Reactive Oxygen –
a clinical perspective in an era of antimicrobial resistance

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Bacterial bioburden and biofilm
Antibiotics do not work well

- Chronic wounds
- Ulcers
- Wound infection prevention
- Chronic sinusitis
- Chronic wet ear
- Chronic respiratory diseases
  - COPD
  - Cystic fibrosis
  - Bronchiectasis
- Chronic recurrent cystitis
- Prosthetic material infection
- MASSIVE DISEASE BURDEN
Mechanism - ROS

Technology allows for accurate delivery of low levels of H$_2$O$_2$ (Reactive Oxygen Species) at a controlled antimicrobial potency and therapeutic dose to the wound site for a sustained period of time.
Criteria for any new product

- Does it work?
- Is it safe?
- Is it worth it?
Engineered honey: In vitro antimicrobial activity of a novel topical wound care treatment

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ABSTRACT

Surgihoney is a novel engineered organic honey product for wound care. Its antimicrobial activity can be controlled and adjusted by the engineering process, allowing preparation of three different potencies, labelled Surgihoney 1–3. Susceptibility testing of a range of wound and ulcer bacterial isolates to Surgihoney by the disc diffusion method, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determination, and time-kill measurements by time suspension tests were performed. Surgihoney demonstrated highly potent inhibitory and cidal activity against a wide range of Gram-positive and Gram-negative bacteria and fungi. MICs/MBCs were significantly lower than concentrations likely to be achieved in topical clinical use. The topical concentration of Surgihoney in wounds was estimated at ca. 500 g/L. MICs/MBCs for Staphylococcus aureus were 32/125 g/L for Surgihoney 1 and 0.12/0.25 g/L for Surgihoney 3. Cidal speed depended on potency, being 48 h for Surgihoney 1 and 30 min for Surgihoney 3. Maintenance of the Surgihoney inoculum preparation for up to 4 weeks demonstrated complete cidal activity and no bacterial persistence. Surgihoney has wide potential as a highly active topical treatment combining the effects of the healing properties of honey with the potent antimicrobial activity of the engineered product for skin lesions, wounds, ulcers and cavities. It is highly active against multidrug-resistant bacteria. It is more active than other honeys tested.
Surgihoney™ Comparison

Staphylococcus aureus
ATCC 9518

Manuka Honey 25+
Non Active Honey

RO Surgihoney active against all bacteria tested

Time kill curves

Staphylococcus aureus

Effect of Surgihoney RO on chronic wound biofilm

SH prevents and reduces biofilm production by Pseudomonas sp and Acinetobacter sp.

- SH can prevent biofilm formation and reduce the seeding of pre-formed biofilms.

- SH is therefore a promising topical antimicrobial agent with potent anti-biofilm activity against key Gram-negative pathogens of burn wounds.

Criteria for any new product

- Does it work?
  - in vivo

Reactive Oxygen™
A technology platform with multiple clinical applications

- Chronic wounds & burns
- Trauma wounds
- Cuts & grazes
- Diabetic ulcers
- Preventing wound infection
- MRSA nasal decolonisation
- Chronic sinus infection
- Chronic urinary infection
- Hand hygiene & infection control
- Pan-surgical opportunities
- Cystic fibrosis
Topical wound treatment

- Hospital
  - Diabetic foot ulcers
  - Ischaemic ulcers
  - Varicose ulcers
  - Intravascular catheter line sites in oncology
  - Surgical wounds
  - Caesarean wounds

- Primary care
  - Diabetic foot ulcers
  - Ischaemic ulcers
  - Varicose ulcers

- Developing world
  - Surgical, traumatic, tropical and non-healing lesions.

Chronic wounds

91 year old independently mobile lady, lived with nephew – progressively severe and painful venous leg ulcers.

Reactive oxygen treatment over 14 days reduced the inflammation and pain, reduced bioburden and slough.

This could all have been managed in the community, saving a hospital admission.

