt biofilm formation in vitro by 16 bacterial isolates (Halstead et al, 2016). In this study, SurgihoneyRO was the most potent with efficacy at lower dilutions than the medical honeys for 5 isolates and equivalent dilutions for a further 6. SurgihoneyRO was superior in antibacterial potency to 3 commercial antimicrobial dressings containing honey.

Antibiotics have greatest efficacy in acute infections. Acute infections are caused by planktonic bacteria invading blood or tissues which react with an innate inflammatory response characterised by the proliferation of polymorphonucleocytes. Antibiotics are usually effective in resolving such acute infections quickly and efficiently. In contrast, biofilm infections do not respond well to antibiotics, although antibiotics in high dose and for prolonged periods are often used in an attempt to treat these conditions (Spoering and Lewis, 2001). This therapeutic approach is not very successful and patients with biofilm infections tend to become progressively colonised with increasingly resistant bacteria (Lipsky at al, 2016).

Wounds, breaches in the normal skin epithelium, become contaminated with bacteria which are present as skin commensals but which may become invasive causing infection. Infection occurs when bacterial growth and spread overwhelms local defences. There may be a state of critical colonisation where heavy bacterial bioburden and biofilm hinders normal healing (Woo et al, 2015; Abbas et al, 2015).

Other biofilm related infections possibly develop in a similar way to soft tissue biofilm pathology. These begin with colonisation, bacterial multiplication and biofilm formation with persistent low grade inflammation. Antibiotics are poor at controlling this process and low concentrations of antibiotic in biofilm helps select progressively resistant bacteria. This is seen in infections that occur in chronic ulcers, burns and other biofilm pathologies such as chronic rhinosinusitis and otitis, chronic bronchitis, cystic fibrosis, bronchiectasis, and chronic recurrent cystitis.

RO technologies offer an opportunity to treat biofilm infections. ROS can be delivered topically to the site of biofilms via delivery mechanisms such as SurgihoneyRO or RO gels for wounds, ears, operative sites, catheters and shunts and to many prosthetic devices. ROS agents can be added to douches and wash outs for rhinosinusitis or infiltrated in liquid form to catheters, shunts and bladders (Dryden et al, 2017a; Dryden et al, 2017b). It may be possible to develop ROS particles for inhalation to coat the respiratory tract in patients with chronic respiratory conditions or in ventilated patients (Dryden et al, 2017a; Dryden et al, 2017b). Slow continuous ROS production through such delivery mechanisms can control the bacterial load and break down the biofilm, probably reducing the need for systemic antibiotics and reducing the selective pressure which so often results in such patients acquiring MDR bacteria.

ROS IN SKIN AND SOFT TISSUE

The disease burden of chronic soft tissue lesions is huge. Superficial wounds and skin ulcers are becoming increasingly common with the rising age of the population in many countries and the global epidemic of obesity and type 2 diabetes (National Institute for Health and Care Excellence

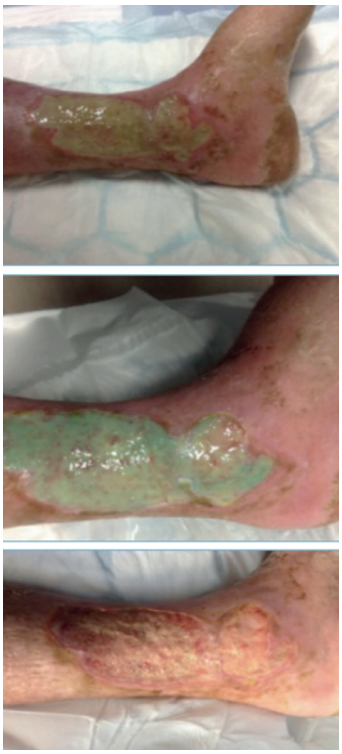

Figure 1. Ischaemic leg ulcer colonised with *Pseudomonas aeruginosa*, MRSA, mixed coliforms treated with topical SurgihoneyRO. Days 1, 4 and 10.

[NICE], 2011). In the UK, community nurses spend as much as half their time dressing leg ulcers and supervision by leg ulcer nurses is essential if standards are to be maintained in community leg ulcer services (Simon and Dix, 2004). Most chronic breaks in the skin become colonised with bacteria (Gjødsbøl et al, 2006; Renner et al, 2012; Leaper et al, 2012). It is difficult to know when and if these are pathogenic but it is likely that even if overt infection is not present, bacterial colonisation plays a role in slowing tissue healing, establishing biofilm and resulting in wound slough and an offensive odour (Scali et al, 2013; Percival et al, 2012).

The *in vitro* studies on the effects of SurgihoneyRO and ROS prototypes on bioburden and biofilm (Halstead et al, 2016) explain why SurgihoneyRO and ROS gels may be so useful in these situations where antibiotics generally perform poorly. Early use of ROS in such lesions can control bioburden and biofilm, thus sparing conventional antibiotic use, and supporting infection control (Halstead et al, 2016; Dryden et al, 2014b; Dryden et al, 2014c; Dryden et al, 2014d).

