Antimicrobial Treatments for Silicones

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Healthcare-Acquired Infections (HAIs)

- 1.7 Million Healthcare-acquired Infections in USA per year\(^1\)
- 5% of hospitalized patients develop HAI\(^1\)
- Nearly 100,000 deaths estimated\(^1\)
- > 5 Billion $ in extra costs\(^1\)
- New reporting rules require hospitals to disclose infection rates
- Medicare no longer reimburses hospitals for costs of HAIs
- Most common HAIs\(^2\) (many are medical-device related)
  - Urinary tract infections (32%)
  - Surgical site infections (22%)
  - Catheter-related blood stream infections (14%)
  - Ventilator-associated pneumonia (15%)

\(^1\)Kleven's Public Health Report 2007
\(^2\)“Antimicrobial Resistance in Healthcare Settings”, CDC online, 2002
What Causes Medical Device-Related Infections (MDRIs)?

- **Microbes!**
  - Bacteria are leading cause of infections
  - Fungi (yeast) are second

- **Microbes from**
  - Patient’s own body
  - Other bodies
  - Environment (fomites)

- **Some common bad actors:**
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus*
  - *Candida albicans* (yeast)
  - *Enterococcus faecalis*
  - *Serratia marcescens*
  - *Pseudomonas aeruginosa*
  - *Escherichia coli*
  - *Klebsiella pneumoniae*

But…it’s also how these microbes live →
Biofilm is...

- The growth of microbes on a surface
- Common names: mildew, scum, plaque and slime
  - usually mixture of species and types of microbes
  - complex structure of channels, pores and clusters
  - requires moisture, food and time
  - involves cell-cell communication
Biofilms and “Resistance”

• Encasement of cells within biofilm matrix limits diffusion of antimicrobials
  – Makes biofilms “inherently resistant”

• Some cells exposed to sub-lethal concentrations of antimicrobial
  – Can lead to development of “acquired resistance”
  – MRSA, VRE, growing list of others
Biofilms and Silicone

• Microbes only need a bit of moisture to survive (days, weeks)
  – No biofilm, but can be transferred while surviving (cross contamination)
• Microbes need moisture and food and time to grow and reproduce
• Silicones themselves fairly inert
  – Nutrients from silicone processing aids?
  – More likely that microbes grow on soiling/organic residues on the silicone
• Silicone applications
  – Medical devices (implants, catheters, IV connectors, respiratory therapy)
  – Tubing (beverage, dental)
Biofilms on Silicone Medical Devices

- Biofilm on and in catheters
- Biofilm in luer access device
- Candida (yeast) biofilm on silicone voice box prosthesis
CPAP / Ventilator Masks

- **Microbes and Health Issues**
  - Skin
  - Respiratory
- **Compliance Issues (CPAP)**
  - CPAPs can be challenging to clean properly
  - Microbes cause foul odors and staining
  - Users don’t...use

![Image of a CPAP device and related components]

- Artificial Airway
- Patient Circuit
- HEPA Filter
- Ventilator Circuit
- Heated Humidifier
CPAP Masks

- CPAP equipment collected from fellow associates and families
- Silicone components rinsed in 50ml buffer; filtered 10ml onto membrane filters
- Filters placed onto differential media; incubated up to 5 days at 30°C
The Cleanest

- TSA (~bacteria)
- SDA (~fungi)
- McKY (~Gram - bacteria)
- MSA (~“Staph”)
The Dirtiest

TSA (~bacteria)

SDA (~fungi)

McKY (~ Gram - bacteria)

MSA (~ “Staph”)
Contamination Isolated from CPAP Masks

- **TSA (~bacteria)**
- **SDA (~fungi)**
- **McKY (~ Gram - bacteria)**
- **MSA (~“Staph”)**
Unique – Only 1-2 species recovered (1 yeast, 1 mold) from CPAP mask (swab)

**BEFORE CLEANING**

- TSA (~bacteria)
- SDA (~fungi)

**AFTER CLEANING**

- TSA (~bacteria)
- SDA (~fungi)
Antimicrobials
Antimicrobials for Plastics and Rubber

Organics
- Triclosan
- CHG
- PHMB
- Quat-silanes
- Antibiotics

Inorganics
- Copper
- Zinc
- Silver
  - Silver Ion
  - Silver Metal
## Organic vs. Inorganic

