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In-vitro antibacterial and anti-encrustation performance of silver-polytetrafluoroethylene nanocomposite coated urinary catheters

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SUMMARY

Background: Catheter-associated urinary tract infections (CAUTIs) are among the most common hospital-acquired infections, leading to increased morbidity and mortality. A major reason for this is that urinary catheters are not yet capable of preventing CAUTIs.

Aim: To develop an anti-infective urinary catheter.

Methods: An efficient silver-polytetrafluoroethylene (Ag-PTFE) nanocomposite coating was deposited on whole silicone catheters, and two in-vitro bladder models were designed to test antibacterial (against *Escherichia coli*) and anti-encrustation (against *Proteus mirabilis*) performances. Each model was challenged with two different concentrations of bacterial suspension.

Findings: Compared with uncoated catheters, coated catheters significantly inhibited bacterial migration and biofilm formation on the external catheter surfaces. The time to develop bacteriuria was an average of 1.8 days vs 4 days and 6 days vs 41 days when the urethral meatus was infected with 10^6 and 10^2 cells/mL, respectively. For anti-encrustation tests, the coated catheter significantly resisted encrustation, although it did not strongly inhibit the increases in bacterial density and urinary pH. The time to blockage, which was found to be independent of the initial bacterial concentration in the bladder, was extended from 36.2 ± 1.1 h (uncoated) to 89.5 ± 3.54 h (coated) following bacterial contamination with 10^3 cells/mL in the bladder. Moreover, the coated catheter exhibited excellent biocompatibility with L929 fibroblast cells.

Conclusion: Ag-PTFE coated Foley catheters should undergo further clinical trials to determine their ability to prevent CAUTIs during catheterization.

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Introduction

Urinary catheters that drain urine for patients during and after surgery or in critical illness are common indwelling medical devices in hospitals, with 23.6% of patients in 183 US hospitals having a catheter [1,2]. However, the resulting risk of catheter-associated urinary tract infections (CAUTIs) is challenging. CAUTIs account for approximately 40% of hospital-acquired infections in the USA each year, and can lead to longer hospital stay, bacteriuria, urosepsis and death [3,4].

The risk of developing bacteriuria increases by 3–7% for each additional day that the indwelling catheter remains *in situ* [5], and bacteriuria is universal in patients after 30 days of indwelling catheterization [1,6]. Another critical issue of catheterization is the encrustation of urinary catheters, caused by *Proteus mirabilis*. *P. mirabilis* increases the pH of urine, and thus crystals of calcium and magnesium phosphates from urine block the eye-hole and lumen of the catheter, leading to painful distension of the bladder or even pyelonephritis and septicemia [7].

Over recent decades, many attempts have been made to cover the catheter surface with coatings that inhibit bacterial colonization (e.g. antibiotics, polymers and silver alloy) in order to prevent CAUTIs [8–10]. However, to date, no coated catheters that are effective for chronic catheterization are commercially available, and bacteriuria remains inevitable [11]. The silver-coated urinary catheter, as one of the few anti-infective catheters widely available on the market, can reduce infections when the indwelling silver-coated catheter is in place for one week or less, but has an insignificant effect for longer durations [12,13]. This may be because the biofilm surrounding silver-coated surfaces could be sticky mucoid, which will inactivate the antibacterial properties of silver coatings [14]. Thus, the authors believe that it would be desirable to develop a silver-coated catheter with non-stick properties. As a biomedical material, PTFE has excellent non-stick properties with an exceptionally low coefficient of friction [15,16], and the Ag-PTFE composite would be a promising antibacterial coating for urinary catheters. The authors' previous research has reported Ag-PTFE composite coatings on stainless steel substrates which exhibited outstanding resistance to bacterial adhesion [17,18]. Thus, in this study, in order to develop an anti-infective indwelling catheter, economical, efficient and biocompatible Ag-PTFE nanocomposite coatings were deposited on whole silicone catheters, with the aim of preventing colonization of *Escherichia coli* which is the most common organism leading to CAUTIs [1,19], and inhibiting the encrustation caused by *P. mirabilis*.

Two in-vitro bladder models were designed to evaluate the ability of whole coated catheters to: (1) impede bacterial migration along external surfaces of the catheter; and (2) inhibit encrustation. Bare silicone catheters were used as the control. For the first model, the coated and uncoated catheters were challenged with two concentrations of *E. coli* suspension: 10^6 and 10^2 cells/mL. For the second model, the coated and uncoated catheters were incubated with two concentrations of *P. mirabilis* suspension: 10^6 and 10^3 cells/mL. Encrustation indicates that urine has been contaminated, so the starting level of bacteriuria was selected as the low concentration.

Materials and methods

Materials

The all-silicone two-way Foley catheters (16 Fr., diameter 5.3 mm) were purchased from Mediplus Ltd (High Wycombe, UK). Silver nitrate and saccharin sodium were purchased from Fisher Scientific (Loughborough, UK), and all other reagents were purchased from Sigma-Aldrich (Gillingham, UK).

