Treating wound infection in the face of antimicrobial resistance

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Modern management of wound infection

• Knowledge of potential pathogens
• Recognising reservoirs of infection
• Preventing infection
• Interrupting cross infection
• Effective antimicrobial interventions
  • Systemic antibiotics
  • Topical antimicrobial agents
• Surveillance systems
• Education
Ancient remedies for wounds

<table>
<thead>
<tr>
<th>Animal</th>
<th>Vegetable</th>
<th>Mineral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile</td>
<td>Bark</td>
<td>Alum</td>
</tr>
<tr>
<td>Blood</td>
<td>Dyes</td>
<td>Antimony</td>
</tr>
<tr>
<td>Butter</td>
<td>Fruit</td>
<td>Arsenic</td>
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<tr>
<td>Cochineal</td>
<td>Herbs</td>
<td>Clay</td>
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<tr>
<td>Cobwebs</td>
<td>Oils</td>
<td>Copper salts</td>
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<tr>
<td>Egg white</td>
<td>Resins</td>
<td>Lead salts</td>
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<tr>
<td>Faeces</td>
<td>Sap</td>
<td>Mercury</td>
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<tr>
<td>Honey</td>
<td>Sugar</td>
<td>Potassium salts</td>
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<tr>
<td>Lard/grease</td>
<td>Turpentine</td>
<td>Tar or pitch</td>
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<tr>
<td>Meat</td>
<td>Vinegar</td>
<td>Silver</td>
</tr>
<tr>
<td>Milk</td>
<td>Wine</td>
<td>Zinc salts</td>
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</tbody>
</table>

Control of infection (pre-antibiotic era)

- Ignaz Semmelweis (1818-1865) showed that incidence of puerperal fever in a hospital in Vienna was reduced by handwashing.

- Antiseptics (iodine) were first used for contaminated traumatic wounds by military surgeons in the American Civil war (1861-1865).

- 1865 aseptic surgery introduced by Sir Joseph Lister.

Surgery often resulted in tetanus and hospital gangrene with 70-80% mortality rates.
Chemical antimicrobials for topical use in wounds

Hypochlorite (EUSOL, Dakins) 1827
Iodine 1839
Phenol 1860
Hydrogen peroxide 1887
Chlorinated phenols 1906
Flavine dyes 1913
QACs 1933
Chlorhexidine 1954
Povidone iodine 1956
Cadexomer iodine 1981
Octenidine 1984
Polyhexamethylene biguanide (PHMB) 1994
Glucose oxidase + lactoperoxidase (ROS) 2005

Selective toxicity

• Paul Ehrlich established the principles of antimicrobial chemotherapy by searching for chemicals that would kill infectious agents without harming the human host

• “Magic bullets”

• Discovery of antibiotics by Alexander Fleming (1928) has provided effective means of treating infections since 1940s

• 1944 penicillin-resistant *Staphylococcus aureus* reported
Priority list for research and development: WHO 27th Feb 2017

- **Priority 1: CRITICAL**
  - *Acinetobacter baumannii*, carbapenem-resistant
  - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

- **Priority 2: HIGH**
  - *Enterococcus faecium*, vancomycin-resistant
  - *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
  - *Helicobacter pylori*, clarithromycin-resistant
  - *Campylobacter* spp., fluoroquinolone-resistant
  - *Salmonellae*, fluoroquinolone-resistant
  - *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

- **Priority 3: MEDIUM**
  - *Streptococcus pneumoniae*, penicillin-non-susceptible
  - *Haemophilus influenzae*, ampicillin-resistant
  - *Shigella* spp., fluoroquinolone-resistant
Effective management of wound infection

• Recognise infection
  • Classic signs and symptoms
  • Ancillary signs
• Initiate empirical antibiosis
• Identify causative agent(s)
• Initiate appropriate antimicrobial intervention
  • Clinical efficacy and susceptibility
Antimicrobial interventions for wounds

