Development of an early warning sensor for urinary catheter encrustation

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Biofilms

Biofilms are ubiquitously distributed and found in environmental, industrial and medical settings.

Oral microbes on teeth (plaque)

The ‘slime’ layer on surfaces in aquatic environments

Biofilms on contact lenses (microbial keratitis)
Urinary catheters

Provide a convenient way to drain urine from the bladder of patients suffering from urinary incontinence or neurological dysfunction:- Foley catheter

- 11% of hospitalised patients
- 5% of nursing home patients
- 4% of patients in home care are catheterised
- 100 million Foley catheters used annually worldwide
- The fastest increasing age group in the developed world is the over 80 year olds
Urinary catheters-problems

1. Provide access for bacteria from a heavily contaminated external skin site to vulnerable organs *i.e.* the bladder and kidneys

2. Undermines the normal filling and emptying of the bladder which flushes out microorganisms that might be contaminating the urethra

3. Provide a reservoir of residual urine in the bladder, allowing proliferation of contaminating organisms
Catheter associated urinary tract infections (CAUTIs)

- CAUTIs account for ~40% of health care associated infections
- Major problem is encrustation and blockage of catheter due to urease positive bacteria and particularly *Proteus mirabilis* (50% of long-term catheterised patients)
Current management and treatment

• Limiting catheter use
• Removal of catheter as soon as possible
• Use of alternative catheter surfaces
• Use of anti-infective agents
• Catheter wash-out solutions

• No single effective strategy has been identified
Objective

To develop a sensor that allows prediction of urinary catheter encrustation following infection with urease positive bacteria

Proteus mirabilis

Colonise and spread over the catheter surface, forming biofilm communities

produce urease

Hydrolysis of urea. Urease generates ammonia and elevates the pH of the urine

calcium and magnesium phosphates crystallise leading to blockage of the catheter
Background to project

Work was supported by MEDLINK grant M191 from the Department of Health. Collaborative project between the Schools of Dentistry and Biosciences within Cardiff University.
Background to project ctd

BJU International

A clinical assessment of the performance of a sensor to detect crystalline biofilm formation on indwelling bladder catheters

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Source of funding: MEDLINK Grant M191 from the Department of Health.
Materials & Methods
Silicone sensor preparation

Polydimethylsiloxanes with a range of molecular weights mixed prior to addition of a silica filler-base

Part A consisted of base, platinum catalyst, a matrix stabiliser and indicator

Part B consisted of base, cross linker, matrix stabiliser and indicator.

Parts A and B cured for 2 h at 90°C in moulds and sensor strips prepared.

*Developed sensors and application are protected by European Patent No. 1761162 and pending patent applications in the USA and Canada*

![Ra 31.0 µm](image1)
![Ra 43.0 µm](image2)
![Ra 92.5 µm](image3)
Evaluation of sensors in an *in vitro* model of catheter infection

Urine at 0.5ml/min

Proteus
Infected urine

Water at 37°C

Sensor
At t=0h

Infected ‘bladder’

Location of sensor

Drainage bag
Test microorganisms

All microorganisms used had previously been recovered from biofilms colonizing the catheters of patients undergoing long-term bladder catheterization.

Urease positive strains:
Proteus mirabilis (n=3), Proteus vulgaris (n=1), Klebsiella pneumoniae (n=1), Morganella morganii (n=1), Staphylococcus aureus NSM 5 (n=1), Providencia rettgerri (n=1).

Urease negative strains:
Escherichia coli (n=1), Enterococcus cloacae (n=1), Providencia stuarti (n=1), Enterococcus faecalis (n=1), Staphylococcus aureus P10 6/9 (n=1) and Pseudomonas aeruginosa (n=1).
Results
pH change of artificial urine and sensor triggering during model infection

Initial sensor appearance

Sensor colour after signalling (started ~22 h post infection)

Blocked
(~43 h; pH 9.0)
Urinary catheter biosensor-colour changes

(sensor holding device is a prototype and subject to change)
### Sensor performance in *in vitro* bladder model

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Urease activity</th>
<th>Catheter blockage</th>
<th>Average time (h) of blocking</th>
<th>Sensor signalling</th>
<th>Average time of signalling before blockage (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Proteus mirabilis</em> RB6</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2</td>
<td>+</td>
<td>+</td>
<td>42</td>
<td>+</td>
<td>23</td>
</tr>
<tr>
<td><em>P. mirabilis</em> NSM 6</td>
<td>+</td>
<td>+</td>
<td>40</td>
<td>+</td>
<td>19</td>
</tr>
<tr>
<td><em>P. vulgaris</em> SDM2</td>
<td>+</td>
<td>+</td>
<td>55</td>
<td>+</td>
<td>33</td>
</tr>
<tr>
<td><em>Providencia rettgeri</em> SDM1</td>
<td>+</td>
<td>+</td>
<td>43</td>
<td>+</td>
<td>22</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2 and <em>Enterococcus faecalis</em> RB1</td>
<td>+</td>
<td>-</td>
<td>37</td>
<td>+</td>
<td>21</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2 and <em>E. coli</em> 10418</td>
<td>+</td>
<td>+</td>
<td>35</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2 and <em>Klebsiella pneumonia</em> RB8(5)</td>
<td>+</td>
<td>+</td>
<td>35</td>
<td>+</td>
<td>17</td>
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<tr>
<td><em>P. mirabilis</em> NSM6 and <em>Morganella morganii</em> SM18</td>
<td>+</td>
<td>+</td>
<td>43</td>
<td>+</td>
<td>17</td>
</tr>
<tr>
<td><em>P. mirabilis</em> NSM6 and <em>Enterobacter cloacae</em> RB19</td>
<td>+</td>
<td>-</td>
<td>35</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> RB8(5)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No blockage within 144 h</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2 and <em>Providencia stuarti</em> NSM24</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No blockage within 170 h</td>
</tr>
<tr>
<td><em>P. mirabilis</em> B2 and <em>S. aureus</em> P10 6/9</td>
<td>+</td>
<td>+</td>
<td>29</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td><em>S. aureus</em> NSM5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No blockage within 170 h</td>
</tr>
<tr>
<td><em>Escherichia coli</em> 10418</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No blockage within 144 h</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> SDM5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No blockage within 170 h</td>
</tr>
</tbody>
</table>
Results summary

• Developed sensors predicted catheter blockage approximately 17–24 h in advance occurrence

• Signalling only occurred with urease positive bacteria and only when catheter blockage followed (no false positives)

• Inhibition of the encrustation potential of the *Proteus mirabilis* strain by *Prov. stuarti* NSM24. *Proteus mirabilis* is encountered in approximately 50% of catheters colonised by *Prov. stuarti* and an antagonistic effect of the latter on catheter encrustation has not previously been reported
Conclusions

Experiments in the laboratory model of the bladder, showed that the sensor was effective in continuously monitoring *P. mirabilis* infection and predicting catheter encrustation.

Clinical evaluation of the silicone sensor is imminent and if these studies prove successful, a valuable tool will have been developed for use in the care of many patients enduring long-term bladder catheterisation.
Current status

• The Sensor currently belongs to Cardiff University and is protected by a granted European patent (1761162) and pending patent applications in the USA (No. 11/630,650) and Canada (No. 2572168)

• Cardiff University has entered into an Option Agreement with MBi Wales Ltd, whereby, upon successful clinical trialling, they will have the right to an exclusive, world-wide Licence for the manufacture and sale of the Sensor
Acknowledgements

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Thank you for your attention