Ag-PTFE nanocomposite coatings on silicone catheters

The detailed coating procedure and the related characterization of the coating surface have been described elsewhere [17,18]. Briefly, an aqueous solution containing 0.05 M Tween 20, 0.03 M silver nitrate and 0.04 M sodium saccharine was stirred for 1 min before placed in a water bath at 70°C. 5 mL/L PTFE emulsion (60.0 wt% with PTFE particle size in the range 0.05–0.5 μm) and 0.2 g/L of FC-4 cationic surfactant were added and mixed thoroughly by sonication for 10 min at room temperature. The entire Foley catheter was immersed in coating solution, and the ratio of catheter surface area/volume of coating solution (RCV) was determined as 72 mm^2/mL (see online supplementary material). After being coated for 4 h at 70°C, the coated catheter was taken out; rinsed successively with 0.1 M HNO_3 , ultra-pure water and absolute ethanol; and dried at room temperature.

Bacterial strains, media and culture

E. coli (F1693) was obtained from the Institute of Infection and Immunity, Nottingham University, UK and *P. mirabilis* (ATCC 51286) was bought from the American Type Culture Collection (Manassas, VA, USA). A single colony of a strain was inoculated into a test tube containing 5 mL of tryptic soy broth (TSB) and grown overnight at 37°C, with agitation at 200 rpm. Fifty microlitres of this overnight culture was transferred into 10 mL of TSB and incubated with shaking until the mid-exponential phase was reached (OD_{600} 0.6) to obtain the bacterial suspension in TSB, corresponding to a bacterial density of $\sim 2 \times 10^8$ cells/mL for *E. coli* or $\sim 1 \times 10^8$ cells/mL for *P. mirabilis*.

In-vitro antibacterial performance of whole coated catheters in bladder model

An in-vitro bladder model was designed as shown in Figure 1a to mimic bacterial infection in most cases of CAUTI, which result from bacteria colonizing the catheter–urethral meatus interface and migrating along the external surface of the catheter into the bladder [8,20]. The model consisted of a glass vessel maintained at 37°C by a water heating jacket ('bladder'), an acrylic tube with a length of 13 cm and an inner diameter of 6 mm ('urethra', based on the average lengths of male and female urethra [21,22]) and two peristaltic pumps. The branch at the bottom of the acrylic tube could allow the source of infection to be injected, thus representing the urethral meatus. After sterilization of the model, the sterile whole catheter with Ag-PTFE nanocomposite coatings or the whole bare silicone catheter was inserted aseptically via the 'urethra' into the 'bladder'.

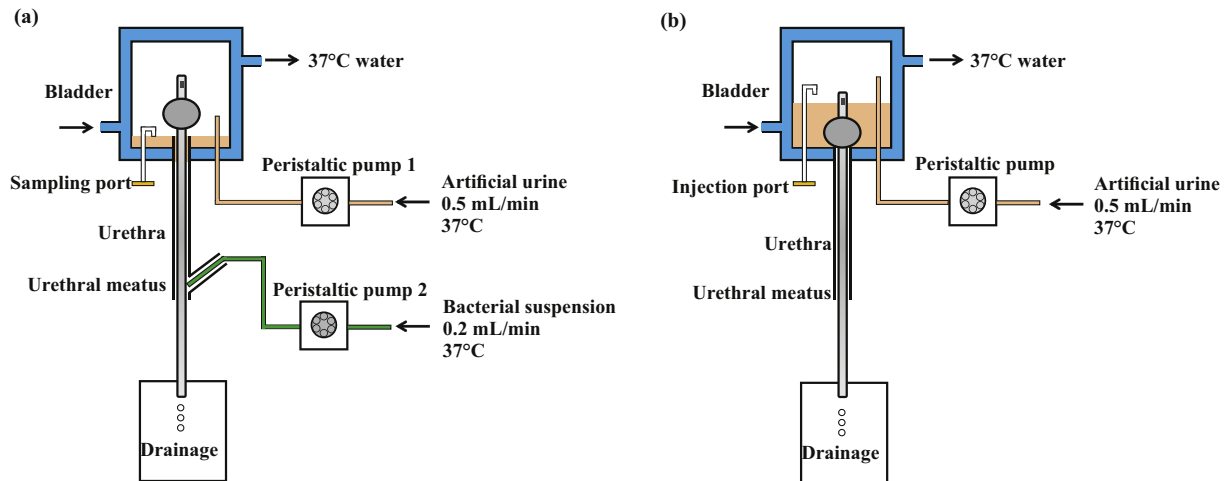


Figure 1. Schematic diagram illustrating in-vitro bladder models to study: (a) bacterial migration along the external surface of catheters; and (b) encrustation of the eye-hole and lumen of catheters.

The catheter retention balloon was filled with 10% aqueous glycerine solution. In order to make the urine medium drip down from the 'bladder' along the 'urethra', there was a 0.5-cm gap between the bottom of the balloon and the top of the 'urethra'. The artificial urine (pH 6.0) was prepared according to the supporting information in the literature [23], but the TSB component was altered to 8.0 g/L. The sterile artificial urine was pumped into the 'bladder' at a rate of 0.5 mL/min. The source of infection was prepared using *E. coli* suspension diluted with 5% dextrose. Two concentrations of $\sim 2 \times 10^6$ and $\sim 2 \times 10^2$ cells/mL were applied to challenge the inserted catheter. The source of infection (prepared and renewed each day) was pumped into the 'urethral meatus' at a rate of 0.2 mL/min, allowing bacteria to attach and colonize on the catheters.