Day 1

77 year old man
Peripheral vascular disease
Large ischaemic ulcers
Non healing

Heavily colonised with MRSA, VRE, coliforms and Pseudomonas aeruginosa.

Day 4

Day 10

Coming to a hospital near you!
Mapping the spread of Acinetobacter baumannii

Multiple, Extremely and Completely Drug Resistant Acinetobacter baumannii

The Acinetobacter Threat

Think MRSA is scary? Since the mid-2000s, a more environmentally persistent, increasingly antibiotic-resistant infection has spread throughout western Europe and the U.S.

The arrival of extensively drug-resistant Acinetobacter at U.S. hospitals caught public health officials off guard. Throughout the 1980s and 1990s, these infections were increasingly rare, with declining infection rates.

But in late 2003, U.S. Army physicians began noting a high rate of antibiotic-resistant Acinetobacter infections among soldiers wounded and initially treated in Iraq — and sporadic reports began to suggest the infections were spreading from wounded soldiers to other patients at military health care facilities.

Cross infection from injured soldiers and contractors was recognized as a "particular problem" in the U.K. But the U.S. military has consistently downplayed the risk of spread. Isolation and infection control...
Safety

- About 1000 patients treated
- No SAEs
- <2% irritation or stinging in SSTI study
- 50+ diabetics treated. No disruption of glucose metabolism
32 yr old IDDM
# Calcaneum. Infected metal work removed. Fluclox + SHRO and vac dressing

Day 0

Day 14
Dryden M. Tawse C. Adams J. Saeed K. Cooke J. The use of Surgihoney to prevent or eradicate bacterial colonisation in dressing oncology long vascular lines. 

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**The use of Surgihoney to prevent or eradicate bacterial colonisation in dressing oncology long vascular lines**

**Objective:** A pilot evaluation was performed to assess the effects of Surgihoney, an engineered honey with highly active antimicrobial activity, on bacterial colonisation in long lines in oncology patients.

**Method:** This prospective service evaluation was conducted at Hampshire Hospitals NHS Foundation Trust (HHFT) in England, UK, between 2012 and 2013. The study population consisted of oncology patients with central intravenous lines who were receiving outpatient chemotherapy. All patients were offered line dressing with or without Surgihoney, applied to the line exit site.

**Results:** The primary outcome measure of the study was the presence or absence of bacterial colonisation of the line site. There were 30 patients in each arm — with or without Surgihoney. In the Surgihoney arm, 2 patients with existing line site colonisation were cleared of bacterial colonisation and none acquired colonisation during the study period. In the non-treatment arm, 6 patients were colonised at the line site prior to screening or during the evaluation. Bacterial colonisation was maintained throughout the period.

**Conclusion:** Surgihoney is an effective antimicrobial line-site dressing, significantly reducing line site colonisation and eradicating existing colonisation. It was well tolerated by the patients.

**Declaration of Interest:** Surgihoney supplies were donated by Healing Honey International (HHI) who also provided some funding to Hampshire Hospitals Foundation Trust for microbial investigation. MD and JC have provided clinical advice in an advisory capacity to HHI.

Oncology patients receive chemotherapy through intravascular lines which are usually inserted surgically, tunnelled under the skin, and enter one of the central veins. So-called long patients to be trained in aseptic procedure to avoid contaminating the line site during dressing changes or contaminating the line lumen at any stage.

The aim of this evaluation was to investigate the role of Surgihoney™ as a topical antimicrobial...
Central line colonised with CPE (the most resistant organisms!)

