The potential use of Reactive Oxygen gel in surgical prophylaxis

Matthew Dryden

Abstract

The principles of antibiotic use in surgical prophylaxis remain the same. The purpose of this review is to introduce the investigational agent Reactive Oxygen as a possible surgical prophylaxis agent, particularly in the light of the global crisis in antibiotic resistance. There is evidence for its efficacy in the treatment of infected soft tissue and early clinical data for its efficacy in reducing infection in clean surgery (caesarean section), and in complex contaminated surgery (abdominal wall repair and prosthetic joint salvage).

Keywords Antibiotic prophylaxis; antibiotic resistance; Reactive Oxygen; surgery

Introduction

The principles of antibiotic prophylaxis in surgery have been established and remain constant. Antibiotic prophylaxis is recommended to reduce surgical site infection (SSI) in some types of surgery where contamination is a risk or where the nature of the surgery is complex or the risks of infection would be devastating. Prophylaxis involves administering antibiotics where there is no sign of infection to reduce the risk of surgical infection. Local guidelines should be referred to for the choice of specific agents in surgical procedures. Local recommendations should be based on a knowledge of local circumstances and resistance patterns amongst organisms, which means that the choice of antibiotic can be specifically targeted.

The principles of surgical prophylaxis[1]

- Antibiotics are given prior to surgery where the risk of contamination is high (e.g. colorectal surgery) or where the consequences of infection would be devastating (e.g. cardiac or prosthetic joint surgery).
- Antibiotics should cover the likely predominant microbial flora, i.e. Enterobacteriaceae and anaerobes for colorectal surgery, Enterobacteriaceae in urological surgery, and staphylococci and streptococci for most other surgery.
- Most antibiotic prophylaxis should be single dose and not extend beyond the operative period.
- Consider pharmacokinetics. Tissue levels of the antibiotic should be present prior to skin incision.
- Topical agents have not been generally recommended except in bone and joint surgery where antibiotics can be added to the cement or matrix. Reactive Oxygen preparations may be useful topical agents to apply to the operative field prior to closure but need further study.

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Conflicts of interest: none declared.

Antibiotic prophylaxis in an era of global antimicrobial resistance

Global spread of antibiotic resistance is a serious concern for the future success of surgery. The potential consequences of antimicrobial resistance (AMR) are increases in morbidity and mortality, increased use of medical resources, increase in hospital length of stay, closure of units and cancellation of surgery. All these may already be a problem in areas where there is high antibiotic resistance with inadequate surveillance and antibiotic stewardship programmes. A recent report suggested that AMR will be the main cause of death by 2050[2] (Figure 1).

What strategies may mitigate these consequences? Good surveillance, antimicrobial stewardship and infection prevention measures should be mandatory in all health settings. Development of rapid diagnostic tests can support the measures above. New classes of antibiotics have not been found. Most antibiotic developments in recent years have been largely within existing classes of agents.

One promising development may be Reactive Oxygen (RO) treatment.[3,4] Originally developed from natural honey, RO is highly antimicrobial, active against most bacteria, even multidrug-resistant (MDR) strains. There is a currently licensed agent Surgihoney (SHRO), RO in a medical honey base. A synthetic RO is being developed in a variety of formats (gel, spray, powder) for the treatment of complex polymicrobial soft tissue infection.

There are advantages to topical prophylaxis. The active agent is placed in the tissue where inoculation with the pathogenic microbes occurs. There is avoidance of the adverse effects of systemic antibiotics such as disruption of the microbiome and antibiotic associated diarrhoea. In the case of RO, there is evidence that as well as infection prophylaxis, RO may support tissue healing and regeneration.

What is RO?

The term 'RO' applies to molecules containing O_2 but which have been reduced with added electrons to become a highly reactive moiety with antimicrobial and cellular signalling properties. Examples of RO include: superoxide anion $\cdot O^{-2}$, peroxide $\cdot O_2^{-2}$, hydrogen peroxide H_2O_2, hydroxyl radicals $\cdot OH$ and hydroxyl OH^- ions. All have different actions and kinetics in cellular metabolism.[5,6]

RO is directly antimicrobial.[7,8] H_2O_2 appears to elicit its antimicrobial action by a reaction with thiol groups in enzymes and proteins, DNA and bacterial cell membranes. 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, RO gels have been manufactured to slowly release RO over a prolonged period of time, allowing sustained continuous release of RO to a target site. In such a format, and there is the potential for many delivery formats, RO can be employed as a therapeutic antimicrobial agent.

