Prevention of bacterial adhesion to medical polymers

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Infection = a public enemy

- 80% of adults are extremely/very worried about bacteria
- 75% consider food contamination by bacteria a serious health risk
- 11 times more articles about bacteria than 10 years ago
- In the past 6 years, 673 different antibacterial products were introduced

*Data from US market*
Nosocomial infections


2.4 Million nosocomial infections occur each year in the U.S.

30,000 related deaths occur each year in the U.S.

5-10 per 100 hospital admissions suffer nosocomial infection

$5-10 Billion is the estimated annual direct cost of nosocomial infection

$2,300 is the average cost of nosocomial infection per incident

Prevention of infection
Medical device and infection

- Biomaterials = **essential components of health care** systems

- 5 to 20% of CVC catheters are potentially infected \(\Rightarrow\) 0.1 to 1 per 100 catheter-days

- 20% of patients with Foley catheters (> 25 days) will develop urinary infections

Use of medical devices = Infectious complications
Microorganisms involved

Part of the environmental flora

- **Bacteria**
  - Gram positive Cocci (10%)
  - Coagulase Negative Staphylococci (CNS) → catheter (venous, peritoneal dialysis), cardiac valves, cardiac electrodes
  - *Staphylococcus aureus* (SA) → hemodialysis shunt, vascular prostheses
  - CNS and SA → hip and knee prostheses
  - Gram positive Bacilli (sporulating or not)
  - Gram negative Bacilli (50%): *E. coli, Pseudomonas* → early and late urinary tubes infections

- **Moulds and yeasts** (10%)
Bacterial infection of polymers

- **Factors of adhesion**
  - **Bacterial factors**: Capacity of the microorganism to adhere to polymer surfaces
  - **Polymer factors**: type of polymer and surface
    - Adherence index = hydrophobic surface
    - Ex: PVC >>> teflon
  - Interfering factors from the host (blood, proteins…)

- **Type of infection**
  - **Early infections**: inoculation at the time of implantation
  - **Long term infections**:
    - inoculation during surgery
    - haematogenous spread from distant sites
    - without associated bacteriemia
Formation of a biofilm
Mark Wiencek

- Reversible adsorption of bacteria (sec.)
- Irreversible attachment of bacteria (sec.-min.)
- Growth and division of bacteria (hrs.-days)
- Exopolymer production and biofilm formation (hrs.-days)
- Attachment of other organisms to biofilm (days-months)

Development of multicellular behaviour
The Biofilm: slime + bacteria

- Slime is produced by some bacteria: *S. epidermidis*, *S. aureus*, *P. aeruginosa*, Legionella

- Slime = extracellular mucilaginous substance: glyco-conjugate complex soluble in water = glycocalix

- Slime is responsible for
  - **Cohesion** between the germs
  - Creation of **cell layers**
Example of bacterial adhesion

*Staphylococcus epidermidis*

G. Pulverer et al.

15 min reversible non-specific adhesion in irregular parts

Formation of microcolonies

12h

12-48h multiple layers of cells irreversible adhesion + secondary erosion areas?

96h multiple layers of cells embedded in mucilagenous substance

Single bacteria

Physicochemical forces

polymer

Growth and division

Production of SLIME

Exopolysaccharide matrix

BIOFILM

Bacteria use N and C of the polymer?
*P. aeruginosa* adsorption to the Teflon strip, one day after inoculation (1)
Three days after inoculation, reveals the beginnings of glycocalyx production (2)
Biofilm development six days after inoculation, with a well developed glycocalyx (3)
Resistance of bacteria in biofilms

Formation of a « bacterial abcess »
- Morphological changes : spore-like
- Reduced bacterial growth (Resistance to antibiotics)
- Genetic changes: under or over expression of some genes related to protein resistance to antibiotics
- Age of the biofilm: resistance increased with age and structuration of the biofilm

Consequences
- Reduced sensitivities to antimicrobial agents
  ➔ No activity of antibiotic on bacteria covered by 100 µm of slime
- Increased resistances to various stresses = protective environment
Removal of the device

Antibiotics
Antimicrobials
Physiological defenses

BIOFILM

bacteria
slime
erosion
Prevention of infection: Ideal antimicrobial surfaces

- Broad spectrum or very specific biocidal activity
- High differential toxicity between mammalian cells and bacteria
- Biocompatible
- Infinite life time
Different technologies

- Polymers with repellent properties
  - No product

- Bulk modified polymers
  - Release of antimicrobial agents and contact efficacy
    - Antibiotics
    - Antiseptics

- Surface modified polymers
### Actual products and technologies (1) non silver agents