In addition, SurgihoneyRO, has all the properties of natural honey, providing healing properties (moist barrier, local nutrition, slough control, and possibly angio- and neurogenerative properties) (Al-Waili et al, 2011; Cooper and Jenkins, 2012; Dryden et al, 2017b).

In clinical studies ROS therapy through SurgihoneyRO has demonstrated satisfactory safety and tolerance and clinical and cost effectiveness in practice (Dryden et al, 2014a; Dryden et al, 2014b; Dryden et al, 2014c; Dryden et al, 2014b; Dryden et al, 2016a), but most strikingly it has demonstrated dramatic clearance of bacterial bioburden and biofilm in chronic wounds best illustrated by its effect on the multidrug resistant bacteria (*Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci) present in an ischaemic ulcer *(Figure 1)*.

SurgihoneyRO is the first ROS product available for topical use delivering sustained release of ROS as an entirely novel solution to controlling and eradicating bacteria (Dryden et al, 2017b; Dryden et al, 2014a; Dryden et al, 2017a). It has perhaps not received as much clinical attention as it deserves as it is confused with other medical honeys which have a more limited effect *in vitro* (Dryden et al, 2014a; Halstead et al, 2016). While there is good evidence that medical honey is effective in wound healing and burns (Al-Waili et al, 2011; Cooper and Jenkins, 2012), medical honeys are variable in potency and being entirely natural products their constituents are not standardised.

In an open-label multi-centre non-comparative clinical evaluation of a variety of chronic wounds SurgihoneyRO presumably through its ROS activity was able to reduce devitalised tissue (slough and necrosis) and thereby support healing (Dryden et al, 2016). This study had a wide range of different chronic wounds with underlying pathologies and comorbidities and was limited by the fact that it was an open label study. However, the study demonstrated the safety of the treatment and improvement in healing. This should pave the way for randomised controlled studies to look at the efficacy of SurgihoneyRO or ROS gels in specific types of chronic wounds, particularly burns and diabetic ulcers. Key outcome criteria are healing time and prevention of deeper infection with important secondary outcome measures such as antibiotic use and colonisation with multidrug resistant (MDR) bacteria. It has potential to reduce inappropriate antibiotic use, support antimicrobial stewardship and reduce selection for antimicrobial resistance in wound care (Cooke, 2014). It is simple to administer and could be applied to any healthcare system anywhere in the world, subject to availability, and regulatory approval. If SurgihoneyRO can do this for wounds, then ROS by other delivery mechanisms could also do this for other mucosal biofilm and internal infections. The findings of all these clinical studies strongly support a role for SurgihoneyRO in wound management, infection control, antimicrobial stewardship and preventing surgical site infections (Dryden et al, 2017a).

ROS AND SOFT TISSUE SURGICAL PROCEDURES

Antibiotic prophylaxis in surgery is well established, and in recent years there has been a tendency to reduce the duration of prophylaxis to single dosing where practical. Nevertheless some surgical procedures still have high rates of post-operative surgical site infection. For example, there has been a national increase in caesarean section (CS) wound infection (8–24.6%) (RCOG Press, 2008; Paranjothy

Table 2. ROS technology – clinical uses and therapeutic potential

Clinical Applications of ROS	Therapeutic benefits	Evidence
Wounds, skin and soft tissue	Reduction in bacterial load and biofilm. Healing promotion	Large observational study (Dryden et al, 2016) *In vitro* studies (Cooke, 2014; 2015; Dryden et al, 2014; 2017a; b; Dunnill et al, 2015; Halstead et al, 2016)
Surgical prophylaxis	Reduction in rates of surgical site infection	Temporal observation study (Dryden, 2014). RCTs required
Infection prevention	Eradication of multiresistant and pathogenic organisms	Observational reports describing effective eradication and control (Dryden et al, 2014a; b)
Antimicrobial stewardship	Great potential for antibiotic sparing around the world, particularly early use in soft tissue lesions. May have potential in respiratory and urinary mucosa to prevent colonization with MDR bacteria and requirement for last resort antibiotics.	Large observational study (Dryden et al, 2016). Further studies required
Prosthetic joint infection	Use as topical suppression therapy on joint.	Small series of case reports demonstrate efficacy and safety. Further studies required (Khan et al, 2015)
Infected Surgical cavities	Potential use in infected cavities — peritoneum, thorax, deep wounds, abscesses	No studies as yet. Two clinical evaluations in complex abdominal and abdominal wall surgery underway. Anecdotal cases of intra-peritoneal use
Upper respiratory tract	Reduction in bacterial load and biofilm. Healing promotion in sinusitis	*In vitro* and clinical studies in progress (Dryden et al, 2017a; b)
Chronic lower respiratory tract conditions	Potential to reduce bacterial load and biofilm and prevent exacerbations in chronic obstructive airway disease, bronchiectasis, cystic fibrosis, ventilator-associated infection	Limited *in vitro* data and anecdotal clinical cases (Dryden et al, 2017a; b). Further studies required
Recurrent urinary tract infection	Potential for ROS use via urinary / nephrostomy catheters to reduce bacterial load and biofilm and eradicate MDR organisms	No studies as yet. *In vitro* efficacy of ROS against MDR pathogens (Dryden et al, 2014; Halstead et al, 2016)

