Biomaterial modification of urinary catheters with antimicrobials to give long-term broadspectrum antibiofilm activity


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A B S T R A C T

Catheter-associated urinary tract infection (CAUTI) is the commonest hospital-acquired infection, accounting for over 100,000 hospital admissions within the USA annually. Biomaterials and processes intended to reduce the risk of bacterial colonization of the catheters for long-term users have not been successful, mainly because of the need for long duration of activity in flow conditions. Here we report the results of impregnation of urinary catheters with a combination of rifampicin, sparfloxacin and triclosan. In flow experiments, the antimicrobial catheters were able to prevent colonization by common uropathogens Proteus mirabilis, Staphylococcus aureus and Escherichia coli for 7 to 12 weeks in vitro compared with 1–3 days for other, commercially available antimicrobial catheters currently used clinically. Resistance development was minimized by careful choice of antimicrobial combinations. Drug release profiles and distribution in the polymer, and surface analysis were also carried out and the process had no deleterious effect on the mechanical performance of the catheter or its balloon. The antimicrobial catheter therefore offers for the first time a means of reducing infection and its complications in long-term urinary catheter users.

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1. Introduction

Urethral catheters are used to drain urine from the bladder (Fig. 1). Bladder catheterization is commonly required, either for short-term bladder drainage or for long-term management of bladder dysfunction, and at least 25% of hospital patients will have a bladder catheter placed at some point in their stay. Short-term catheters are used for the temporary relief of reversible bladder voiding difficulties, for urine output monitoring or after lower urinary tract surgery and are typically used for between 1 and 14 days. Long-term catheterization may be used to manage intractable urinary problems such as chronic urinary retention or incontinence not treatable by other means, and here the aim is to keep the catheter functioning and infection-free for as long as possible but while medical opinion varies, and despite careful hygiene in handling they usually need to be changed every 4–8 weeks [1]. Catheter-associated urinary tract infection (CAUTI) is the commonest hospital-acquired infection, accounting for 40% of all nosocomial infections and over 100,000 admissions to hospital within the USA annually [2]. CAUTI rates have continued to rise in almost every care unit type [3]. The most common CAUTI pathogen is Escherichia coli, followed by Proteus mirabilis [4]. Others, such as Klebsiella pneumoniae, Enterobacter spp, enterococci and staphylococci are important but less common, and Pseudomonas aeruginosa and Candida spp may be seen in longer-catheterized patients, particularly after repeated courses of antibiotics. Increasingly, strains of E. coli and K. pneumoniae produce extended spectrum beta-lactamases (ESBL), making them susceptible to even the newer cephalosporin antibiotics and presenting added therapeutic challenges. As in other devices, CAUTI pathogens are able to attach to the catheter material and to develop biofilms. CAUTI due to P. mirabilis is
especially important due to associated biomineralization [4,5] that can block the catheter lumen, causing obstruction and risking kidney infection and septicemia.

At least two approaches for prevention of biomaterial infection have been used. One involves modification of the biomaterial surface to reduce bacterial attachment, a pre-requisite event in biofilm development. This is usually aimed at making the biomaterial surface hydrophilic [6,7] but a class of weakly amphiphilic polymers that resist bacterial attachment have also been identified [8,9]. The second approach has been to attach active biocides such as antibiotics to biomaterial surfaces, or to impregnate them into the biomaterial itself. One example of the use of surface biocides is silver-processing using various techniques [10]. However, these have been disappointing in clinical use [11] and few “anti-biofilm” urinary catheters have reached the market. Urinary catheters containing nitrofurazone have been evaluated in a large randomized controlled clinical trial alongside silver-processed and plain catheters, and neither of these “antimicrobial” commercially available catheters showed a clinically significant reduction of infection [12]. International guidelines now state that the evidence is not sufficient to support their use in short-term (<30 days) or long-term (>30 days) users [13] and nitrofurazone catheters are now no longer available. In general, antimicrobial coatings either are depleted rapidly by urine flow, or become obliterated by a host protein conditioning film. We have previously reported an antimicrobial neurosurgical catheter produced by an impregnation process that has a long duration of activity confirmed by thousands of successful implants [14–17] and the process has been adapted for use in dialysis [18]. Our previous research on dialysis catheters, using a different antimicrobial combination, concentrated on in vitro assessment of antimicrobial activity and included investigation of potential for inflammatory reaction in the extremely sensitive peritoneal cavity. Here we report the evaluation of duration of activity of a different antimicrobial combination, drug concentrations and their distribution in the catheter material as well as their release characteristics, effect of processing on mechanical properties, particularly of the important retention balloon, and surface analysis on a novel antimicrobial catheter intended for long-term urinary drainage, with enhanced antimicrobial spectrum and duration of activity. The antimicrobials chosen, rifampicin, sparfloxacin and triclosan, were chosen for their spectrum of activity against CAUTI pathogens (rifampicin and triclosan against staphylococci, sparfloxacin and triclosan against *E. coli*, *K. pneumoniae* and *P. mirabilis*). The choice was also governed by their physicochemical characteristics: solubility in chloroform and ability to diffuse through the crosslinked silicone matrix.

