Review

Catheter-associated urinary tract infections: new aspects of novel urinary catheters

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Abstract

Nosocomial urinary tract infection is the most common infection acquired both in hospitals and nursing homes and is usually associated with catheterisation. These catheter-associated urinary tract infections (CAUTIs) have been reported to increase mortality and have a considerable economic impact. To date, the sole effective preventative strategy is the use of a closed drainage system and removal of the catheter as soon as possible. The underlying cause of CAUTI is the formation of a pathogenic biofilm on the surface of the indwelling urinary catheter. Currently, researchers seek to alter the catheter surface in order to inhibit biofilm formation. Many substances are being studied for their potential as biofilm-disrupting catheter coatings. Among these substances, recently developed antibiotic-coated catheters may provide promise for the control of CAUTI. More basic research at the level of pathogenesis and catheter substance is needed to design novel strategies.

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1. Introduction

Urinary tract infection (UTI) is the most prevalent cause of nosocomial infections, with an incidence of ca. 40% of all cases of nosocomial infection \cite{1}, among which 80% involve catheter-associated urinary tract infection (CAUTI) \cite{2,3}. Although most CAUTIs are asymptomatic, it has been reported that a close relationship exists between symptomatic expression and increased rate of mortality in diabetic, immunocompromised, debilitated patients \cite{4}.

The major route of infection in CAUTI is ascending (i) at the time of insertion of a catheter through the urethra, (ii) via the mucosal layer between the catheter and urethra and (iii) through the catheter lumen \cite{2}. The risk of acquiring CAUTI depends on the method and duration of catheterisation, the quality of catheter care and host susceptibility. The most effective way of preventing CAUTI is to keep the system of urine drainage closed from the bladder to the collection bag \cite{2,4,5}. CAUTI is seen within several days in 100% of cases when the system of urine drainage could not be maintained as closed \cite{6}. However, maintaining a closed system of urine drainage is actually difficult and, even if the system is maintained as closed, CAUTI is reported to occur in 50% of cases when the system is in operation for more than 5 days \cite{7}.

Many innovations have been tried in clinical settings to prevent CAUTI. These have included the use of antiseptic lubricating gel at catheter insertion \cite{8}, the use of a tape seal applied to the catheter drainage tubing junction \cite{9}, antireflux valves, or anti-infective irrigation of the bladder or instillation of antiseptics in the collection bag \cite{10–12}. However, compared with the closed drainage system, all of these have failed to show significant benefits.

In the last few years it has been reported that biofilm formation on the urinary catheter may play a key role in the pathogenesis of CAUTI and in the resistance of CAUTI to management. Renewed interest has therefore arisen in altering the catheter surface to inhibit biofilm formation. A recent
approach to solve some of the problems associated with CAUTI has been the application of a range of different coatings to the surface of the catheter. The results have been varied but promising.

The purpose of this article is to analyse and review up-to-date reports published on the pathogenesis of and prevention strategies for CAUTI. Reviewed articles mainly concern biofilms and recently developed urinary catheters coated with various materials targeted against the pathogenesis of biofilms. Reviewed clinical studies are focused on randomised clinical trials of currently marketed catheters coated with novel materials; trials with inclusion of long-term catheterisation (>30 days) or insufficient data were excluded. These reports provide a better understanding of CAUTI and enable us to step forward in the prevention of CAUTI.

2. Pathogenesis of CAUTI-associated biofilm

Previous studies confirmed that bacteria associated with CAUTI grow in glycocalyx-enclosed microcolonies in a biofilm on the catheter surface [13]. On scanning electron micrographs, such microcolonies were easily seen to be enveloped in a slime or glycocalyx exuded by the adherent bacteria. Beginning with only loosely bound bacteria and their products, the biofilm of glycocalyx readily coalesces with other bacterial exopolysaccharides and host products to produce a thick and condensed biofilm, occluding the inner or outer surface of the catheter [14]. Adherent bacterial colonies within a biofilm form a functional union in which a microenvironment is maintained. This microenvironment is characterised by concentration of enzymes and metabolic products and the relative exclusion of gases such as oxygen [15]. Consequently, adherent biofilm bacteria in such an environment are metabolically inactive compared with their planktonic counterparts and appear to be resistant to antibiotics, the potencies of which are related to bacterial growth rates [16]. Furthermore, the biofilm might be expected to act as a mechanical barrier, protecting the entrained bacteria from natural host defence mechanisms and antibiotic activity [17,18]. Previous studies showed that systemic antibiotics kill planktonic bacteria in urine and reduce the initial rate of catheter-associated bacteriuria, but fail to eradicate the sessile biofilm bacteria, except when a very high dose of antibiotic was noted to kill the biofilm bacteria on a Foley catheter [19,20].