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheaper than inorganics</td>
<td>Poor thermo-, chemical stability</td>
</tr>
<tr>
<td>Migration/Blooming allows most of antimicrobial to reach surface</td>
<td>Rapid migration may lead to premature depletion on shelf or use</td>
</tr>
<tr>
<td>Some organic AMs not as sensitive to soiling as silver</td>
<td>Poor biocompatibility</td>
</tr>
<tr>
<td>Potentially less impact on discoloration and clarity than inorganic</td>
<td>Limited spectrum of activity against microbes (eg triclosan)</td>
</tr>
<tr>
<td>May be easier to disperse within silicon matrix or apply topically</td>
<td>May increase risk of resistance (eg antibiotics)</td>
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### Inorganic (silver) vs. Organic

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermostability</td>
<td>Cost</td>
</tr>
<tr>
<td>Carrier of silver ion or silver metal does not migrate, so reservoir is preserved</td>
<td>Silver ions are only available to release from surface or bulk that is accessed by moisture</td>
</tr>
<tr>
<td>Biocompatible; accepted by FDA and clinicians</td>
<td>Negative effects on color and clarity of resin</td>
</tr>
<tr>
<td>Efficacy against broad range of microbes (esp. among bacteria)</td>
<td>Relatively weak against fungi (yeast and mold) compared to bacteria</td>
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<tr>
<td>Resistance to silver extremely rare</td>
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Zeolites and other Inorganic “Sponges”

Silver ZrP (eg SelectSilver® Zr2k)

-\(\text{Zr}_2^+-(\text{PO}_4)_3^-\text{Ag}^-\)

\(\text{NaCl} \rightarrow \text{Na}^+ \rightarrow \text{Ag}^+ \rightarrow \text{Ag}^+ \)

\(\text{Cl}^- \quad \text{Ag}^+ \quad \text{Ag}_2\text{Cl}_3^- \)

\(\text{PO}_4^- \quad \text{AgCl}_2^- \)

\(\text{Cl}^- \quad \text{AgCl} \)
Silver salts, Silver metal (nanoAg)

nano silver

silver salt (AgCl)

\[ \text{Ag}^+ \quad \text{Ag}_2\text{Cl}_3^- \quad \text{Cl}^- \quad \text{AgCl}_2^- \]

H\(_2\)O

AgCl
Silver Glasses

Silver Glass (e.g., SelectSilver® SR12)

\[
\begin{align*}
\text{Ag}^+ & \quad \text{Ag}^+ \\
\text{Ag}^+ & \quad \text{Ag}_2\text{Cl}_3^{-} \\
\text{Cl}^{-} & \quad \text{AgCl}_2^{-}
\end{align*}
\]

\( \text{H}_2\text{O} \)
What Happens Next?

Silver ions bind and inactivate proteins inside cells.

Some Ag⁺ will bind to proteins and salts in the local environment.

Ag⁺ released from treated article.

Ag⁺ released inside some polymers can discolor.
Antimicrobial Performance of Silver in LSR
Evaluation of Silver Antimicrobials in LSR

- Injection molded coupons with different doses of SelectSilver SR12 (silver-based antimicrobial)
  - SR12 contains ca. 2% w/w of silver ions
  - Dose level range (1.5 - 15% of SR12)
- Concentration of antimicrobial in LSR
  - X-Ray Fluorescence
- Release of silver from treated LSR over time
- Efficacy against microbes
  - Reduction in viable bacteria in 24hr with “Film-Contact Assay”
Silver Antimicrobials and LSR

- Determining Dose of Silver-based Antimicrobials in LSR
  - Normal process of ashing/digesting matrix very difficult with LSR
  - X-Ray Fluorescence Spectroscopy (XRF) can be used to detect silver
    - Or signature element for carrier of silver
  - Must establish calibration curves with known dose of antimicrobial
Silver – Speed of Kill

- Release of silver ions from treated LSR
  - Soak treated coupons in saline or buffer
  - Measure released silver with Induction Coupled Plasma - Optical Emission Spectrometry (ICP-OES)

- Speed of Kill related to Rate of silver release
Silver-treated Wound Dressings

Topical application of high loadings of silver (1-2%)

Several hours required for silver ion to reach efficacious level, enter microbes, inactivate enzymes and...kill

**Efficacy of Silver Dressings Against MRSA**

**Efficacy of Silver Dressings Against P. aeruginosa**
For most devices, extended release is more critical than fast release.
Repeated exposures to fluids will (eventually) deplete antimicrobial from surface.
Release in saline (with no nutrients) often results in equilibrium of Ag+ with AgCl at 400-500ppb Ag.
Release rate from SR12-treated LSR often increases after material is wetted.
Different silver-based antimicrobials can behave quite differently.
Why Doesn’t Zr2k Work Well in LSR?

