Proposed standard method for testing the efficacy of antimicrobial urinary catheters

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Acknowledgements

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CAUTI Rates

- 2009-2014: CAUTI was the only HAI to not see a reduction in infection rates between

- 2015-2016: Nationally, acute care hospitals report decrease CAUTI rates ~7%

<table>
<thead>
<tr>
<th></th>
<th>States better than 2015 baseline</th>
<th>States worse than 2015 baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Care Hospitals</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Inpatient Rehab Facilities</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Long Term Acute Care Hospitals</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

2016 National and State Healthcare-Associated Infections Progress Report
Strategies to Prevent Catheter-Associated Urinary Tract Infections in Acute Care Hospitals: 2014 Update

III. Approaches that should not be considered a routine part of CAUTI prevention

1. Do not routinely use antimicrobial/antiseptic-impregnated catheters (quality of evidence: I).

I. High

Highly confident that the true effect lies close to that of the estimated size and direction of the effect. Evidence is rated as high quality when there is a wide range of studies with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.
The goal of this project was to develop and validate a standard quantitative in vitro method that will assist FDA regulators in evaluating the efficacy of surface modified urinary catheters.
1. Patient had an indwelling urinary catheter that had been in place for \textbf{> 2 days}. 

2. Patient has at least one of the following signs or symptoms. 
   • Fever(\(>38^\circ\) C) 
   • Suprapubic tenderness 
   • Urinary urgency 
   • Urinary frequency 
   • Dysuria

3. Patient has a urine culture with \textit{no more} than two species of organisms identified, at least one of which is a bacterium of \(10^5\) CFU/ml.
## CAUTI Microorganisms – Top 5

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percent of Pathogenic Isolates</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>23.9</td>
<td>1</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>11.7</td>
<td>2</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>10.3</td>
<td>3</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>10.1</td>
<td>4</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>7.0</td>
<td>5</td>
</tr>
</tbody>
</table>
Routes of Infection

Extraluminal
- Early, at insertion
- Late, by capillary action

Intraluminal
- Break in closed drainage
- Contamination of collection bag urine

Maki and Tambyah, 2001
In vitro Urinary Catheter Model

- Pump
- Foley catheter
- Valve
- Flow break
- Valve
- Vent
- Artificial urine
Patient Urinary Catheter
In vitro Urinary Catheter Model
The 7 R’s for Standard Methods

- **Reasonableness** (expense, lab techniques)
- **Relevance** (lab outcome ~ field/clinical outcome)
- **Repeatability** (intra-laboratory, SDr)
- **Resemblance** (controls similar between experiments)
- **Responsiveness** (detect changes)
- **Reproducibility** (inter-laboratory, SDR)
- **Ruggedness** (unaffected by slight changes)
The 7 R’s

- **Reasonableness** (expense, lab techniques)
- **Relevance** (lab outcome ~ field/clinical outcome)
- **Repeatability** (intra-laboratory, SD_r)
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Intraluminal Catheter Model

- *Escherichia coli* ATCC 53498
- Artificial Urine Medium
- 16 French, silicone, 2 way Foley
- 0.75mL/min
- 37°C
Intraluminal Catheter Model

Day One:
- Run sterile AUM through catheter for 2 hours
- Inoculate catheter with $10^3$ CFU/mL of UPEC

Daily
- Collect Samples
  - Effluent
  - Catheter segment
- Disaggregate through vortex and sonication series
- Plate for viable cell counts
Catheter Segment Samples

Controls

Treated

Log (CFU/cm²)

Days

MSU □ Center for Biofilm Engineering
Repeatability

Independent repeats of the same experiment in the same laboratory produce nearly the same response

Acceptable repeatability: $SD_r < 1.0$
# Repeatability

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Catheter Samples</th>
<th>Effluent Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Log (CFU/cm²)</td>
<td>St Dev</td>
</tr>
<tr>
<td>24</td>
<td>7.07</td>
<td>0.28</td>
</tr>
<tr>
<td>48</td>
<td>7.42</td>
<td>0.62</td>
</tr>
<tr>
<td>72</td>
<td>8.46</td>
<td>0.19</td>
</tr>
<tr>
<td>96</td>
<td>8.69</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Control Catheter Samples  CSDr = 0.79  
Control Effluent Samples CSDr = 0.29
A standard laboratory method is said to be rugged if the outcome is unaffected by slight departures from the protocol.