## 2. Materials and methods

### 2.1. Impregnation process

The impregnation process (Fig. 2) was carried out as described previously [14]. The antimicrobials, rifampicin (Sigma-Aldrich, Poole, UK), triclosan (Ciba Specialty Chemicals, Macclesfield, UK) and sparfloxacin (Sigma-Aldrich) were chosen for their activity against the target bacteria (CAUTI pathogens) and their chemical compatibility with the impregnation process. Briefly, the antimicrobials were dissolved together in chloroform (Fisher Scientific, Loughborough, UK) to give concentrations w/v of 0.2% rifampicin, 1% triclosan and 1% sparfloxacin. Foley catheters/segments (Coloplast, Peterborough, UK) or silicone test discs 1 mm × 6 mm (Goodfellow, Cambridge, UK) were immersed in the solution for 1 h, during which the silicone swelled to approximately twice its volume. The catheters and discs were then removed and rinsed in absolute ethanol (Fisher Scientific) to remove residual solvent and drug, and allowed to dry overnight at room temperature in a current of air. During evaporation of the solvent the catheters returned to their previous dimensions (Fig. 2), leaving the antimicrobials distributed evenly throughout the silicone matrix. Separately, a series of silicone test discs was produced containing the above antimicrobial concentrations as single agents. The segments and discs were then packaged and sterilized by autoclaving at 121 °C for 15 min. The sterilization process had no significant effect on the antimicrobial activity (data not shown).

### 2.2. Assay of drug content and drug release profiles

Total drug content was determined by extracting catheter segments in chloroform which was then evaporated at room temperature. Drug residues were re-dissolved in acetone and HPLC analysis was performed (Agilent 1090 HPLC, Agilent Technologies, Berkshire, UK) (Supplementary Method 1). The total concentration of each drug extracted from the catheter segments was calculated using peak areas from calibration curves and the total drug content per catheter was calculated. All experiments were carried out in triplicate. Calibration curves showed good linearity, with correlation coefficients ($R^2$) for rifampicin, triclosan and sparfloxacin of 0.9961, 0.9955 and 0.9997 respectively. To establish drug release concentrations, antimicrobial catheter segments were placed into HPLC grade water (pH 7) (Fisher Scientific) in a 37 °C incubator with constant agitation. Segments were transferred daily or every 2–4 days into fresh water over a period of 28 days. After concentration by liquid–liquid extraction using chloroform, eluates were evaporated and drug residues were re-dissolved and analyzed by HPLC. Drug release concentrations were determined from calibration curves. All tests were carried out in triplicate. Calibration curve correlation coefficients ($R^2$) for triclosan and sparfloxacin were 0.9998 and 0.9999.