One millilitre of urine medium in the 'bladder' was collected daily through the sampling port to measure bacterial density using the plate count method. When bacteriuria ($\geq 10^3$ cells/mL) occurred, the time taken to develop bacteriuria was recorded, and the catheter was removed from the model. The catheter section infected in the 'urethra' was cut into 2-cm-long segments, and then the biofilm formation on these segments was determined using crystal violet staining [24]. Briefly, each segment was incubated with 1 mL of crystal violet dye in deionized water (0.4% wt/vol) for 15 min, and then rinsed three times with deionized water. Each segment was then incubated with 1 mL dimethylsulfoxide (DMSO) for 4 h to resolve the crystal violet staining biofilms on the segment surface. The biofilm formation was evaluated using the absorbance of each DMSO sample (OD_{600}).

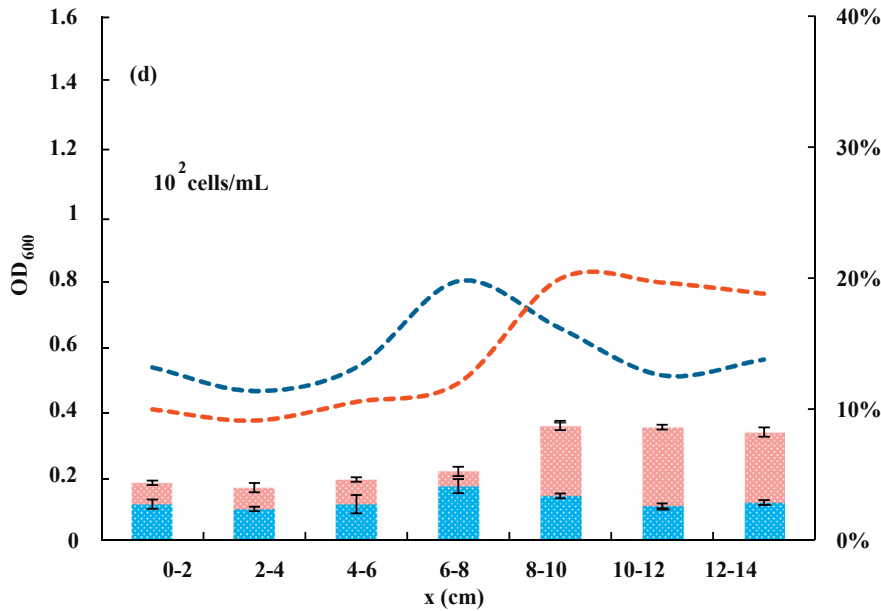
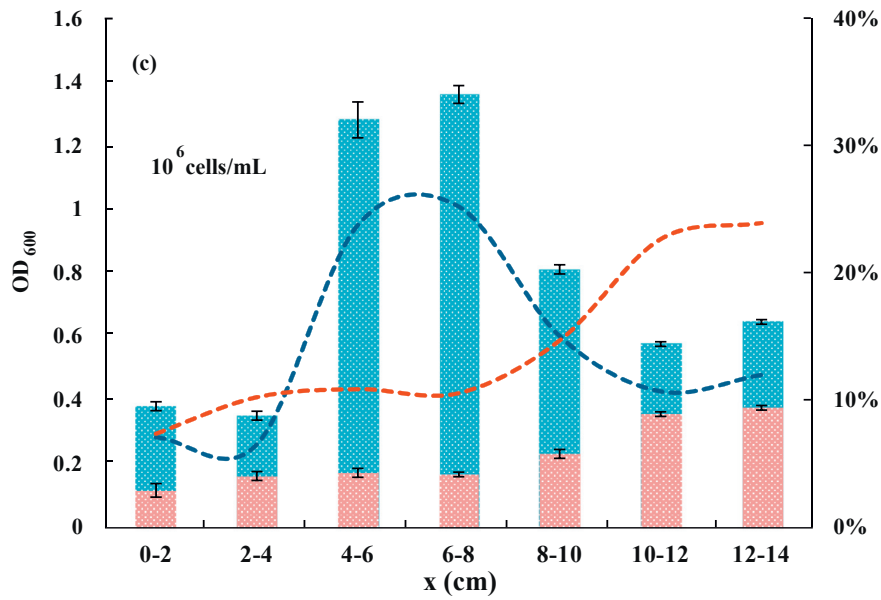
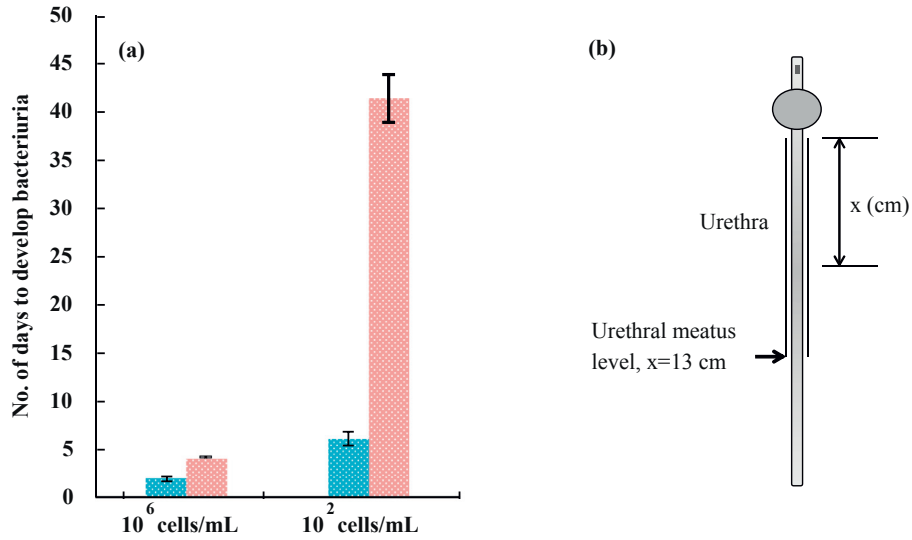
In-vitro anti-encrustation performance of whole coated catheters in bladder model