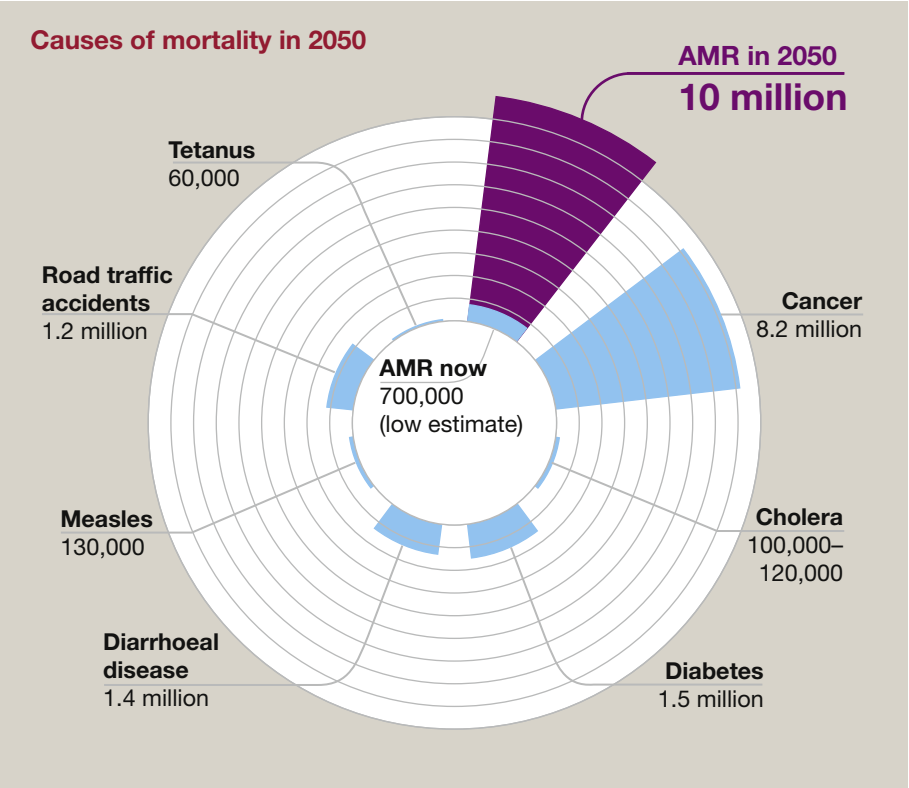


Figure 1

RO has potent antimicrobial activity against bacteria, fungi and viruses. RO is rapidly active in vitro against all Gram positive and Gram negative bacteria tested, including MDR strains which are causing such infection control and therapeutic concern.[7,8] Minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) are very 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 delivery. Cidal activity is very swift with threefold log reduction in colony forming units in 30 minutes of exposure and complete eradication in 2 hours, when the lowest potency of RO gel was used against *Staphylococcus aureus*. The unique property of SHRO and RO gel is the sustained and steady release of the oxygen radicals over 48 −72 hours, giving sustained antimicrobial activity and prolonged microbial suppression (Figure 2). This has the protentional for maintaining a sterile field in healing trauma and surgical wounds without the use of systemic antibiotics.