Carbapenemase-producing enterobacteriaceae (CPE) at line insertion site cleared with Reactive Oxygen treatment

Paediatric MRSA wound infection

Day 0

Surgihoney

Day 10

CA MRSA superficial infection treated with Surgihoney

Day 1

Day 5

Day 10
Trauma wound treated with SHRO
<table>
<thead>
<tr>
<th>Feature</th>
<th>Hydrocolloid / Alginate products</th>
<th>Silver dressings</th>
<th>Antiseptics (e.g. iodine, chlorhexidine)</th>
<th>Surgihoney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Local wound nutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-toxic</td>
<td>✅</td>
<td></td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Promotes wound healing at a cellular level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound barrier</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Moisture control</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>De-soughing agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odour control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain suppressant</td>
<td>✅</td>
<td></td>
<td></td>
<td>✅</td>
</tr>
</tbody>
</table>
Using antimicrobial Surgihoney to prevent caesarean wound infection

Abstract

Caesarean section (CS) wound infection rates are unacceptably high, around 10% according to figures from the Health Protection Agency (2012). This service evaluation assessed the effects of Surgihoney on surgical site infection rates in women undergoing caesarean section. All women presenting for CS were offered Surgihoney as a single application wound dressing at the end of the procedure. All women were followed up and examined for surgical site infection for 30 days after CS. A single application of Surgihoney dressing reduced surgical site infection (SSI) by 60.33% from a rate of 5.42% (n=590) to 2.15% (n=186) (p-value=0.042). The potential saving to the NHS of using Surgihoney as a single application achieving this level of wound infection reduction is considerable. Surgihoney offers a simple, cost-effective intervention to reduce SSI in women undergoing CS. It is applicable to practice in all health economies and could potentially save considerable surgical infective morbidity in patients undergoing surgical delivery.

Methods

Clinical Evaluation

The evaluation was an observational study with temporal comparison of CS surgical site infection (SSI) rates. It was primarily a service evaluation for the use of Surgihoney antimicrobial dressing.
Severe fungal kerion infection (T. tonsurans) treated with topical SHRO
Skin scraping results –
Trichophyton tonsurans
Prosthetic device surgery

Honey as a Novel Antimicrobial Coating in Salvage Revision Total Knee Arthroplasty
Rhodri Llywelyn Williams, Wasim Khan, Amisha Metha, Rhysian Morgan-Jones
Department of Orthopaedic Surgery, University Hospital of Wales, Cardiff UK

Keywords: Revision, Arthroplasty, Infection, SurgiHoney

Aim: Honey has been used as a topical antiseptic for at least 5,000 years. SurgiHoney is a CE licensed sterile product, which has been proven to be non-toxic and effective when used topically in the treatment of chronically infected wounds. The key difference from other medical grade honey is the broad spectrum antimicrobial characteristics with activity against Gram +ve, Gram -ve and multi-resistant organisms. Its novel role against the bacterial biofilm and biofilm-associated with periosteal infections around total knee arthroplasties (TKA’s) is therefore considered.

The Cardiff Debridement Strategy
- Surgical: Excision & Sharp Dissection
- Mechanical: Curettage, Reraming, Levage
- Chemical: Honey
- Repeated Cyclic Debridement

Methods: SurgiHoney was used as an implant coating immediately prior to wound closure after implantation of salvage endoprostheses for multiply revised, infected TKA’s undergoing staged reconstruction.

Results: During application of the SurgiHoney we report no systemic adverse features. Physiological parameters including heart rate, respiratory rate and blood pressure were recorded and did not change significantly during and after the application. We also report good soft tissue and wound healing. Post-operatively we did not experience any wound complications or delayed wound healing. No early recurrent infection has been identified at early follow-up (6 to 12 months).

<table>
<thead>
<tr>
<th>Operation (*previous multiple surgeries)</th>
<th>Microbe</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2nd stage</td>
<td>Polymicrobial: Pseudomonas, Mycellial fungus, CNS, Eterobacter</td>
<td>6 months</td>
</tr>
<tr>
<td>*2nd stage</td>
<td>Polymicrobial: CNS aureus, Enterobacter, Mycellial fungus</td>
<td>8 months</td>
</tr>
<tr>
<td>*2nd stage</td>
<td>Polymicrobial: CNS aureus, Aspergilus</td>
<td>12 months</td>
</tr>
<tr>
<td>*2nd stage</td>
<td>Polymicrobial: including CNS aureus and various anaerobes</td>
<td>11 months</td>
</tr>
</tbody>
</table>