To test the ability of coated and uncoated silicone catheters to prevent encrustation and blockage, an in-vitro bladder model (Figure 1b), similar to that described previously by Stickler *et al.* [25], was applied. After sterilization of the model, insertion of a sterile catheter and inflation of a catheter balloon as described above, artificial urine (TSB concentration 1.0 g/L, prepared as described before [23]) was pumped into

the 'bladder' at a rate of 0.5 mL/min, and the urine drained via the eye-hole of the catheter. Next, the urine supply was switched off and *P. mirabilis* suspension in TSB was added to the 'bladder' through the injection port, with initial bacterial densities of $\sim 1 \times 10^6$ or $\sim 1 \times 10^3$ cells/mL. The model was maintained for 1 h to allow *P. mirabilis* to establish itself in a new environment before the supply of sterile urine was switched on. The time taken for catheters to block was recorded, and the pH and viable bacteria counts (plate counting) of the urine drained through the catheter were monitored throughout the experimental period. The catheter was removed from the model after blockage. The eye-hole section and the lumen section immediately below the eye-hole were cut, washed, fixed and dehydrated as described previously [26], and were then observed using an optical microscope (Meiji Techno, Karnataka, Japan), and a scanning electron microscope after being gold/platinum sputter-coated (JSM-7400F, Jeol Ltd, Akishima, Japan).

Cytotoxicity assay

The extract test and direct contact test were performed to evaluate the cytotoxicity of catheter segments with Ag-PTFE nanocomposite coatings (RCV 72 mm²/mL) according to ISO 10993-5:2009. To prepare the extract, sterile segments of silicone catheter and coated catheter were extracted with Eagle's Minimum Essential Medium (EMEM) with 10% fetal bovine serum (FBS) at 37°C for 24 h (ratio of coated surface area/volume of extraction vehicle 1.5 cm²/mL). L929 fibroblast cells (NCTC clone 929, Catalogue No. 88102702, European Collection of Authenticated Cell Cultures, London, UK) were cultured with EMEM supplemented with 2 mM glutamine, 1% non-essential amino acids and 10% FBS. The cell suspension was prepared and adjusted to a density of 1×10^5 cells/mL, and 100 μ L of the suspension was seeded in each well of a 96-well plate. After 24 h of incubation at 37°C in a humidified atmosphere of 5% CO₂, 100 μ L of the extract medium or fresh culture medium (blank) was used to replace the culture medium in each well. The cells were then incubated for 24 h, and the extract medium was removed before the addition of 50 μ L 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT)