• Antibiotics
Antimicrobial interventions for wounds

• Antibiotics

• Non-antibiotic antimicrobial strategies
  • Antiseptics: silver, iodine, PHMB, octenidine, chlorhexidine, honey, ROS, gentian violet, KMnO$_4$
Resistance training experiments (manuka honey)

with manuka honey  
without manuka honey

\[ E. \text{coli} (\blacktriangle), \ MRSA (\blacklozenge), \ P. \text{aeruginosa} (\bullet) \text{ and } S. \text{epidermidis} (\blacksquare) \]

Resistance to antiseptics

- Innate resistance
- Acquired resistance (mutation or gene acquisition)
  - QAC (benzalkonium chloride, cetrimide)
  - Povidone-iodine
  - Sodium hypochlorite
  - Hydrogen peroxide
  - Gentian violet
  - Triclosan
  - Chlorhexidine
  - Silver

Cross-resistance (antibiotic and antiseptic)

• Chlorhexidine
  • and mupirocin in *S. aureus*
  • and vancomycin in *Ent. faecium*
  • and colistin in *K. pneumoniae*
  • and β-lactamases in *A. baumannii*

• Silver
  • and β-lactamases in *E. coli*
Antimicrobial interventions for wounds

• Antibiotics

• Non-antibiotic antimicrobial strategies

  • Antiseptics: silver, iodine, PHMB, octenidine, chlorhexidine, honey, ROS, gentian violet, KMnO₄

  • Additional: biotherapy, NPWT, physical removal by binding to dressings
Additional non-antibiotic interventions for wounds

- Biotherapy
  - antimicrobial peptides: lucifensin, lucimycin
  - Ammonia
  - Chymotrypsin
  - Nuclease
  - Proteolytic enzymes
- Negative Pressure Wound Therapy (NPWT)
  - Reduce bacterial load?
  - + antiseptics to disrupt biofilm
- Physical removal at dressing change
  - Hydrophobic binding
Mechanical removal of microbial cells (DACC-coated dressings)

- Dialkylcarbamoyl chloride (DACC) is a fatty acid derivative that is highly hydrophobic
- Microbial surfaces are generally hydrophobic
- Microbial cells bind irreversibly to DACC-coated dressings and are physically removed at dressing change
- Low risk of resistance emerging
- No cytotoxicity

Planktonic (free living) microbes

- Pseudomonas aeruginosa
- Staphylococcus aureus
- Klebsiella
- Candida albicans
Biofilm bound to DACC-coated dressing

- *Pseudomonas aeruginosa*
- MRSA

Cooper & Jenkins (2016) J Wound Care 25(2): 76-82
Emerging non-antibiotic interventions

- Cold plasma
  - Partially ionised gas generates ROS and nitrogen species
- Phototherapy
  - Photodynamic therapy
  - UV
  - Blue light
  - Low-level laser
- Ozone
- Bacteriophage therapy
Bacteriophage therapy

• Using cocktails of lytic phage to infect bacteria
  • \textit{P. aeruginosa} in burns (UK, Belgium)
    • Verbeken et al (2016) Burns 42(1): 11-12

• Phase I safety trial in VLU (USA)

• Control of infection in DFU (USA, Europe)

• Using viral endolysins to attack peptidoglycan
Wound management in the post-antibiotic era?

Prevent infection

- Hygiene
  - Hand washing
  - Effective cleaning of hospital surfaces and equipment

- Infection control
  - Aseptic no touch technique (ANTT)

- Vaccines
  - *Pseudomonas aeruginosa*
  - *Candida*
  - *MRSA*

- Probiotics
  - *Lactobacilli*
Wound management in the post-antibiotic era?
Use current resources judiciously

• Use antimicrobial agents effectively
  • Rapid diagnostic tests for infection and/or biofilm (POC); reliable biomarkers of infection
  • Determine susceptibility for non-antibiotic antimicrobials (chlorhexidine, silver)
  • Surveillance of resistance genes for non-antibiotic antimicrobial agents
  • Monitor efficacy
  • Improve guidelines (non-antibiotic antimicrobial agents)
  • Educate/update knowledge
Selecting antimicrobial strategies

• 50% of all medicines are inappropriately prescribed, dispensed or sold, and half of all patients fail to take them correctly)
  • WHO (2010)
• In one British hospital a retrospective study showed a varied choice of treatment regimens for patients admitted with infections
• Managing wounds requires specialist training
• Evidence of ritualistic wound care
Key factors for the general misuse of antimicrobial agents in wounds

• Diagnostic uncertainty
  • Is there an infection in this wound?