- LSR loaded with 20% silver hydrogen zirconium phosphate (cubic particles)
- Scanning electron microscopy of surface vs. cross section of bulk material
- Evidence that most particles on surface are covered by silicone (“skinning”)
Test Methods (for Screening)

**Quantitative**
- “Film Contact”
  - JIS Z 2801
  - ISO 22196
- AATCC 100
  - JIS L 1902
  - ISO 20743
- Shake Flask
  - ASTM E2149
- Agar Inoculum
  - ASTM 2180

**Qualitative**
- MIC / MBC
- ISO 846
  - (fungi)
- TTC
  - StainTest
- ZOI
  - AATCC 147
Film Contact Method
JIS Z 2801, ISO 22196

Method for hydrophobic, non-porous materials

0.4 ml of bacterial suspension (~1 x 10^6 cells/ml) in saline with nutrients

Cover with 4 x 4 cm film

10 ml of wash solution (for deactivation and cell recovery)

37°C, o/n, static, 90% RH

Enumerate # of Survivors with Serial Dilution + Spread/Pour Plate or Alternative Methods (eg MPN)

Results are compared vs. T₀ and or Untreated Control
Efficacy by Film-Contact Method; 24hr exposure at 37 °C in saline + nutrients

- Efficacy by Film-Contact Method; 24hr exposure at 37 °C in saline + nutrients
- As with silver release, efficacy sometimes increases after material exposed to moisture
- As with all silver-based antimicrobials, efficacy against Gram negative bacteria often higher than against Gram positive bacteria
Effects of Post-Curing

- Post-curing does not appear to impact antimicrobial performance
*in vitro* Test Methods and FDA Registration

- Must test **safety** and **efficacy** of antimicrobial treatment in medical device
  - Safety = Biocompatibility
  - Efficacy = Reduction of microbes
- Testing for registration must be conducted on the actual device, or in few circumstances, just the treated components of device
- FDA issued draft guidelines for Antimicrobials in Devices (2007)
  - Primarily concerned with path forward if new antimicrobial agent vs. previously approved agent
  - [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071380.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071380.htm)
- FDA also has changed the types of data that are acceptable
  - Quantitative reduction (so, no ZOI data)
  - In most cases, require ≥4 log reduction
  - In most cases, require initial bioburden (inoculum) of ≥10^6 cells
Regulation of Antimicrobial-Treated Materials

- **Medical Devices**
  - Regulated by FDA and EU Medical Device Directive

- “Treated Articles” (AlphaSan® RC2000, RC5000)
  - Pesticidal use regulated by USA-EPA and BPD
  - Claims restricted to material preservation and aesthetic benefits
    - No public health claims
  - Cannot claim activity beyond treated surface
  - Restricted to use levels on EPA label
Resistance and Tolerance to Antimicrobials

- **Acquired Resistance:**
  - The effect of a given concentration of antimicrobial is diminished due to genetic change within the microbe (that affects target access)
- **Resistance to Biocides <-> Resistance to Antibiotics**
  - Biocides (most) → non-specific target
    - = ↓ rate and degree of resistance
  - Antibiotics → specific target
    - = ↑ rate and degree of resistance
- **Multitude of cellular targets for silver, other anaseptics**
  - Difficult for selection for resistance by target change as with antibiotics
  - The mechanism of action is critical to understand resistance and tolerance
How to Reduce MDRIs?

- Use of an antimicrobial agent may appear to be the sole missing ingredient to solve MRDI problems
- However, go to conferences like APIC, meet with OEMs and IC Professionals, and one gets the feeling:
  - 70-80% reduction through better hygiene
  - 10-20% through device design and composition
  - Leaving perhaps 10-20% through use of antimicrobial additive