Statistical tool: *mixed effects* regression or ANOVA (e.g., repeated measures regression or ANOVA)
Operational Parameters

- Inoculum Concentration: $10^2$, $10^3$, $10^4$ CFU/mL
- Incubator Temperature: 34, 37, 40 °C
- Flow Rate: 0.25, 0.75, 1.25 mL/min
- pH of AUM: 6, 6.5, 7
- Biofilm Removal Technique: **Sonicate**, Scrape
# Ruggedness

<table>
<thead>
<tr>
<th>Run</th>
<th>Inoc (CFU/mL)</th>
<th>Temp (°C)</th>
<th>Flow (mL/min)</th>
<th>pH</th>
<th>Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>$10^4$</td>
<td>34</td>
<td>0.25</td>
<td>7</td>
<td>sonicate</td>
</tr>
<tr>
<td>1B</td>
<td>$10^2$</td>
<td>40</td>
<td>1.25</td>
<td>6</td>
<td>scrape</td>
</tr>
<tr>
<td>2A</td>
<td>$10^2$</td>
<td>40</td>
<td>0.25</td>
<td>6</td>
<td>sonicate</td>
</tr>
<tr>
<td>2A</td>
<td>$10^4$</td>
<td>34</td>
<td>1.25</td>
<td>7</td>
<td>scrape</td>
</tr>
<tr>
<td>3A</td>
<td>$10^2$</td>
<td>40</td>
<td>1.25</td>
<td>7</td>
<td>scrape</td>
</tr>
<tr>
<td>3B</td>
<td>$10^4$</td>
<td>34</td>
<td>0.25</td>
<td>6</td>
<td>sonicate</td>
</tr>
<tr>
<td>4A</td>
<td>$10^2$</td>
<td>34</td>
<td>1.25</td>
<td>7</td>
<td>sonicate</td>
</tr>
<tr>
<td>4A</td>
<td>$10^4$</td>
<td>40</td>
<td>0.25</td>
<td>6</td>
<td>scrape</td>
</tr>
<tr>
<td>5A</td>
<td>$10^2$</td>
<td>34</td>
<td>0.25</td>
<td>7</td>
<td>scrape</td>
</tr>
<tr>
<td>5B</td>
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<td>40</td>
<td>1.25</td>
<td>6</td>
<td>sonicate</td>
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<tr>
<td>6A</td>
<td>$10^2$</td>
<td>34</td>
<td>0.25</td>
<td>6</td>
<td>scrape</td>
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<tr>
<td>6B</td>
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<td>40</td>
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<td>7</td>
<td>sonicate</td>
</tr>
<tr>
<td>7A</td>
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<td>40</td>
<td>0.25</td>
<td>7</td>
<td>sonicate</td>
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<tr>
<td>8B</td>
<td>$10^4$</td>
<td>34</td>
<td>1.25</td>
<td>6</td>
<td>scrape</td>
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<tr>
<td>9A</td>
<td>$10^2$</td>
<td>34</td>
<td>1.25</td>
<td>6</td>
<td>sonicate</td>
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<tr>
<td>9B</td>
<td>$10^4$</td>
<td>40</td>
<td>0.25</td>
<td>7</td>
<td>scrape</td>
</tr>
</tbody>
</table>
## Ruggedness

Control Catheter Samples, log(CFU/cm²)

<table>
<thead>
<tr>
<th>Sample Points</th>
<th>Factor</th>
<th>Low pH, 6</th>
<th>High pH, 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 hours</td>
<td>Inoculum</td>
<td>0.69</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>0.08</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td>Flow</td>
<td>0.13</td>
<td>0.54</td>
</tr>
<tr>
<td>24 hours</td>
<td>Inoculum</td>
<td>0.63</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>0.41</td>
<td>-0.07</td>
</tr>
<tr>
<td></td>
<td>Flow</td>
<td>1.05</td>
<td>2.85</td>
</tr>
<tr>
<td>48 hours</td>
<td>Inoculum</td>
<td>0.45</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>0.23</td>
<td>-0.35</td>
</tr>
<tr>
<td></td>
<td>Flow</td>
<td>1.09</td>
<td>3.37</td>
</tr>
</tbody>
</table>

Method is rugged with respect to parameter if effect is less than +/- 0.30 log
No standard for ruggedness has been set
- $\pm 0.30$

Ruggedness Testing
- Never performed
- Key for developing a method predictive of clinical outcomes
Changes to SOP

- Scraping vs sonication
  - Improved removal (increased plate counts)

- pH
  - Increased effect with time
    - UPEC: pili expression
Changes to SOP

- Connector may have been a source for bacteria
- Higher SD in effluent compared to segment data
Conclusions

- Validated an Intraluminal Catheter Model (ICM)
- Increase ICM ruggedness
  - Optimization of AUM (pH)
  - Change biofilm harvesting

- Future
  - Test other relevant uropathogens
  - Develop and validate an extraluminal model
Reproducibility of antimicrobial test methods
Patient Catheter