Medical Device Technologies: Potential to Treat and Prevent Biofilm Implant-Related Infections

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 Disclosure

• Curza
• Chief Scientific Officer
• Sponsored research – University of Utah
• Travel
Reminiscing Moment

• Dr. Darouiche

• Journal of Inconsequential Results
Goal

• Provide overview of what the world is facing with biofilm implant-related infections / how we are addressing the issues.

• 3-fold approach
  • Background – impact of biofilms on medical devices
  • Current strategies in clinical use to address biofilm-related infections
  • Technologies under development / factors to consider – what more can we do?
Early Indicators

A Scanning and Transmission Electron Microscopic Study of an Infected Endocardial Pacemaker Lead

Thomas J. Marrie, M.D., Joyce Nelligan, and J. William Costerton, Ph.D.

Bacteria-Laden Biofilms: A Hazard to Orthopedic Prostheses

Anthony G. Gristina, M.D.
Boyer Medical School of Medicine
J. William Costerton, Ph.D.
University of Calgary

Marrie et al. Circ 1982;66:1339-1341
Impact of Biofilms on Medical Devices

• Infection is a catastrophic outcome

• Hospital Associated Infections (HAI) pose tremendous burden

In hospital resource prices, the overall annual direct medical costs of HAI to U.S. hospitals ranges from $28.4 to $33.8 billion (after adjusting to 2007 dollars using the CPI for all urban consumers) and $35.7 billion to $45 billion (after adjusting to 2007 dollars using the CPI for inpatient hospital services). After adjusting for hospital resource expenditures, the annual direct healthcare costs of HAI range from $27.2 to $32.7 billion (after adjusting to 2007 dollars using the CPI for all urban consumers) and $34.8 to $44.1 billion (after adjusting to 2007 dollars using the CPI for inpatient hospital services).
Impact of Biofilms on Medical Devices

• Rates of device-related infection range from 1-10%, as high as 50%
Problem: Antibiotic Resistance

- Biofilms up to 1,000x more resistant to antibiotics
- CDC Threat Report 2013
  "Antimicrobial resistance is one of our most serious health threats."

www.cdc.gov
Drenkard, Microbe Infect 2003;5:1213-1219
Williams et al., Curr Microbiol 2011;62:1657-1663
How Do We Currently Fight Biofilms?

Antibiotics

Coatings:
Active release
Passive

Common agents:
Silver
Gentamicin
Triclosan

Klemm, *Clin Microbiol Infec* 2001;7:28-31
Products in Clinical Use

Synthes Expert Tibial Nail PROtect

Bard Bardex IC Catheter

Arestin Microspheres

PDLLA Coated Gentamicin Initial 21 patients, good results

Silver-loaded hydrogel Variable results Short term more beneficial

Minocycline Variable results

Schmidmaier et al., Biom Assoc Infect 2012; Chpt 37:436-454
Verleyen et al., Eur Urol 1999;36:240-246
Thibon et al., J Hosp Infect 2000;45:127-124
Karchmer et al., Arch Int Med 2000;160:3294-3298
Genovesi et al., Minerva Stomatol 2014; Epub
Javed et al., Curr Drug Deliv 2013;63:369-376
Products in Clinical Use

ArrowGard and Vantex CVC

Vicryl Plus Sutures

More effective:
- Silver/chlorhexidine
- Silver/platinum/carbon

Less effective:
- Silver only
- Benzalkonium chloride

Triclosan release
Variable, but mostly beneficial

Darouiche, Biom Assoc Infect 2012;Chpt 19:485-503
Brooks et al., Biom Assoc Infect 2012;Chpt 13:307-354
Chen et al., Eur J Surg Oncol 2011;37:300-304
Ueno et al., Spine J 2013;Epub
Additional Devices in Clinical Use

- Palacos G bone cement - gentamicin
- Palacos R+G bone cement – gentamicin
- CMW2 bone cement - gentamicin
- Agento IC Endotracheal tube – silver
- ACTICOAT dressing – silver
- HyGentic – silver
- Tegaderm Ag dressing – silver
- ACTISORB dressing – silver
- Contreet Foam dressing – silver

Variable results
Why the Variability?

• Few suggestions:
  • Stagnant broth solutions
  • MIC values ≠ to antibiofilm activity
    • 70 kg male, 40 L volume
    • Final concentration of 25 µg/mL
  • Biofilms as initial inocula

Williams et al., Biomaterials 2012;33:8641-8656
Williams et al., J Biomed Mat Res B 2012;100:1163-1169
Summary of Current Technologies

• Polytherapy

• Silver alone
  • Variable  Consistent

• Primarily antibiotic agents
  • Resistance, reduced efficacy global concern

• Innovation still in demand
Future Technologies

Imagination Fosters Innovation
Smart Coatings

- Degrade when bacteria are present
- Nano / microsensors to detect bacteria

Zhou et al., JACS 2010;132:6566-6570
Quanterix.com
Combination Therapies

Possible applications:
- Contact lenses and lens cases
- Catheters
- Voice prostheses
- Dental implants (subgingival component)

Nonadhesive surfaces:
- Unsuitable for any implant application in absence of other antimicrobial functionalities
- Useful added functionality for all applications requiring nonadhesive surfaces

Tissue-integrating surfaces:
- Highly suitable in revision surgery after biomaterial-associated infection to clear infection from surrounding tissues and local antibiotic prophylaxis in primary surgery

Contact-killing surfaces:
- Ideal for applications requiring tissue integration:
  - Vascular grafts
  - Bone anchoring in dental implants and joint prostheses
  - Scaffolds in tissue engineering
Modified Surfaces

- Superhydrophobic / hydrophobic coatings
  - Black silicon
    - Dragonfly wing
- $\text{Si}_3\text{N}_4$
- Sharklet

Neverwet.com
Ivanova et al., Nat Comm 2013;4:2838
Amedica.com
Sharklet.com
New Antimicrobials: Biofilms in Mind

- Bismuth thiols – Microbion
- Seldox – Selenium, Ltd. / Emergent Technologies, Inc.
- \(\text{cis}-2\)-decenoic acid – disperse biofilms, Dr. David Davies
- CSA-13 - n8 Medical / Biocare
- Imidazoles – disperse biofilms, Agile Sciences
- Dispersin B – inhibit and disperse biofilms, Kane Biotech
- Quorum sensing inhibitors – inhibit biofilm, Dr. Bonnie Bassler
- CZ Compounds – inhibit, disperse and kill biofilms, Curza
Efficacy of CZ Compounds

**Vancomycin**

<table>
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<th>Organism</th>
<th>MIC (µg/mL)</th>
<th>MBEC (µg/mL)</th>
<th>EBEC (µg/mL)</th>
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<tr>
<td>MRSA</td>
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<td>&gt;500</td>
<td>&gt;20,000</td>
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**CZ-86**

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<th>MIC (µg/mL)</th>
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<td>MRSA</td>
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<td>15</td>
<td>250</td>
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10^5 planktonic bacteria

10^3 biofilm bacteria

10^9 biofilm bacteria
Dispersing MRSA Biofilms

- Water Only: 27%
- 0.25% Glutaraldehyde: 51%
- 0.25% CZ-86: 83%

Heavy Biofilm | Light Biofilm | Clean
Dispersing MRSA Biofilms

Water Only

0.25% CZ-25
Active Release Coating Strategy
Conclusion

• Biofilm-related infections pose threat

• Current technologies efficacy declining
  • Innovations necessary

• Promising technologies under development
Acknowledgments

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