Reactive Oxygen: a new solution to antimicrobial resistance

In April of this year tissue viability nurses, professors, surgeons, and microbiologists met at the University of Birmingham to discuss a real solution to the developing antibiotic resistance catastrophe.

The symposium 'Reactive Oxygen (RO): transforming wound care & infection control in an age of antimicrobial resistance' featured presentations from researchers at Southampton, Birmingham and Manchester universities, who are collaborating with British biotech company Matoke Holdings Ltd to develop its innovative Reactive Oxygen technology as a new solution that could make a real difference in rich countries and poor. Surgihoney RO (SHRO) is already approved as an antimicrobial and antibiofilm dressing for use on topical wounds, ulcers and burns. Now the technology is being developed to tackle other complex, clinical infections where existing antibiotics are failing.

Reactive Oxygen allows for the accurate delivery of low levels of hydrogen peroxide (H_2O_2)—a reactive oxygen species—at a controlled antimicrobial potency and therapeutic dose to the infection site for a sustained period.

Professor Jonathan Cooke

Professor Jonathan Cooke, Visiting Professor of Infectious Diseases, Department of Medicine, Imperial College London and Honorary Professor, Faculty of Medical and Human Sciences, University of Manchester, opened by stating: 'There are a number of innovations from nature that are now mainstream.' These include Taxol, an anti-cancer drug derived from the Pacific Yew tree; Ergometrine, a medicine used to control heavy bleeding after childbirth, obtained from a fungus found on rye plants, and penicillin, the first antibacterial drug, developed from the Pencillium fungus.

Meanwhile SHRO is a bioengineered honey. The active ingredient is Reactive Oxygen. 'No cases of antimicrobial resistance have been identified to this molecule at all', said Professor Cooke, adding 'It is positively lethal to bacterial organisms.'

Prof Cooke explained reactive oxygen species (ROS) have a pivotal role in the normal wound healing process as a host defence against infection, stimulating growth of new blood vessels and tissue repair. He listed considerations when developing therapeutic innovations for clinical use, including:

- Safety and tolerance; there is no point producing something that works in the lab that is toxic to humans
- Clinical effectiveness; does it work in the clinical environment, the conditions (chronic/acute wounds) we face on a daily basis?
- Cost effectiveness; is it worth it?
- Professor Cooke told delegates SHRO met all the criteria.

Dr Matthew Dryden

Dr Matthew Dryden, Director of Infection at Hampshire Hospitals NHS Foundation Trust, Public Health England and visiting lecturer at the University of Southampton School of Medicine, started by identifying the problem:

- Inappropriate antibiotic use
- Global antimicrobial resistance
- Wound infections, colonisation and biofilms
- Toxic/ineffectual topical agents.

Dr Dryden, a consultant microbiologist, pointed out that none of us know what it is to live without antibiotics; they have saved more lives than any other drug, and we have an impending global crisis. We have very few new antibiotics; most are 'cousins' of existing agents.

He then presented 'The Solutions':

- Better stewardship
- Good infection control and public health
- Better (and faster) diagnosis
- Invigoration of antibiotic discovery
- Antibiotic alternatives: bacteriophages, probiotics, AR breaker molecules, bioelectronics, and Reactive Oxygen.

Asking, 'Is Reactive Oxygen a solution?' he explained that it is powerful, non-toxic, highly antimicrobial and has a sustained release.

Dr Dryden was the first clinician to use SHRO in the clinical environment, and he recognised that it had indications for:

- Chronic wounds
- Burns
- Ulcers
- Infection prevention
- Chronic sinusitis
- Chronic wet ear
- Chronic obstructive pulmonary disease
- Recurrent urinary tract infections
- Prosthetic material infection.

Initially he tested the effectiveness of SHRO in the laboratory on a range of bacteria, including *Staphylococcus aureus*. His clinical evaluations, included a cancer patient with a central line colonised with carbapenemase-producing *Enterobacteriaceae* and a paediatric patient who had contracted MRSA after abdominal surgery. In both these cases no antibiotics were used and outcomes was positive Another was an open fracture of the leg (the woman had been run over by tractor). SHRO cleared all bacteria from the surface and prevented deep-seated infection.

In an interview following Dr Dryden's presentation he explained that a developing area for the use of Reactive Oxygen is mucosal infections; respiratory and possibly urinary tract infections.

'I see Reactive Oxygen as a potential solution to antibiotic resistance' Dr Dryden said, emphasising that it is not a replacement but could minimise the use of antibiotics in some cases, and prevent infection, for example diabetic foot ulcers if applied at first signs of excoriation.

Mr Rami Salib

Mr Rami Salib, Associate Professor of Rhinology, Consultant Ear, Nose and Throat Surgeon and Head of Upper Airway Research Group at the University of Southampton, presented Reactive Oxygen as a novel, topical, biofilm-targeted therapy in chronic rhinosinusitis (CRS). CRS is an expensive condition with significant impact on quality of life of sufferers, costing the NHS £100 m a year, with some patients needing multiple operations during their lifetimes.

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Mr Salib is currently researching the repurposing SHRO by dissolving it into a nasal douche to deliver into the sinuses of patients following sinus surgery. The hypothesis is that the SHRO will kill the resistant bacteria that cause recurrent infections. In an interview after his presentation, Mr Salib said he was confident this could reduce the number of operations needed by patients with CRS. This would in turn reduce the amount of antibiotics prescribed to CRS patients, a potentially significant development in the fight against antibiotic resistance. Mr Salib's research is currently in the lab, but he and his team hope to progress this to a clinical trial within 2 years.