Recently, Anderson et al. [21] suggested that this bacterial reservoir may be within the living tissue of the bladder itself. They found that clinical isolates of uropathogenic *Escherichia coli* formed tightly packed, biofilm-like pods in mouse bladder epithelial cells. This article is the first description of biofilm formation within eukaryotic cells. If supported by further studies, these intracellular biofilms could certainly account for the persistence of pathogens in the damaged mucosa of a catheterised urinary tract [15]. An intricate understanding of the pathogenesis of CAUTI, such as biofilm formation, may lead to novel mechanisms to prevent this disease.

3. Disrupting biofilm formation with novel catheter coatings

3.1. Silver-coated catheters

Silver has antiseptic effects and several studies have investigated the efficacy of silver-coated catheters, with mixed results (Table 1) [22–26]. In 1979, Akiyama and Okamoto [22] first described the use of a silver-coated urinary catheter in 102 patients and found that none of those treated with a silver-coated catheter developed bacterial infections.

Schaeffer et al. [23] reported 74 patients with spinal cord injury or neurological injury who were randomised to receive either a silver oxide-coated silicone catheter or an uncoated silicone catheter. Bacteriuria was documented in 27% of cases in the silver-coated catheter group and in 55% of the control group (*P* = 0.02). More recent research has also found that there was a statistically significant difference in the occurrence of bacterial infection in patients treated with a silver alloy-coated catheter compared with those treated with a standard device [24,25].

These trials increased interest in silver-coated catheters for the prevention of CAUTI. However, since these trials were too small to determine the efficacy of silver-coated catheters, two large clinical trials were conducted.

In a clinical trial involving 1309 hospitalised patients, Riley et al. [26] not only failed to demonstrate the efficacy of silver-coated catheters in the prevention of CAUTI, as suggested in prior studies, but also showed a significantly increased incidence of bacteriuria in male patients. A second investigation reported that silver-coated catheters reduced the incidence of UTI only among women not receiving antimicrobial agents in a prospective clinical trial involving 482 hospitalised patients [27].

More recently, a prospective crossover study involving 3036 patients evaluated the efficacy of a silicone-based, silver-impregnated urinary catheter [29]. This study found that silicone-based, silver-impregnated urinary catheters were not effective in preventing CAUTI.

The apparent superiority of silver-impregnated catheters in earlier studies [22–25] compared with more recent clinical studies [26–29] may be due to the fact that in earlier studies controls were usually latex-based and in more recent studies silicon-based catheters were used. Until now, the use of more expensive silver-coated catheters to prevent CAUTI has not been supported by quality data, and resistance to silver was likely to become a problem with widespread use. However, the concept of disrupting biofilm formation is also applicable to other agents used to impregnate urinary catheters, including hydrogels and antibiotics.
Table 1

<table>
<thead>
<tr>
<th>Study design</th>
<th>P-value</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Test group</strong></td>
<td><strong>Control group</strong></td>
<td><strong>Clinical trials suggesting that catheters coated with silver or silver hydrogel have a protective effect</strong></td>
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<tr>
<td>Clinical trials suggesting that catheters coated with silver or silver hydrogel have a protective effect</td>
<td></td>
<td>Akiyama and Okamoto [22] Silver 0/102 (0) 20/20 (100) Effective Uncontrolled</td>
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<td></td>
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<td>Schaeffer et al. [23] Silver oxide 11/41 (27) 18/33 (55) 0.02 Catheter and tube collector junction coated with silver, small samples</td>
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<td>Liedberg and Lundeberg [24] Silver hydrogel (latex) 6/60 (10) 22/60 (37) Randomised, controlled &lt;0.01 Small samples</td>
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<td></td>
<td></td>
<td>Liedberg and Lundeberg [25] Silver hydrogel (latex) 8/75 (11) 23/96 (24) Randomised, controlled 0.02 Incidence on Day 5 of catheterisation</td>
</tr>
<tr>
<td><strong>Clinical trials suggesting that catheters coated with silver or silver hydrogel do not have a protective effect</strong></td>
<td></td>
<td>Riley et al. [26] Silver oxide (silicone) 85/745 (11) 73/564 (13) Randomised, controlled N.S. Increased incidence of bacteriuria in men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Johnson et al. [27] Silver oxide (silicone) 19/207 (9) 28/275 (10) Randomised, controlled N.S. Effective only in women not receiving antibiotics</td>
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<td></td>
<td></td>
<td>Thibon et al. [28] Silver hydrogel (latex) 9/90 (10) 13/109 (11.9) Randomised, double-blind, multicentre study N.S. A total of 3036 patients evaluated; study groups were not identical (more men, shorter duration of catheterisation in test group)</td>
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<td></td>
<td></td>
<td>Srinivasan et al. [29] Silver (silicone) 14.29/1000 catheter-days 16.15/1000 catheter-days Randomised with cross-over N.S. A total of 3036 patients evaluated; study groups were not identical (more men, shorter duration of catheterisation in test group)</td>
</tr>
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</table>