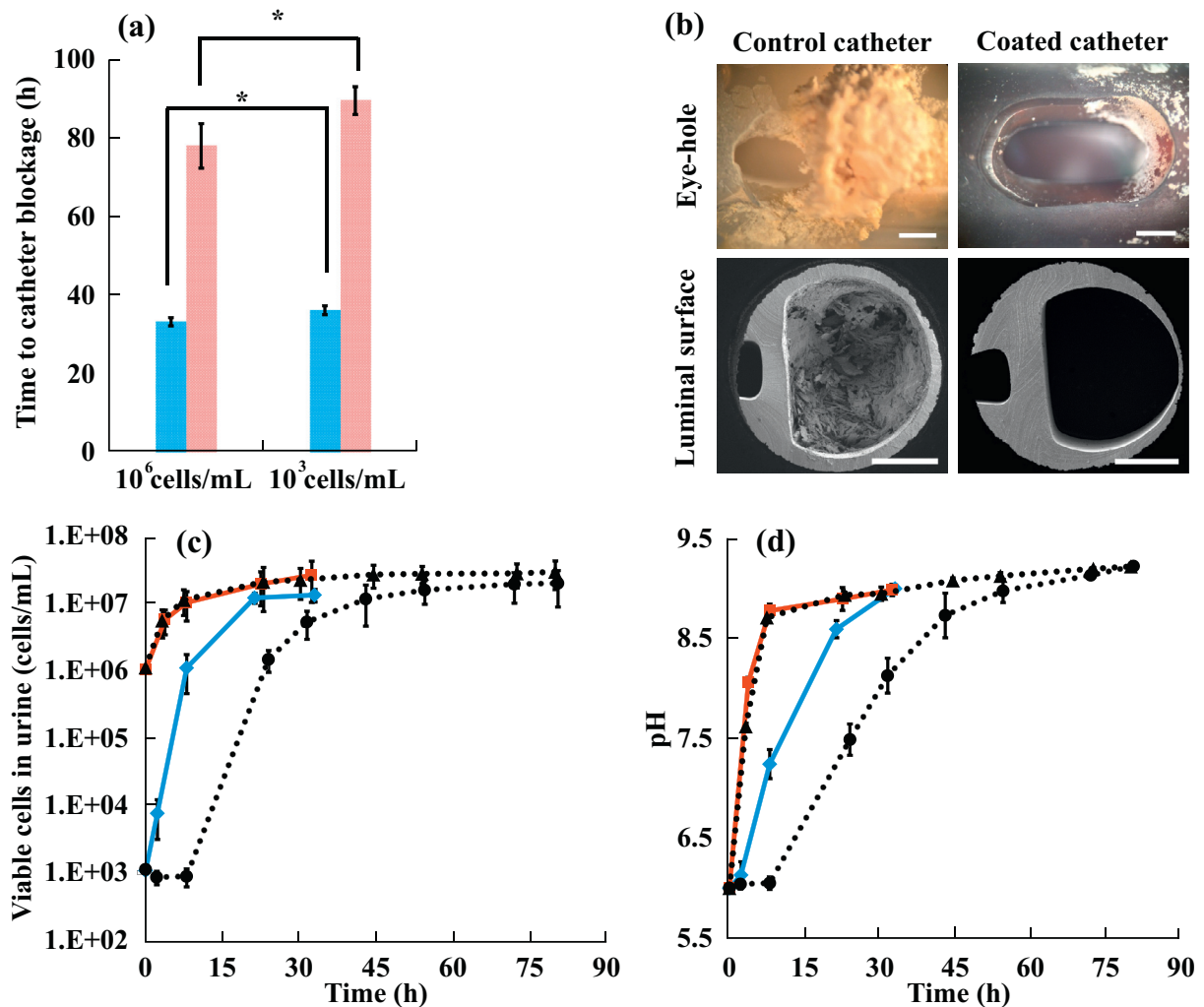


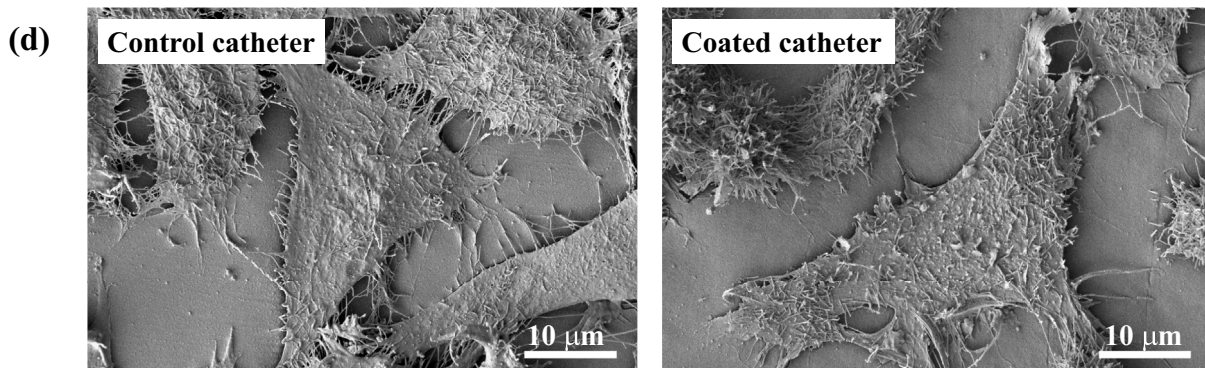
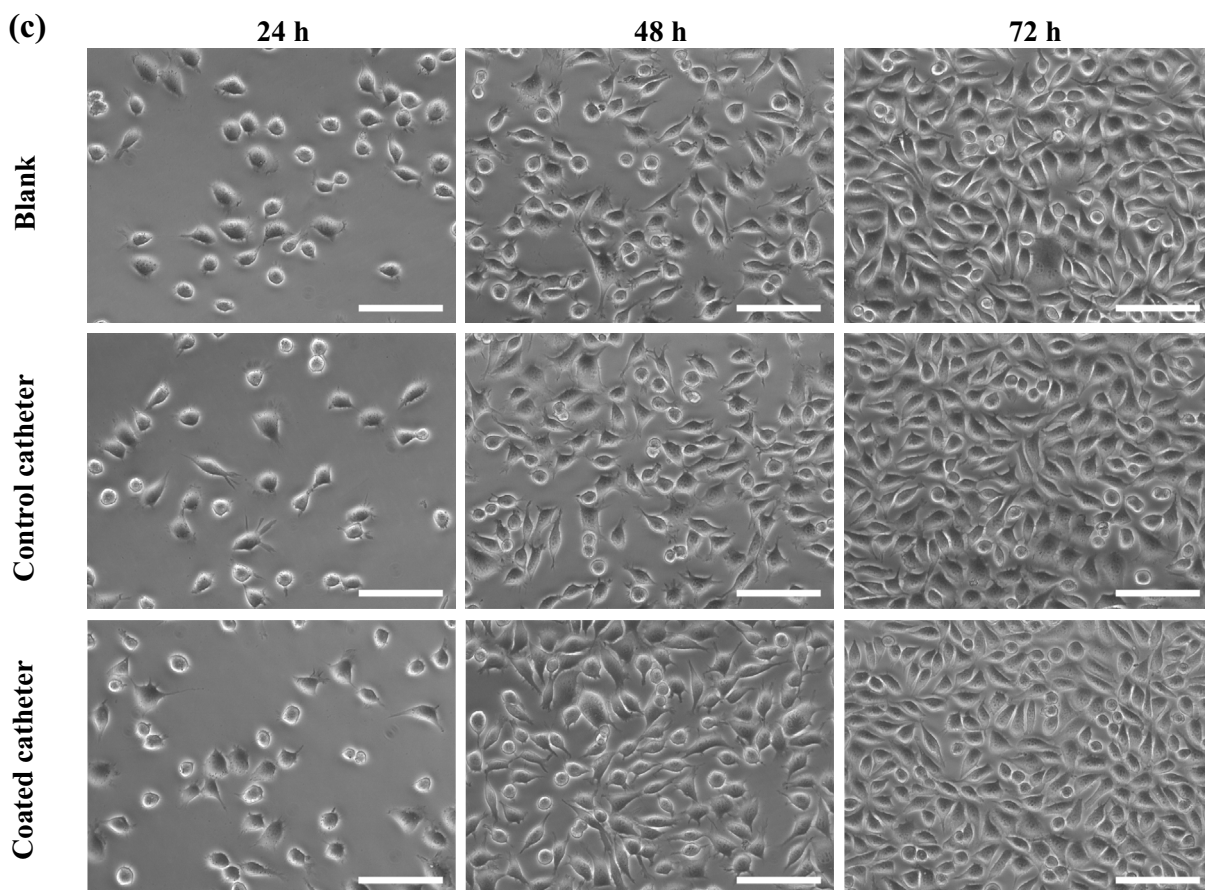
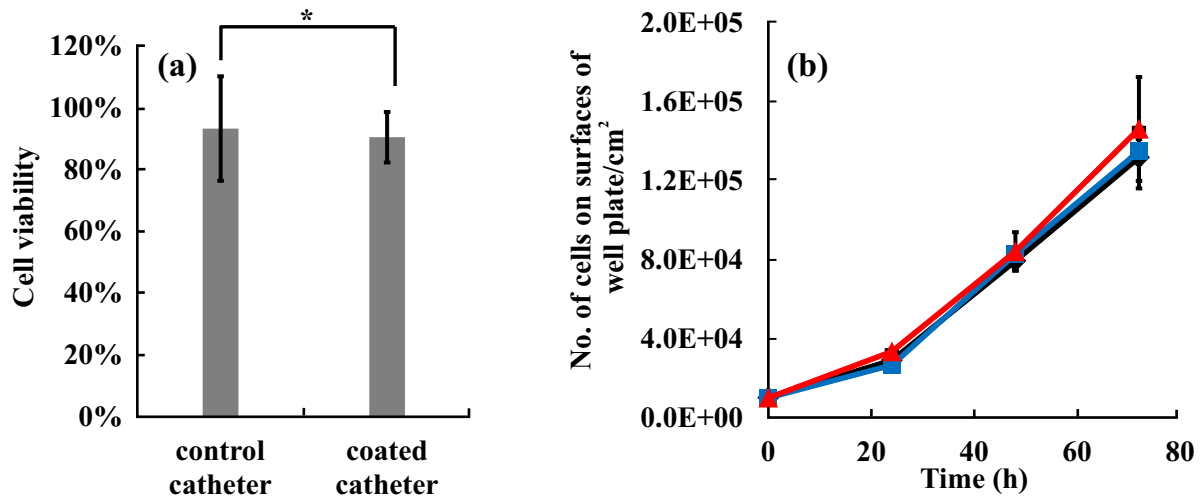
Figure 3. In-vitro evaluation of anti-encrustation performances of whole silicone (control, blue bar) and Ag-PTFE nanocomposite coated (red bar) catheters using the bladder model shown in Figure 1b. (a) The time to blockage. * $P > 0.1$. (b) Optical images of eye-hole sections and scanning electron microscope images of lumen sections. Scale bar: 1 mm. (c) Density of viable cells in the drained urine. (d) pH of drained urine. Blue lines, 10^3 cells/mL, control catheter; red lines, 10^6 cells/mL, control catheter; solid black lines, 10^3 cells/mL, coated catheter; dashed black lines, 10^6 cells/mL, coated catheter.

solution (1 mg/mL). The cell cultures were incubated for 2 h, followed by the removal of MTT solution and the addition of 100 μ L of isopropanol to dissolve the formazan crystals. Optical absorbance of the samples was measured at 570 nm using a microplate reader. The cell viability is the ratio of the mean value of the measured optical density of the extracts of the test sample and that of the blanks.