Reactive Oxygen preparations

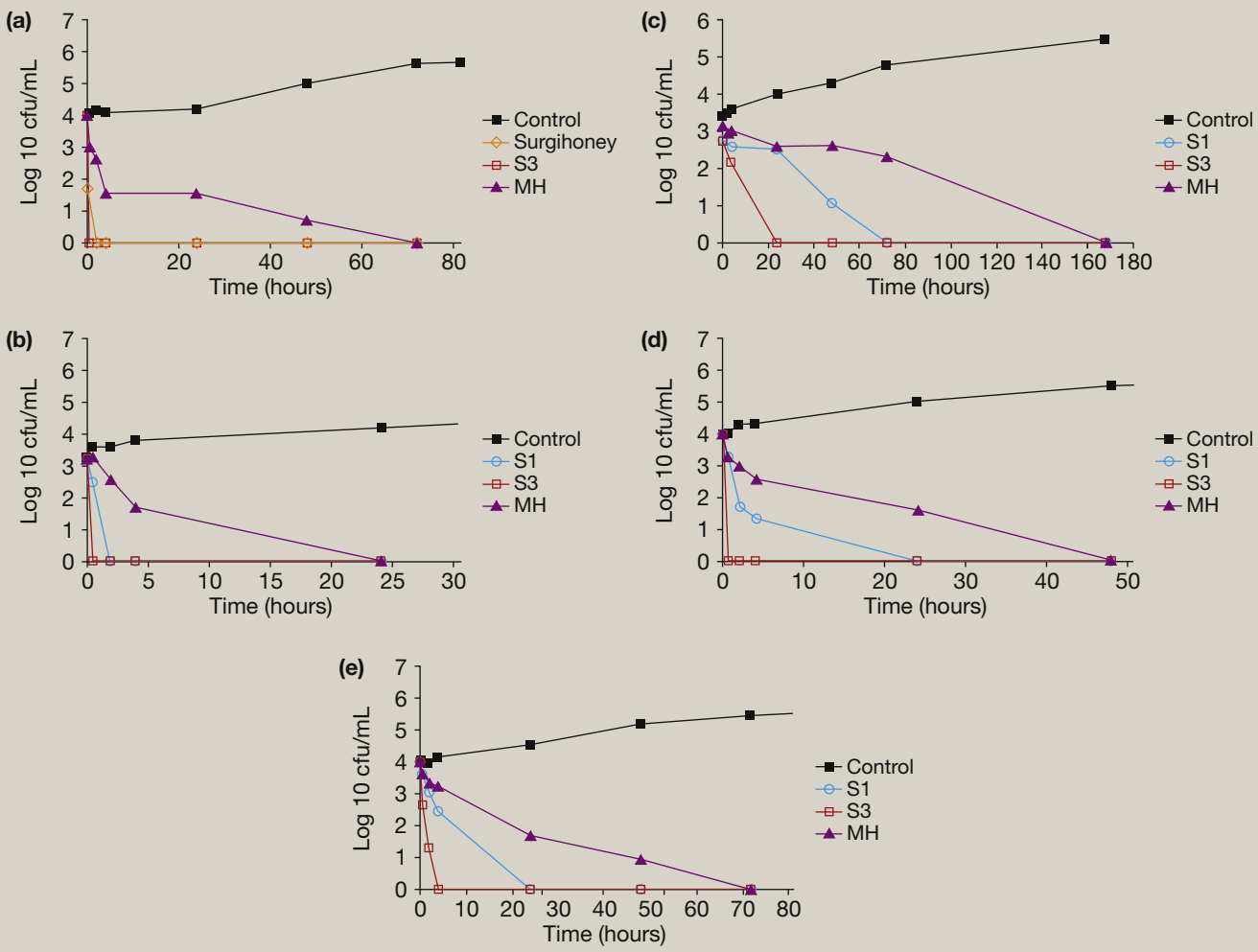
Reactive Oxygen (www.matokepharmaceuticals.co.uk) is a topical treatment for soft tissue. SHRO (www.surgihoney.co.uk) is a licensed agent with RO technology in a medical honey base. Other synthetic forms of RO are currently in development. RO has several advantages over existing treatments. It has cidal activity against soft tissue pathogens; it prevents biofilm and disrupts existing biofilm; it can be applied topically, avoiding systemic exposure and disruption of normal flora; and it is well tolerated and appears safe. Its advantage must lie in preventing and treating soft tissue infection, preserving the use of systemic antimicrobials and combatting MDR bacteria.

There is observational clinical evidence to support RO treatment in soft tissue infection, surgical prophylaxis and other clinical indications.[9–12] What is lacking at present is high-quality clinical evidence for therapeutic efficacy. The purpose of this review is to communicate the potential of RO therapy which could deliver improved clinical outcomes as well as reducing the volume of inappropriate antibiotic use and to encourage further clinical research in this area.

Antibiofilm activity

Bacterial and fungal biofilms are a significant problem in many clinical settings by virtue of their increased tolerance towards conventionally prescribed antimicrobials.[13] Antibiotic use in such conditions (chronic wounds, burns, chronic respiratory conditions and cystic fibrosis, recurrent cystitis) leads to intense selective pressure often resulting in further antibacterial resistance. There is therefore a pressing need for the development of alternative therapeutic strategies that can improve antimicrobial efficacy towards biofilms. Prevention of biofilms may be particularly relevant in surgery where biofilms cause issue, e.g. in prosthetic joint surgery, burn debridement and plastic surgery.