3.2. Hydrogel-coated catheters

Hydrogels, macromolecular polymers that absorb relatively large volumes of liquid within their polymeric structures [30], result in the formation of a thin water film on the contacting surface, thus improving its smoothness and lubricity. These properties might act as potential barriers to bacterial infection and reduce the adhesion both of Gram-positive and Gram-negative bacteria to catheters [31] and thus may be used to impregnate urinary catheters.

Trials of hydrogel-coated catheters have yielded mixed results. Some reports have indicated that there is promising potential for these catheters, whilst other reports conflict this positive result [28,32–34].

Bologna et al. [32] reported a trend towards a reduction in nosocomial UTI in an experimental group. However, several other reports that conflicted this result showed no significant differences between the incidence of bacterial infection in hydrogel or silver and hydrogel-coated and standard catheters [28,33]. A study conducted to test for migration of microorganisms found that hydrogel coatings facilitate the migration of urinary tract pathogens over hydrogel-coated catheters [34]. As a result, it was concluded that there was insufficient evidence to support or recommend the use of hydrogel-modified catheters.

3.3. Antibiotic-coated catheters

Reid et al. [35] reported that pre-treatment of urinary silicone latex catheters in vitro with ciprofloxacin significantly reduced the adhesion and survival of the clinical isolate *Pseudomonas aeruginosa*. Results of these in vitro studies suggest that there could be a clinical role for antibiotics in preventing CAUTI associated with bacterial adherence to prosthetic devices. Further research has continued into the use of various antibiotics, including gentamicin, norfloxacin, nitrofurazone and minocycline with rifampicin for impregnated material. Some of these devices might hold promise for reducing CAUTI.

3.3.1. Gentamicin

As mentioned above, the antimicrobial coating method has received increasing attention as a method of inhibiting CAUTI during catheterisation. Local and sustained delivery of an antibiotic within a therapeutic range is required. Cho et al. [36] attempted to prepare catheters that can effectively inhibit infections by releasing an antibiotic in a sustained manner. Drug release studies demonstrated that the coated catheter with gentamicin-containing poly(ethylene-co-vinyl acetate) (EVA) and EVA/poly(ethylene oxide) (PEO) exhibited sustained release and antibacterial activity for 7 days against *Proteus vulgaris*, *Staphylococcus aureus* and *Staphylococcus epidermidis* in vitro. These results imply that catheters coated with EVA/PEO have a potential for short-term catheterisation.
In in vivo studies using rabbits to determine the efficacy of gentamicin-releasing urethral catheters against microorganisms causing catheter-associated bacteriuria, the incidence of bacteriuria between two groups after 3 days and 5 days of catheterisation (8 and 10 rabbits for the control catheter vs. 2 and 4 rabbits for the gentamicin-releasing catheter, respectively) was significantly different [14]. Scanning electron microscopy showed the formation of bacterial biofilm throughout the 3-day and 5-day catheterisation for control catheters, but deterioration of the bacterial biofilm was visible on the surface of the gentamicin-releasing catheters. The authors concluded that the gentamicin-releasing catheter produced an antibacterial barrier that inhibited CAUTI for 5 days and may be useful for controlling infection in patients undergoing short-term urethral catheterisation.