### 2.3. Distribution of drugs in the polymer

The distribution of the antimicrobials at the catheter surface after impregnation and after soaking in phosphate-buffered saline (PBS, Oxoid, Basingstoke, UK) for 12 weeks with weekly changes was studied by time of flight secondary ion mass spectrometry (ToF-SIMS) depth profiling. Transmission electron microscopy, on samples prepared by focussed ion beam milling or ultramicrotomy, was used to determine the distribution of the three drugs in the polymer matrix and to investigate their particle size. Elemental analysis was performed for the presence of nitrogen, fluorine and chlorine, expected to be present in the antimicrobials but absent from the polymer (Supplementary Method 2).
2.4. Mechanical properties of the catheter and balloon

It is important that any post-manufacture processing does not damage the biomaterial, and the inflatable retention balloon is an obvious site of susceptibility for any deterioration in mechanical properties. In addition, the catheter itself is subject to tensile force during insertion and removal. Urinary catheters were used in the “as-received” state from the manufacturers (controls) and following impregnation with the antimicrobial agents as described. Half of the control and antimicrobial catheters were placed in simulated urine [19] while the other half remained in an unchanged state. Mechanical performance of catheter shafts was assessed using an M985 (Imetrum Ltd., Bristol, UK) with a 5 kN loadcell connected to a video extensometer. Data were recorded using Bluehill 2 software. A specialized clamping configuration was devised to connect the catheter tubing to the Instron as shown in Fig. 6a. Catheters were clamped to expose a 5 cm length along the mid-section of the catheter and coated metal targets were applied 3 cm apart to allow for tracking by the video extensometer. A force was applied at a rate of 100 mm/min as the apparatus recorded the stress. The force applied was continued until either the apparatus reached its maximum length limit or until catheter failure (breakage) occurred. All tests were conducted at room temperature and in all cases three replicates of each analysis were performed. From the resultant relationship between the stress and strain, the load (N), ultimate tensile strength (MPa), elongation at break (mm) and modulus (MPa) determined at 280–320% elongation were calculated. Tests on catheter balloons (Supplementary Table 1) were adapted from ASTM F623 99 [20] and BSEN1616: 1997 [21]. The control and antimicrobial balloons were immersed in artificial urine [19] for 30 days at 37 °C. Balloon security was tested by inserting the catheter tips, with balloon inflated, through an inverted funnel and a 1 kg weight applied to pull the balloon against the neck of the funnel. Failure consists of leakage or rupture of the balloon and distortion so that the eye-holes of the catheter become occluded. All control and impregnated balloons, before and after soaking, passed the test. Balloon volume retention was tested by inflating them with 10 mL of 0.5 g/L methylene blue and placing on an absorbent white background (to detect dye leakage) for 30 days.

2.5. Atomic force microscopy

An increase in surface roughness might facilitate mineral encrustation and could cause discomfort on catheter removal. Segments of control and impregnated catheters 1 cm long were placed in PBS at 37 °C for 12 weeks to simulate drug elution over the period of catheter use, with fresh solution replaced every week and a second identical set was left unsoaked. Atomic force microscopy was used to determine surface roughness (Rq value). All tests were performed in triplicate. Sections (approx 2 × 2 mm) of catheter segments were mounted onto metal stubs for analysis by AFM, and measurements were conducted on a MultiMode 8 AFM (Bruker) with a Nanoscope V controller operated in a PeakForce Quantitative NanoMechanics (QNM) mode in air using a silicon nitride cantilever with a 0.1 N/m nominal spring constant. Two 5 μm × 5 μm surface area scans were performed on each catheter segment.