RO agents are effective at preventing the formation of and disrupting existing biofilm. SHRO and RO prototypes of increased antimicrobial activity were compared to pharmaceutical grade honeys (Activon manuka honey and Medihoney manuka honey) and five antimicrobial dressings (AMDs) in their ability to prevent biofilm formation *in vitro* by 16 bacterial isolates.[14] In serial



Two potencies S1 and S2, and MH (medical honey) compared with control: (**a**) Methicillin sensitive *Staphylococcus aureus*, (**b**) Methicillin resistant *Staphylococcus aureus*, (**c**) Vancomycin resistant enterococci, (**d**) *Escherichia coli*, (**e**) *Pseudomonas aeruginosa*.

Figure 2

dilution SHRO and RO protoypes were most effective in disrupting established biofilm. Additionally, SHRO was superior in antibacterial potency to three commercially available antimicrobial dressings (AMDs).

RO prophylaxis and treatment in surgical procedures

Systemic antibiotic prophylaxis in surgery is well established, and apart from skin disinfection, topical prophylactic antimicrobial agents are not routinely used except in some orthopaedic surgery. Some surgical procedures still have high rates of postoperative surgical site infection despite systemic antibiotic prophylaxis. For example, there has been a national increase in caesarean section (CS) wound infection (8–24.6%) and a wide variation across UK NHS hospitals (13.6–31.9%) associated with the 147,726 CS procedures each year in the UK.[15] CS wound infection results in prolonged hospital stay, resource consumption, as well as other morbidities and mortality. Recovery from CS is more difficult for women who develop postoperative wound infection and the burden on healthcare resources is huge. In an observational temporal study, RO via a single application of the licensed product SHRO was used as prophylaxis in CS procedures. SHRO was applied as a single dose into the wound at skin closure and this was associated with reduction in the rate of wound infection in this open study of CS by 60% with follow-up to 30 days after the procedure.[11]

SHRO or RO infiltration may also benefit deeper surgical procedures, such as abscess drainage or intra-abdominal surgery