### 3.3.2. Norfloxacin

Gentamicin-releasing catheters have a limited role for short-term catheterisation because gentamicin is a hydrophilic antibiotic, thus with rapid release from the surface of coated catheters to aqueous media. Norfloxacin, a fluoroquinolone antibiotic of hydrophobic nature, was investigated as an anti-infectious substance for use in long-term catheterisation [37]. The norfloxacin-releasing catheters, coated with EVA and PEO (the same matrix that previous gentamicin-releasing catheters were coated with), showed continuous delivery of norfloxacin for up to 30 days owing to the hydrophobic nature of norfloxacin and EVA/PEO incorporated in a coating layer. The coated catheters created considerable inhibition zones for 10 days against _E. coli_, _Klebsiella pneumoniae_ and _P. vulgaris_ and have a promising potential for clinical use in patients undergoing long-term catheterisation.

### 3.3.3. Nitrofurazone

Nitrofurazone is active in vitro against a broad range of Gram-positive and Gram-negative bacilli isolated from patients with indwelling urinary catheters [38]. The in vitro inhibitory activity of a nitrofurazone-coated urinary catheter against species implicated in CAUTI was determined using an agar diffusion assay [39]. The activity of the nitrofurazone-coated catheter was compared with that of a silver hydrogel urinary catheter. Results showed that the nitrofurazone-coated catheter was broadly active in vitro against species characteristic of CAUTI. There are a few randomised clinical trials that have evaluated the efficacy of nitrofurazone-coated catheters (Table 2) [40–42].

Recently, a multicentre study including 177 patients was conducted to determine the CAUTI inhibition effect by nitrofurazone-coated catheters [42]. In this study, the incidence rate of CAUTI was lower in the nitrofurazone-coated catheter group compared with the control group. When the catheters were maintained for >5 days but <7 days, the incidence rate of CAUTI was statistically significantly lower in the experimental group compared with that in the control group. Considering that the incidence rate of CAUTI is

<table>
<thead>
<tr>
<th>Reference</th>
<th>Test catheter coating (base)</th>
<th>Test catheter coating</th>
<th>Control group</th>
<th>Study design</th>
<th>P-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maki et al. [40]</td>
<td>Nitrofurazone (silicone)</td>
<td>8/170 (5)</td>
<td>14/174 (8)</td>
<td>Randomised, controlled</td>
<td>&lt;0.01</td>
<td>Relatively low incidence rate of CAUTI in the control group</td>
</tr>
<tr>
<td>Al-Habdan et al. [41]</td>
<td>Nitrofurazone (silicone)</td>
<td>0/50 (0)</td>
<td>6/50 (12)</td>
<td>Randomised, controlled</td>
<td>0.002</td>
<td>Different base catheter between two groups (latex catheter used in the control group)</td>
</tr>
<tr>
<td>Lee et al. [42]</td>
<td>Nitrofurazone (silicone)</td>
<td>14/92 (15)</td>
<td>19/85 (22)</td>
<td>Randomised, controlled, multicentre study</td>
<td>N.S.</td>
<td>Duration of catheterisation &gt;7 days; significant reduction in CAUTI only in the 5–7 days group (13% vs. 19%)</td>
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</tbody>
</table>

N.S., not significant; CAUTI, catheter-associated urinary tract infection.
very low within 5 days of catheter insertion provided the catheter was inserted aseptically and a closed drainage system is maintained [43], this result is clinically important since the effect of inhibiting CAUTI was proven during the clinically important period of CAUTI expression between 5–7 days of catheterisation.

Maki and Tambyah [44] also reported that novel urinary catheters impregnated with nitrofurazone or minocycline and rifampicin significantly reduced the risk of CAUTI for short-term catheterisation not exceeding 2–3 weeks. It is necessary to confirm further the effectiveness of nitrofurazone-coated catheters over long-term periods.

4. Conclusion

Numerous strategies have been tried to reduce the incidence of CAUTI, but few have proven effective. Recently, the role of biofilms in the pathogenesis of CAUTI was discovered and new strategies including novel urinary catheters to disrupt the biofilm have been investigated. Antibiotic-coated catheters could prevent or delay the onset of CAUTI during short-term catheterisation and hold promise for the possibility of suppression of CAUTI.

However, greater understanding of the pathogenesis of CAUTI as well as well designed, randomised clinical studies are required to produce ideal urinary catheters for control of CAUTI.

References

[34] Sabbuba N, Hughes G, Stickler DJ. The migration of *Proteus mirabilis* and other urinary tract pathogens over Foley catheters. BJU Int 2002;89:55–60.