2.6. Antimicrobial activity: serial plate transfer test

Test bacteria, chosen from isolates from patients with CAUTI in our urology clinic, were one strain each of: Staphylococcus aureus (MRSA), E. coli, P. mirabilis, K. pneumoniae, Staphylococcus saprophyticus and Enterococcus faecalis. In addition, we tested a strain of ESBL – producing E. coli. Both S. aureus and S. saprophyticus were susceptible to rifampicin; E. faecalis had an MIC of rifampicin two logs higher, and the gram-negative bacteria were predictably resistant to this drug. All were susceptible to sparfloxacin except S. aureus and the ESBL strain of E. coli. Minimum inhibitory concentrations (MICs) were determined by agar incorporation or in the case of rifampicin, by Etest (AB Biodisk, Solna, Sweden) and were shown in Supplementary Table 2. While a simple zone plate is sufficient to demonstrate antimicrobial activity, serial transfer of the material to fresh plates will show how long the material produces a zone of inhibition (Serial Plate Transfer Test, SPTT) [14]. ISA agar (Oxoid) plates were seeded with the test bacteria (Ano 0.6, ~1 × 10⁵ cfu/mL) and impregnated silicone discs were placed in triplicate on their surfaces and incubated overnight. Zones of inhibition were measured with calipers and the discs were transferred to a fresh seeded plate and incubated [22]. The process was repeated for 100 days or until no zones were produced (Fig. 5a). All tests were carried out in triplicate.

2.7. Antimicrobial activity: time–kill study (tK100)

It is now recognized that, when bacteria attach to a surface, their susceptibility to antimicrobials is markedly reduced [23] and it is important to determine the ability of antimicrobial biomaterials to kill all, or most, of attached bacteria within a reasonable time. This assay has been termed the tK100 test, that is the time taken to kill 100% of attached bacteria. It is also recognized that when urinary catheters are contaminated by bacteria in vivo, the bacteria usually encounter a biomaterial surface that is overlaid with a host-derived conditioning film [24]. This was simulated by immersing the test discs and plain controls in filter-sterilized human urine (pH 6.8) for 1 h at 37 °C. XPS was used to determine if a conditioning film had been deposited on the surface (Supplementary Method 3). XPS confirmed the presence of a protein conditioning film (Fig. 5b). The discs were then immersed in a suspension (approximately 1 × 10⁸ colony-forming units/mL) of early log phase test bacteria and incubated at 37 °C for 1 h for attachment to take place. After rinsing to remove unattached bacteria, triplicates of discs were placed in diluted Tryptone Soya Broth (TSB, Oxoid) for up to 72 h, the dilution necessary for survival of attached controls without planktonic multiplication being found by experiment for each test isolate. For staphylococci 1% was suitable but for others 0.1%–0.5% was best (data not shown). At
intervals of 0, 24, 48 and 72 h, after rinsing and medium replacement each day, triplicates of discs were removed and sonicated (50 Hz for 20 min) and surviving colonies plate counted.

2.8. Antimicrobial activity: serial bacterial challenge in flow conditions

In order to simulate the flow aspects of the catheters in use and to ensure that any depletion of antimicrobial activity due to leaching was detected, we used an established catheter challenge model [18]. This consisted of a modular heating jacket into which the test catheters, with balloon removed, were inserted and kept hydrated by a secondary water jacket (Fig. 3a).

Tryptone Soya Broth was pumped through the catheters constantly at 0.5 mL/min (representative of human urinary production rate) until the test ended. Each week, the test catheters (in triplicate) were inoculated with a suspension of \(1 \times 10^6\) CFU/mL of early log phase cultures of S. aureus (MRSA), E. faecalis, E. coli (including the ESBL strain) or P. mirabilis and the catheters clamped for 1 h to allow bacterial attachment (Fig. 3b). Fresh plain unimpregnated control catheters were included at each new inoculation. Flow was then restarted. Effluent samples from the distal end of the catheters were collected aseptically each day and plated (200 µL per plate × 3) for colony counting. If no growth was present after 7 days, a further inoculation was made, and so on until either colonization occurred or 12 weekly challenges had passed. Colonized control catheters were removed and renewed for each challenge.

3. Results and discussion

3.1. Drug distribution and content of catheters and drug release profiles

The method of post-manufacture impregnation of Foley catheters described here differs from others in that it allows post-extrusion introduction of antimicrobials in a state that is not detectable by light or electron microscopy, and it allows the antimicrobials to migrate through the silicone matrix to replenish those lost from the catheter surface due to fluid flow, thus giving an extended duration of activity. Processed catheters were found to contain a total of 0.49 mg rifampicin (%RSD = 12.3%), 14.0 mg triclosan (%RSD = 5.1) and 13.25 mg sparoxacin (%RSD = 11.8) equivalent to 0.006%, 0.17% and 0.16% w/w respectively (Fig. 4a).