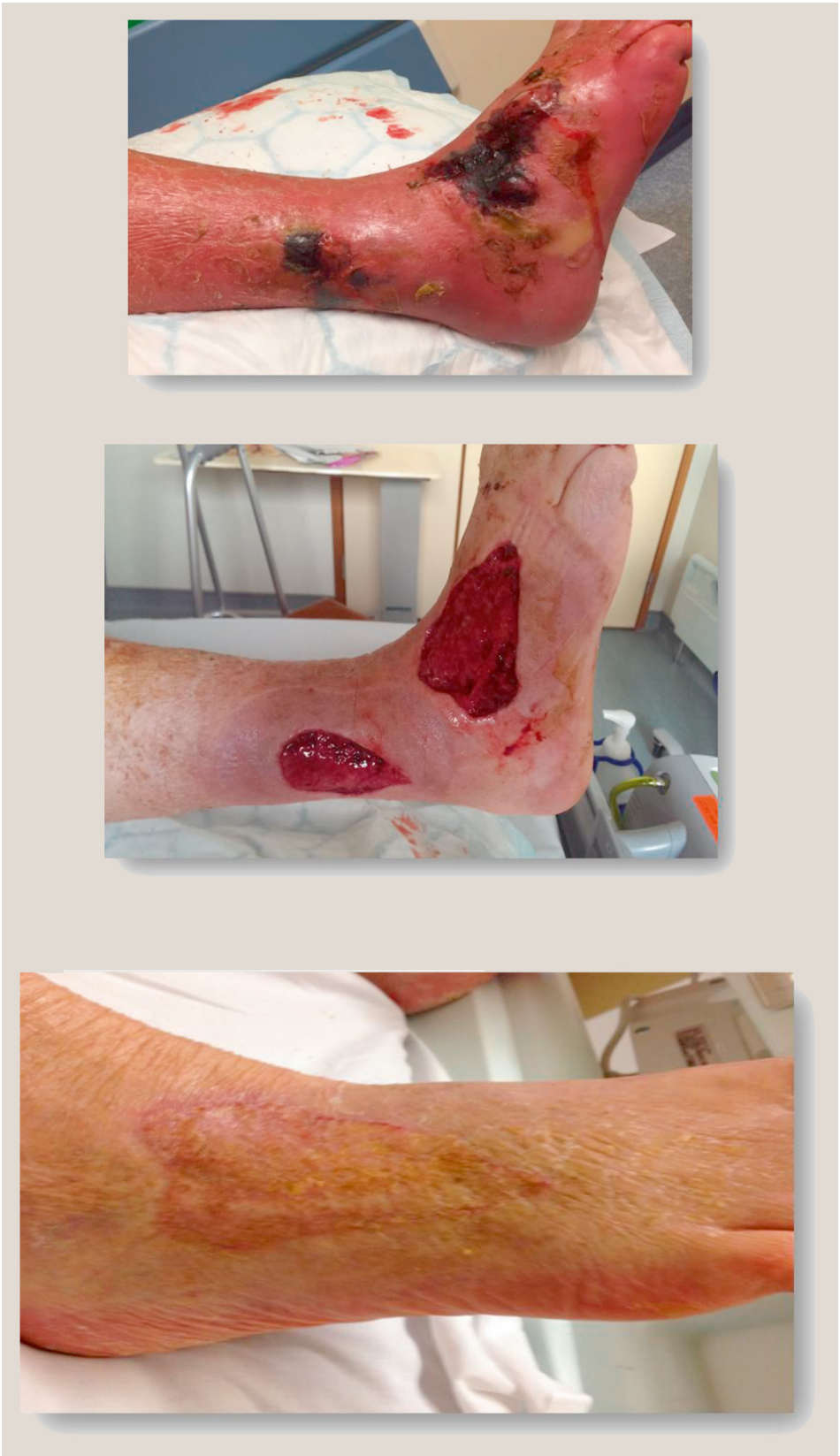


Figure 3 Surgical debridement in the presence of MDR bacteria. (a) On admission, (b) Day 7 post debridement and SHRO treatment, (c) At 2 months after plastic surgery with SHRO prophylaxis.

where there has been peritoneal contamination. SHRO has been used in a small number of complex revisions of prosthetic joints.[16] Topical application of SHRO 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 and MDR bacteria. In a pilot study of complex surgical reconstruction of abdominal walls, SHRO demonstrated a reduction in infection in analysis of preliminary data.[17] There is anecdotal information of the use of SHRO to prevent infection in wounds from trauma, military and terrorist activity. MDR *Acinetobacter* spp. have caused soft tissue and deeper infection in traumatic conflict injuries,[18] and RO has been shown to be effective against these strains, leading to investigation into its use as prophylaxis in the resuscitation and recovery of trauma victims.

Further randomized controlled trials need to be carried out, but prophylaxis with RO is a very promising development. It could reduce selection and colonization with MDR bacteria and preserve systemic antibiotics for serious 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. As SSIs in general are a leading cause of increased mortality, prolonged duration of hospital stay and increased use of resources, further exploration of RO to prevent SSI seems logical.

Case studies

- A 77-year-old man (Figure 3) suffered minor trauma while on holiday in India. He was admitted to hospital in India with soft tissue infection and gastroenteritis, and repatriated to hospital in the UK with suspected necrotizing fasciitis. Microbiology revealed MRSA, *Streptococcus* Group A, *E. coli*, *Acinetobacter* spp. and *Enterobacter cloacae*. The latter three isolates were carbapenemase producers, bacteria highly resistant to most antibiotic classes including, by virtue of the production of the enzyme carbapenemase, resistance to meropenem and its related carbapenems. SHRO was used prophylactically at surgical debridement and as therapy subsequently. MDR bacteria were eradicated with minimal systemic antibiotics.
- A17-year-old female (Figure 4) was run over by a tractor on a farm, resulting in a fractured tibia and fibula. There was no major vascular or nerve damage, but there was considerable soft tissue compression and excoriation. External fixation was required. Soft tissue colonization and mild inflammation and discharge was noted. Microbiology revealed mixed Enterobacteriaceae. There was concern about infection of the healing bone and development of osteomyelitis. SHRO was applied daily to the external pin sites to minimize the chance of bacterial migration to bone and to reduce bacterial load and inflammation to soft tissue.
- SHRO was used as prophylaxis in the operative site of a complex revision of infected knee prosthesis (Figure 5).