<table>
<thead>
<tr>
<th>Products</th>
<th>Antimicrobial</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC™ Thromboshield</td>
<td>Benzalkonium Chloride + heparin</td>
<td>PUR CVC</td>
</tr>
<tr>
<td>Hydrocath Assure</td>
<td>Benzalkonium Chloride + hydrophilic matrix</td>
<td>PUR CVC</td>
</tr>
<tr>
<td>Cook Spectrum</td>
<td>Minocycline/rifampicin</td>
<td>PUR CVC</td>
</tr>
<tr>
<td>Spectramed hydrocath</td>
<td>PVP with an isocyanate prepolymer</td>
<td>PUR CVC</td>
</tr>
</tbody>
</table>
Rationale for selecting silver (2)

- Old antiseptic ➔ new technologies
- Different active forms: ions, salts ...
- Broad spectrum:
  - Bacteria Gram + and Gram –
  - Yeasts
  - Active on biofilms
- Very low toxicity
- No actual case of resistance described
## Surface treatments by silver ions (3)

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<thead>
<tr>
<th>Product</th>
<th>Antimicrobial</th>
<th>Application</th>
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<tbody>
<tr>
<td>Arglaes</td>
<td>Silver in alginate polymer</td>
<td>Wound dressing (burns) + urology devices</td>
</tr>
<tr>
<td>SPI-Ag</td>
<td>Silver ion (PVD + IBAD)</td>
<td>Medical devices</td>
</tr>
<tr>
<td>Acticoat</td>
<td>Silver (PVD)</td>
<td>Burn dressing</td>
</tr>
<tr>
<td>Infectguard</td>
<td>Silver ion implantation</td>
<td>PUR CVC</td>
</tr>
</tbody>
</table>
## Surface treatments by silver in hydrogel (4)

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<th>Antimicrobial</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bard-X I.C.</td>
<td>Silver/hydrogel</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>LubriLAST-K</td>
<td>$\text{Ag}_2\text{O}_3\text{AgCl}/\text{hydrogel}$</td>
<td>Medical devices</td>
</tr>
</tbody>
</table>
Other surface technologies using silver (5)

<table>
<thead>
<tr>
<th>Product</th>
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<tbody>
<tr>
<td>SLIP-COAT</td>
<td>AgX, Antibiotics in hydrophilic polymers</td>
<td>Coating for medical devices</td>
</tr>
<tr>
<td>SURFACINE</td>
<td>Photolink technology and UV radiation + silver</td>
<td>Medical devices</td>
</tr>
<tr>
<td>ARROW GARD I and II</td>
<td>Chlorhexidine and silver sulfadiazine</td>
<td>PUR CVC</td>
</tr>
</tbody>
</table>
SLIP-COAT®: STS biopolymer

Hybrid polymer system (polyvinylpyrrolidone and cellulose esters formulated in organic solvent solutions)

Not coated

Coated with the polymer system
Surfacin® inert antimicrobial surface

- Kill microorganisms upon **contact** with the surface
- **Does not elute or leach** into solution ➔ Insignificant elutables (80° C, 5 days ~ 1 year ambient temperature)
- Long-term and broad spectrum of antimicrobial efficacy
- Treatment of **external surfaces** only
- **Non toxic** for cells: biologically inert
- **Durability**: blood, urine, autoclaving, EtO, E-beam, Gamma radiation
- **Compatibility**: almost all materials
Incorporation of silver into the material (6)

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<tbody>
<tr>
<td>OLIGON (IMPLEMED)</td>
<td>Silver-platinum iontophoresis</td>
<td>Polyurethane CVC catheter</td>
</tr>
<tr>
<td>Erlanger silver catheter</td>
<td>Silver particules</td>
<td>PUR CVC</td>
</tr>
<tr>
<td>AgION</td>
<td>Silver zeolites</td>
<td>Medical devices</td>
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OLIGON Technology – IMPLEMENTED

- Composite polymers containing silver and platinium particles that generate silver ions via iontophoresis to provide antimicrobial action

- Microscopic electrical fields within that drive Ag+ into the surrounding environment (Ag, Pt act as electrodes)

- **Substrate compatibility**: plastics, rubbers, fibers through the entire material

- Bacteria killing on the device surface and surrounding environment

- *In vitro* and *in vivo* tests indicate a ten-fold reduction of bacterial colonization for 2 months (to years)

- **Inside and outside surfaces** (catheter, tubings) can be treated
AgION technology

• Completely inorganic antimicrobial treatment
• Medium = bio-inert ceramic = zeolite
• Active ingredient = silver ionically bounded to the zeolite
• Long term antimicrobial protection
• Broad range of microbes, no antibiotic resistance
• Surface coating or compounded into the material
Conclusion

- At least, 7-10 new antimicrobial products and technologies are under development.
- At least 10 companies, worldwide are active in antimicrobial coatings area.
- BUT
  - Cost
  - Development of bacterial resistances to antibiotics/antiseptics
  - Biological secondary risks (hypersensitivities to antiseptic agents)

Strategies for infection prevention
- Large scale prevention for everybody
- Specific prevention only for particular risk patients

Selection of the appropriate product