and Thomas, 2005) and a wide variation across NHS hospitals (13.6–31.9%) associated with the 147,726 cases of CS each year in the UK (Bragg et al, 2010). CS wound infection results in prolonged hospital stay, resource consumption, as well as other morbidities and mortality (Bragg et al, 2010). Recovery from CS is more difficult for women who develop postoperative wound infection and the burden on healthcare resources is huge (Wloch et al, 2012a). A study to investigate the potential of SurgihoneyRO to prevent CS wound infection was designed as a temporal study comparing surgical site infection (SSI) rates in CS wounds before and after an intervention with a single application of SurgihoneyRO at wound closure (Dryden et al, 2014c).

This open labelled service evaluation compared SSI rates for 3 months before the intervention, a single application of SurgihoneyRO to the CS wound at closure, and for the 3 months of using the intervention (Dryden et al, 2014c). There was a striking reduction in CS wound infection rates, from 5% prior to the intervention to 2% using SurgihoneyRO. While this study has significant limitations, it nevertheless paves the way for future randomised controlled trials of ROS in surgical prophylaxis. Considering the fact that SSIs are a leading cause of healthcare-associated infection leading to increased mortality, prolonged duration of hospital stay and increased use of resources, further SSI preventative measures are required (Wloch et al, 2012a; Wloch et al, 2012b). SurgihoneyRO application to all soft tissue surgery could potentially reduce infection rates, use of antibiotics and possibly even improve healing times, particularly when extensive soft tissue debridement or manipulation has occurred in plastic or breast procedures.

SurgihoneyRO or ROS infiltration may also benefit deeper surgical procedures such as abscess drainage or intra-abdominal surgery where there has been peritoneal contamination. SurgihoneyRO has been used in a small number of complex

revisions of prosthetic joints (Khan et al, 2015). Topical application of SurgihoneyRO directly on to the prosthetic joint has been shown to be safe and to suppress infection for up to a year and possibly eradicate biofilm associated infection. If such a simple and cheap intervention can reduce SSI to such a degree, its potential for more widespread surgical use needs urgent investigation.

ROS TO SUPPORT INFECTION PREVENTION AND ANTIMICROBIAL STEWARDSHIP

ROS has been successfully used in infection prevention (Dryden et al, 2014b). This report highlighted the efficacy of SurgihoneyRO in clearing methicillin resistant Staphylococcus aureus from wounds and carbapenemase-producing bacteria from a colonized line site, and intravascular line care (Dryden et al, 2014d). In vitro work has additionally demonstrated greater anti-MRSA biofilm efficacy for ROS than mupirocin, suggesting a possible role for topical clearance of MRSA colonized patients (Dryden et al, 2017b).

Antimicrobial stewardship as a solution for the global antibiotic resistance crisis requires a reduction or indeed even an eradication of inappropriate antibiotic use. Antibiotics are frequently used in biofilm based infections in wounds, burns, and chronic respiratory conditions with generally poor efficacy and it is notable that the organisms found in these chronic inflammatory conditions are frequently multi-resistant, selected by antibiotic pressure. ROS has great potential for the control of bioburden and biofilm at many sites, thus providing an alternative to systemic antibiotics on epithelial/mucosal surfaces.

OTHER THERAPEUTIC POSSIBILITIES FOR ROS

ROS antimicrobial activity is activated by contact with water (Cooke et al, 2015), so if ROS can be delivered directly or in a protected format to the site of bacterial load in respiratory or uroepithelium or deep surgical sites, then there is potential for antimicrobial control. Novel delivery mechanisms such as nano-particles, emulsions and nebulised aspirate may help with delivery. It may therefore be possible to use ROS in chronic respiratory, urinary and surgical sepsis *(Table 2)*.

CONCLUSIONS

With a pressing need for solutions to the crisis of global antibiotic resistance, ROS has emerged as the only antibiotic alternative to date to reach clinical use in skin and soft tissue infection and with a large range of potential clinical therapeutic uses at other sites in early development. Early clinical data supports ROS treatment in skin and soft tissue lesions to reduce bacterial bioburden and biofilm in critical colonisation and in preventing surgical site infection. This review has demonstrated the mechanism, efficacy and the wide range of existing and potential clinical applications for ROS technology. The applications of ROS technology for global health could be immense, as the agents are relatively simple to produce, safe to use, economical, simple to transport, store and administer to colonized, infected and biofilm-affected structures. As such this technology could be applicable to all health economies, developed and developing. New mechanisms of delivery should allow ROS to be applied to sites other than topical wounds, such as deep surgical cavities, and the respiratory and uroepithelium where multi-resistant organisms may cause chronic inflammation. ROS therapy may reduce the requirement for systemic antibiotics and thus reduce the selection pressure on microbes from antibiotics. ROS may suppress MDR organisms and thereby reduce transmission of these strains. ROS technology requires much further research but has the potential to deliver exciting novel therapeutic options. WUK

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