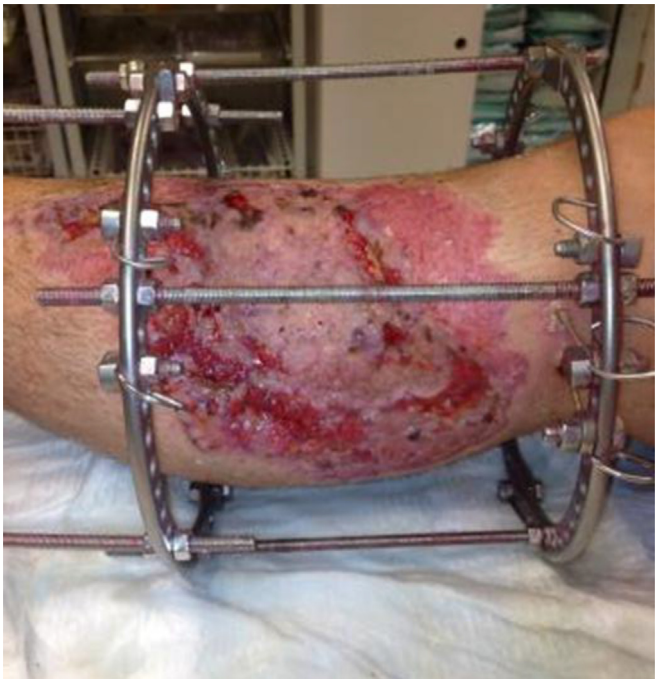


Figure 4 SHRO prophylaxis in compound fracture of the tibia and fibula with external fixation following trauma.

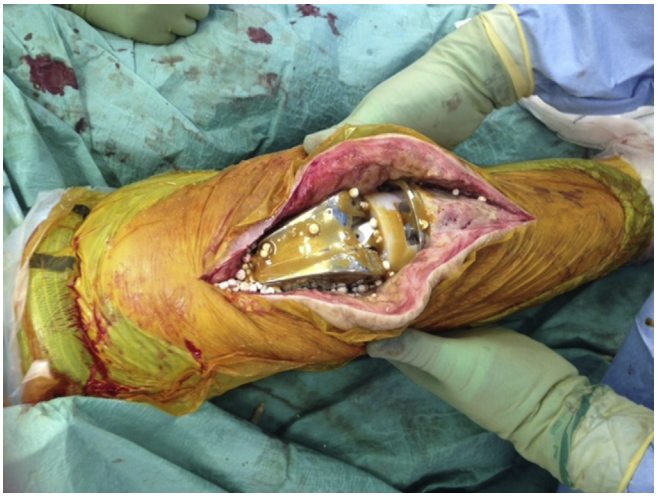


Figure 5 SHRO prophylaxis in joint replacement.

RO to support infection prevention and antimicrobial stewardship

RO has been successfully used in infection prevention.[10] This report highlighted the efficacy of SHRO in clearing meticillin-resistant *S. aureus* from wounds and carbapenemase-producing bacteria from a colonized line site. In vitro work has additionally demonstrated greater anti-MRSA biofilm efficacy for RO than mupirocin, suggesting a possible role for topical clearance of MRSA colonized patients.[7]

If RO can be used in surgical prophylaxis and in the management of complex wounds with heavy bacterial colonization and biofilm, then it may be a successful tool in antimicrobial stewardship by supressing MDR bacteria, limiting transmission and reducing the use of unnecessary antibiotic prescribing.

Conclusions

RO is an entirely novel bactericidal agent in early clinical development. The future of medicine and surgery is threatened by the spectre of antimicrobial resistance. Further investigation

will show if RO can play a role in preventing surgical site infection and whether it can support the management of complex surgical lesions including soft tissue reconstruction, plastic surgery, ENT surgery of the upper respiratory tract, burns and, possibly, deeper surgery including prosthetic joints. Clinical use to date shows that RO is well tolerated and appears safe. RO could play a role in limiting use of systemic antibiotics and reducing selection pressure of MDR bacteria. ◆

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Practice points

- Follow local/national guidelines for surgical antibiotic prophylaxis
- Surgical prophylaxis should be single dose in most cases and not extend beyond the operation
- Reactive Oxygen gel administered to the operative site is a novel surgical prophylaxis in development
- Reactive Oxygen gel is highly antimicrobial and may aid tissue healing
- Reactive Oxygen gel is active against multidrug-resistant bacteria