For the direct contact test, the catheter segment was cut into small pieces, sterilized and placed at the bottom of the well in a 12-well plate (sample pieces evenly covered approximately one-third of the bottom area in each well). Blanks were

the wells without catheters. L929 cells were seeded at a density of 1×10^4 cells/cm². The culture medium was refreshed every two days. The amount and the morphology of cells growing on the well bottom were monitored using an optical microscope (Leica DFC3000, Leica, Wetzlar, Germany). After over 72 h of incubation, catheter samples were removed from the well plate, rinsed with PBS and fixed with 2.5% glutaraldehyde overnight at 4°C. The samples were dehydrated in a series of ethanol solutions and critical point dried, before they were sputter-coated with gold/platinum and observed using a scanning electron microscope.

Figure 2. In-vitro evaluation of antibacterial performances of whole silicone (control) and Ag-PTFE nanocomposite coated catheters using the bladder model shown in Figure 1a. (a) Time taken to develop bacteriuria. (b–d) Biofilm formation along the external surfaces of catheters. The distribution is the ratio of biofilms forming around the position of x (2 cm long) to the whole biofilms forming on the catheter section inserted in the urethra. Blue bars, control catheter; red bars, coated catheter; blue dashed lines, distribution for control catheter; red dashed lines, distribution for coated catheter.



Statistical analysis

The above process was repeated twice independently. All statistical analyses were performed using analysis of variance testing within Excel (Microsoft Corp., Redmond, WA, USA). Values were reported in the text as mean value \pm standard deviation.

Results

In-vitro antibacterial performance of whole coated catheters

Figure 2 summarizes the in-vitro results of coated catheters in inhibiting the migration of *E. coli* along the external surface of the catheter into the bladder. When the source of infection around the urethral meatus was 10^6 cells/mL, it took less than two days for *E. coli* to cause bacteriuria on control catheters, which was consistent with the results presented by Darouiche et al. [8]. In contrast, the time taken for coated catheters to develop bacteriuria was more than twice as long, and the biofilm formation on the external surface of coated catheters was largely reduced (Figure 2a–c). It is noteworthy that when the source of infection was 10^2 cells/mL, the coated catheters significantly extended the time to develop bacteriuria from an average of six days (control) up to 41 days ($P < 0.005$), but formed a similar amount of biofilm on catheter surfaces as control catheters (Figure 2a,d).

In-vitro anti-encrustation performance of whole coated catheters

To test the anti-encrustation properties of Ag-PTFE nanocomposite coated catheters, coated and uncoated catheters were challenged with a continuous flow of urine medium following bacterial contamination of the bladder. Figure 3a reveals that control catheters blocked at 33.3 ± 1.1 h and 36.2 ± 1.1 h with an initial concentration of 10^6 and 10^3 cells/mL in the bladder, respectively, whereas the coated catheters resisted encrustation to 78 ± 5.66 h ($P < 0.01$) and 89.5 ± 3.54 h ($P < 0.005$), respectively. It can be seen from Figure 3b that when the eye-hole and the lumen of uncoated catheters were heavily blocked, little sign of encrustation was visible on the coated catheter.

When the bladder was initially infected by *P. mirabilis* 10^6 cells/mL, the quantitative changes of the viable cells in the urine drained through the catheter were found to be the same between the 'bladder' with uncoated and coated catheters. In both cases, bacteria grew steadily from $\sim 1.0 \times 10^6$ to $\sim 2.6 \times 10^6$ cells/mL. Likewise, the coated catheter did not dramatically affect the variation of urinary pH; pH was sharply increased from 6.0 to approximately 8.7 before slowly increasing to approximately 9.0 (Figure 3c,d).

When the initial bacterial density was 10^3 cells/mL, the coated catheter yielded a 'lag phase' for 0–8 h, in which no obvious increase in the density of viable cells or in the pH of the

drained urine was observed. In contrast, in uncoated silicone catheters, bacteria grew immediately and rapidly raised the urinary pH upon the addition of bacteria into the bladder (Figure 3c,d). After the 'lag phase', the number of bacteria and the pH gradually ascended.

Cytotoxicity assay

As extracts of coated catheters and coatings on surfaces may contact with human cells, the extract test and the direct contact test were conducted herein for future clinical translation. The MTT assays revealed that cell viability in extracts of coated catheter segments was higher than 90%, comparable to the control silicone samples ($P > 0.1$) (Figure 4a). As shown in Figure 4b,c, compared with cells growing in wells of blanks and in those containing control samples, no dramatic difference in cell growth caused by co-incubation with coated catheter segments was observed, and Figure 4d shows that cells adhered on both coated and uncoated surfaces spread well. Together, the MTT assays, cell growth and cell morphology suggest that the novel Ag-PTFE nanocomposite coating was not cytotoxic but was highly biocompatible with cells.