• Clinical ignorance
  • When to treat?

• Clinical fear
  • Failure to treat properly or of having a bad outcome

• Patients demands
  • For unnecessary antimicrobial therapy

Wound management in the post-antibiotic era?
Find new antimicrobial interventions

• Search for new antibiotics
• Re-evaluate existing antibiotics
• Search for new antimicrobial interventions
  • Antimicrobial peptides
  • Quorum sensing inhibitors
  • Efflux pump inhibitors
  • Combination therapy
Combination therapy - SYNERGY: honey + antibiotics

Jenkins, Cooper. PLoS One (2012) 7(9)e45600
<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Combined with</th>
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<tbody>
<tr>
<td>Antiseptic</td>
<td>Acetic acid</td>
</tr>
<tr>
<td></td>
<td>Octenidine</td>
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<tr>
<td></td>
<td>Povidone iodine</td>
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<tr>
<td>Honey</td>
<td>Manuka honey</td>
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<td></td>
<td>Manuka honey</td>
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<tr>
<td></td>
<td>Heather honey</td>
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<tr>
<td>Silver</td>
<td>Silver sulphadiazine (SSD)</td>
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<td></td>
<td>Ionic silver</td>
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<td></td>
<td>Ionic silver</td>
</tr>
<tr>
<td>Bacteriophage</td>
<td>Linezolid</td>
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## Future remedies for wounds (non antibiotic)

<table>
<thead>
<tr>
<th>Animal</th>
<th>Vegetable</th>
<th>Mineral</th>
<th>Microbial</th>
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</thead>
<tbody>
<tr>
<td>Larvae of <em>Lucilia sericata</em></td>
<td>Bark</td>
<td>Biguanides: - chlorhexidine - PHMB</td>
<td>Bacteriophage</td>
</tr>
<tr>
<td>Antimicrobial peptides</td>
<td>Dyes (gentian violet)</td>
<td>Chelating agents - EDTA</td>
<td>Clay</td>
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<tr>
<td>Chitosan</td>
<td>Fruit</td>
<td>Hydrogen peroxide - alginogel</td>
<td>Endolysins</td>
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<td></td>
<td>Herbs – garlic</td>
<td>Iodine (PVP + cadexomer iodine)</td>
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<td>NPWT</td>
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<td></td>
<td>Oils – essential oils</td>
<td>Ozone</td>
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</tr>
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<td></td>
<td>Oligosaccharides</td>
<td>Phototherapy</td>
<td></td>
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<tr>
<td>Honey</td>
<td>Sugar</td>
<td>Potassium salts (KMnO&lt;sub&gt;4&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>Propolis</td>
<td>Tannins</td>
<td>Tar or pitch (phenolics)</td>
<td>Probiotic bacteria</td>
</tr>
<tr>
<td></td>
<td>Vinegar (acetic acid)</td>
<td>Silver</td>
<td></td>
</tr>
<tr>
<td>Vaccines</td>
<td>Surfactants – octenidine, QAC</td>
<td>Hydrophobic binding</td>
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<td></td>
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<td>Cold plasma</td>
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Future management of wound infection

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• Preventing infection
• Interrupting cross infection
• Effective antimicrobial interventions
  • Systemic antibiotics
  • Topical antimicrobial agents
• Surveillance systems
• Education
Conclusions

• Antibiotic resistance is a global problem
• Resistance to antiseptics may become a problem in wound care
• New antimicrobial interventions will always be needed
• Increase awareness of Antimicrobial Stewardship in wound care (WHO guidelines)
  1. Improve awareness and understanding of AMR through effective communication, education and training;
  3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
  4. Optimize the use of antimicrobial medicines in human