Dr Ray Allan

Dr Ray Allan, Southampton NIHR Wellcome Trust Clinical Research Facility Post-doctoral Research Fellow and member of the Upper Airway Research Group, emphasised the emerging threat of antimicrobial resistance. He explained that to find alternative therapeutic strategies we need to better understand the bacteria causing disease. He has been looking at bacteria that cause otitis media (middle ear infection). This is a common infection in young children, has a high socioeconomic cost, and is the number 1 reason for paediatric antibiotic prescriptions. The results of their research show that SHRO targets a weak spot in *Haemophilus influenzae*, a bacterial species responsible for causing otitis media. SHRO was found to be a more effective treatment than commonly prescribed antibiotics.

Dr Beryl Oppenheim

Dr Beryl Oppenheim, consultant microbiologist, University Hospitals Birmingham NHS Foundation Trust, has been working with clinical scientist Fenella Halstead at the NICH Surgical Reconstruction Microbiology Research Centre to examine the performance of SHRO as an alternative topical agent in light of problems of antimicrobial resistance. She highlighted chronic biofilms are involved in 60% of infections, are difficult to treat and resistant to antibiotics. She emphasised that there is now a body of evidence to support the idea that biofilms delay wound healing (Percival et al, 2012).

SHRO was compared to five other honey products and proved to be the most potent and was most effective at lower dilutions (Halstead et al, 2016). The NICH study found SHRO prevented biofilm formation for all 16 bacteria tested, both Gram-positive and Gram-negative and several multi-drug resistant species, including MRSA, E.coli and Pseudomonas aeruginosa. Dr Oppenhem said the research demonstrated; 'SHRO is effective at preventing and eradicating biofilms in vitro.' She concluded: 'We think it is potentially an exciting option for chronic wounds.' Delegates heard the next step is a small-scale, clinical trial on long-term venous leg ulcers.

Dr Jill Brooks

Dr Jill Brooks, former head of tissue viability for the NHS in Oxfordshire and expert in tropical disease nursing, visits Uganda and Ethiopia to provide support in wound care. The most common problems she sees are:

- Lack of access to healthcare facilities
- Lack of literacy and health literacy
- Poverty
- Untreated comorbidities, e.g. diabetes
- Lack of resources and equipment.

Burns are common, especially in children, from open cooking fires and kerosene lamps as many homes lack electricity.

Products used in wound care in Uganda and Ethiopia, in Dr Brooks' experience, include Savlon, sterile saline and bleach. Dry gauze (autoclaved), cotton wool padding, Vaseline gauze, gauze bandages and tape are used as dressings. She introduced SHRO to the healthcare teams she worked with and it was used on 20 patients in Uganda and 20 in Ethiopia. In an interview following her presentation Dr Brooks said that, in her experience, SHRO aided wound healing more quickly than any other product she had tried. She has not seen a single adverse reaction to it and would be confident in using it on any wound she was faced with. The only issue of note was that it produced more exudate and so required more frequent dressing changes.

Dr Brooks concluded that SHRO is ideal for the developing world because it is an effective antimicrobial and antifungal, easy to store, has a long shelf life, is unaffected by high ambient temperatures, easy to apply, and does not cause trauma when dressings are changed.

Michel Clough and Claire Stephens

Michel Clough, veteran amputee, British Army Infantry, and Claire Stephens, complex wound manager and CEO of Woundcare4Heroes, presented together on Mike's experience of using SHRO as a patient. Following a complex open fracture to his left leg after a parachute jump, Mike had five episodes of surgery, plates, screws and an external fixation frame in an attempt to stabilise his injury. It was eventually decided, after 4 years of complex pain and infection, the limb should be amputated and Michael was put in touch with Woundcare4Heroes, a veteran's charity, which provided vital clinical support. Since the amputation, Mike's CRPS has reduced significantly and the wound treated predominantly with SHRO. Following some simple guidance from Claire, Mike's partner is able to apply the SHRO topically to the wound and as a wound cleanser.

Unfortunately, Michael suffered a setback following a decision by his local limb centre to stop using SHRO and the wound became infected again. He ended up back in hospital where he endured further surgery to treat the infection and SHRO was reintroduced. The infection cleared up and healing resumed. Mike emphasised to delegates how easy SHRO was to use and his concern it was not more widely known and available. 'We have a saying in the military, 'first line of defence'', said the former soldier, adding: 'I think it should be readily available to paramedics and within the military to stop infections developing in the first place in everything from injury blasts to minor injuries. Claire said Michael 'lost his leg to infection' and he needed 'the most powerful antimicrobial they could get their hands on' to save his residual limb, so he could have a prosthetic limb fitted in future. **BJN**

Close of symposium

In his closing remarks, Dr Dryden said:

> 'This has been an historic symposium with many different disciplines talking about a novel innovation ... SHRO has so much potential and I hope it will go from strength to strength.'

Halstead FD, Webber MA, Rauf M, Burt R, Dryden M, Oppenheim BA (2016) *In vitro* activity of an engineered honey, medical grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates. *J Wound Care* **25**(2): 93–102

Percival SL, Hill KE, Williams DW, Hooper SJ, Thomas DW, Costerton JW (2012) A review of the scientific evidence for biofilms in wounds. *Wound Repair Regen* **20**(5): 647–57

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