Discussion

With the significant increase in antibiotic resistance, new anti-infective coatings on urinary catheters have been developed as promising strategies to prevent CAUTIs (e.g. antimicrobial peptide [27], multiblock copolymers [9] and silver nanoparticle-polydopamine bilayers [23]). However, in these studies, the antibacterial assays were only performed on coated catheter segments which had been co-incubated with bacterial suspensions for several hours; the antibacterial efficacy of whole coated catheters, and whether coated catheters could be applied for chronic catheterization, remain largely unknown. This study used the in-vitro bladder model in Figure 1a, and found that catheters coated with novel Ag-PTFE nanocomposites exhibited excellent ability to impede migration of *E. coli* along the external catheter surface and to reduce biofilm formation on the catheters.

The time taken for coated and uncoated catheters to develop bacteriuria following contamination with *E. coli* depended on the bacterial concentration around the urethral meatus. As expected, a lower concentration resulted in a longer time to develop bacteriuria. With the infection source lowered to 10^2 cells/mL, the time for coated catheters to inhibit bacteriuria ascended to 6.9 times longer than that of bare silicone catheters. The non-bacteriuric female patients with a spinal cord injury undergoing bladder catheterization, taken as an example, had a mean log number of 0.65 *E. coli* around the urethral meatus [28]. As such, it was speculated that coated catheters could prevent bacteriuria for more than seven times longer than uncoated catheters (i.e. for >41 days) in a patient.

It is interesting to note that the distribution pattern of biofilm formation along the section inserted into the urethra was independent of the bacterial concentration around the

Figure 4. Cytotoxicity results of silicone (control) and Ag-PTFE nanocomposite coated catheters. (a) MTT assays of extracts from catheter segments. (b,c) Growth curves and optical images of cells on well plates under direct incubation with catheter segments, respectively. Scale bar: 100 μ m. (d) Scanning electron microscope images of cells growing on catheter surfaces. Black line, blank; blue line, control catheter; red line, coated catheter.

urethral meatus. The Gaussian-like distribution of biofilms developing on control catheters implied that the middle section of the urethra was the most susceptible to infections when the silicone catheter was *in situ*. Unlike the uncoated catheter, the majority of biofilms on the coated catheter developed near the distal section of the urethra, which identified the role of the coatings in inhibiting bacterial migration along the catheter surface. Together with the effect of reducing biofilm formation, catheters coated with Ag-PTFE nanocomposites may reduce the risk of occurrence of symptomatic CAUTIs and reduce the dose of antibiotics applied for necessary treatment [19].

Besides bacteriuria, the blockage of the eye-hole and lumen of the urinary catheter by encrustation is another critical issue for patients undergoing catheterization, seriously compromising patients' health and welfare [7]. The use of antimicrobial coatings on indwelling catheters [23,29], which could elute into the bladder and kill surrounding planktonic bacteria, seems the simplest way to prevent encrustation. However, this is limited due to difficulties in delivering effective concentrations of antimicrobial agents for prolonged periods [30]. Therefore, filling the retention balloon with solutions of sodium nitrite [24] or triclosan [30,31] to control the urinary pH and bacterial amount in the urine by diffusion has been widely investigated. The toxicity of these solutions, however, needs to be considered very carefully.

The anti-encrustation mechanism of the Ag-PTFE nanocomposite coatings was mainly due to its non-stick properties, rather than its effect on surrounding *P. mirabilis* cells in the urine medium (Figure 3); the presence of ammonia generated by bacterial urease enzyme [7] leads to precipitation of calcium and magnesium phosphates in the urine under alkaline conditions, but few such precipitations attached to the eye-hole and lumen of the coated catheters. The non-stick properties of Ag-PTFE nanocomposite coatings are due to its surface energy, not just the contribution of PTFE [17,18,32]. It was demonstrated that the Ag-PTFE coating with the electroless plating technique gives an inherently uniform coating thickness and mechanical integrity [17,18]. The PTFE content in the Ag-PTFE coating was only approximately 5%, and the coating thickness was approximately 1–2 μm , so the coating on the balloon should not be an issue. However, the integrity of the coating on the balloon during inflation/deflation has not been determined to date, and will be investigated in future studies.

The urinary pH was elevated to approximately 7.5 after *P. mirabilis* cells grew to $>10^6$ cells/mL in the bladder with uncoated or coated catheters inserted; nevertheless, the time to resist encrustation of control or coated catheters was independent of the initial densities of bacteria infected in the bladder, as no significant difference was found between the blockage time for 10^6 cells/mL and 10^3 cells/mL ($P>0.1$ for both control and coated catheters). This suggested that the stage of bacterial growth from 10^3 to 10^6 cells/mL could contribute to encrustation, even without the occurrence of visible precipitations.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2019.02.012>.

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