Conclusion: The use of SurgiHoney as a novel anti-microbial is established in the management of complex wound infections. This is the first reported use of SurgiHoney as a deep, implant coating in the salvage of prosthetic joint infection.
Future developments

Nebulised RO in COPD/bronchiectasis

Chronic sinusitis
Complex joint replacement surgery

Chronic urinary infection with multi-drug resistant organisms
<table>
<thead>
<tr>
<th>Clinical Applications of ROS</th>
<th>Therapeutic benefits</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wounds, skin and soft tissue</strong></td>
<td>Reduction in bacterial load and biofilm. Healing promotion</td>
<td><strong>Large observational study</strong>. (^{11}) <strong>In vitro studies</strong> [4,5,26,27,28]</td>
</tr>
<tr>
<td><strong>Surgical prophylaxis</strong></td>
<td>Reduction in rates of surgical site infection</td>
<td><strong>Temporal observation study</strong>. (^{39}) <strong>RCT’s required.</strong></td>
</tr>
<tr>
<td><strong>Infection prevention</strong></td>
<td>Eradication of multiresistant and pathogenic organisms</td>
<td><strong>Observational reports describing effective eradication and control</strong> (^{38,40})</td>
</tr>
<tr>
<td><strong>Antimicrobial stewardship</strong></td>
<td>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.</td>
<td><strong>Large observational study</strong>. (^{11}) <strong>Further studies required.</strong></td>
</tr>
<tr>
<td><strong>Prosthetic joint infection</strong></td>
<td>Use as topical suppression therapy on joint.</td>
<td><strong>Small series of case reports demonstrate efficacy and safety. Further studies required.</strong> (^{49})</td>
</tr>
<tr>
<td><strong>Infected Surgical cavities</strong></td>
<td>Potential use in infected cavities – peritoneum, thorax, deep wounds, abscesses</td>
<td>No studies as yet.</td>
</tr>
<tr>
<td><strong>Upper respiratory tract</strong></td>
<td>Reduction in bacterial load and biofilm. Healing promotion in sinusitis</td>
<td><strong>In vitro and clinical studies in progress</strong> (^{4})</td>
</tr>
<tr>
<td><strong>Chronic lower respiratory tract conditions</strong></td>
<td>Potential to reduce bacterial load and biofilm and prevent exacerbations in chronic obstructive airway disease, bronchiectasis, cystic fibrosis, ventilator-associated infection</td>
<td><strong>Limited in vitro data and anecdotal clinical cases</strong> (^{4}) <strong>Further studies required.</strong></td>
</tr>
<tr>
<td><strong>Recurrent urinary tract infection</strong></td>
<td>Potential for ROS use via urinary / nephrostomy catheters to reduce bacterial load and biofilm and eradicate MDR organisms</td>
<td>No studies as yet. <strong>In vitro efficacy of ROS against MDR pathogens</strong> (^{26,28})</td>
</tr>
</tbody>
</table>
Novel approach

Contamination

Debridement / Antiseptics / Reactive Oxygen prophylaxis

No colonisation with MDR

Reduction in infection / effective antibiotics

No colonisation with MDR

Contamination

Debridement / Antiseptics / Reactive Oxygen prophylaxis

Reduction in infection / effective antibiotics
Reactive Oxygen - Summary of a significant medical development

- RO has wide antibacterial properties in vitro tested in several sites
- Development of a pharmaceutical grade product
- Role in infection prevention and antimicrobial stewardship
- Potential for a wide range of clinical applications for treating skin and mucosal bacterial overgrowth and biofilm production
- Initiation and delivery of a diverse programme of clinical evaluation with highly promising results.
Thank you

Reactive Oxygen
-active against bacterial bioburden and biofilm
– a solution for healing and antimicrobial resistance.

www.reactiveoxygen.co.uk