The release profiles for the drugs from the silicone catheter segments over a 28 day period were determined (Fig. 4b). Release of rifampicin from the catheter segments was not detected (limit of detection 1 µg/mL), probably because of the low initial total rifampicin content in the catheters. At time-points over the 28 day release, the %RSD of triclosan varied between 5.9–33.4% and 11.1–44.3% for sparoxacin, with the higher RSD% being associated with concentrations of the drugs close to the analytical limits of detection. After 28 days in water, 30% of the initial triclosan and 20% of the initial sparoxacin had been released, suggesting sufficient drug left to diffuse over a prolonged time.

In ToF-SIMS analysis, the Si\(^+\) secondary ion was characteristic of the silicone substrate, the F\(^-\) ion was characteristic for sparoxacin and the Cl\(^-\)/37Cl\(^-\) ions were characteristic for triclosan (Supplementary Fig. 1). The CN\(^-\) ion was representative for both sparoxacin and rifampicin. Sparoxacin and triclosan were shown to be evenly distributed laterally but before soaking there were some aggregates of both drugs at the surface, due to residues accrued during drying, that disappeared after soaking, though the drugs were still detected in the matrix (Fig. 4c).

ToF-SIMS depth profiles of the impregnated catheters showed an elevated level of ions characteristic of drug compared with the untreated catheter (Fig. 4d), and a heightened intensity at the surface of the catheter. An even distribution of sparoxacin and triclosan was observed throughout the remainder of the catheter wall (Fig. 4e). The presence of rifampicin could not be confirmed by ToF-SIMS for the catheter containing all three antimicrobials as representative ion for rifampicin (CN\(^-\)) was also observed in the ToF-SIMS spectra for sparoxacin.

Therefore, to confirm that impregnation of rifampicin occurred, a catheter loaded only with this antimicrobial was assessed by ToF-SIMS depth profiling. An elevated intensity of the CN\(^-\) ion was observed compared to an untreated catheter, which continued into the wall of the catheter, confirming that rifampicin was successfully loaded into the catheter using the methodology described. After a 12 week elution, a reduction in secondary ions characteristic of the drugs was observed throughout the catheter wall, suggesting that eluted drug is able to diffuse evenly from the catheter matrix (Fig. 4f) as intended.

TEM was unable to detect the antimicrobials on any scale (data not shown), and simulations indicated that the GIP Triedium TEM would be sensitive to localized drug concentrations of 10% or more by volume. This would indicate an upper size limit on aggregates of antimicrobials sensitive to localized drug concentrations of 10% or more by volume. These results extend the duration of activity considerably in excess of other experimental antimicrobial catheters. Cho et al. dipped their catheters in a mixture of gentamicin and poly(ethylene-co-vinyl acetate but reported gentamicin release for only 7 days [25] and reported 5 days in a rabbit model [26]. The same group reported inhibition zones for 10 days but did not report a quantitative release profile [27]. Rafienia et al. reported 12 days’ release of the same group to catheters dipped in a gentamicin–copolymer mix [28].

The same group reported inhibition zones for 10 days but did not report a quantitative release profile [27]. Rafienia et al. reported 12 days’ release from catheters dipped in a gentamicin–copolymer mix [28]. However, the extreme heterogeneity of antimicrobials, processing technology and test methods makes the published reports difficult to compare with each other and with our very different processing and testing. Our duration data are also far in excess of those reported for commercially available antimicrobial catheters [11,12] whose duration of activity is a few days at the most. Our previous studies on these two commercial catheters, silver-processed and nitrofurad coated, showed a duration of activity of ≤2 days in the SPTT, and both failed the first challenge in the flow challenge test (data not shown), therefore validating the in vitro tests in respect of the clinical trial results.

In this SPTT study, discs impregnated with a combination of all three drugs (Fig. 5a) showed continued inhibition of all except E. faecalis for
> 100 days, with reductions of zone diameter of between 17% (staphylococci) and 36% (P. mirabilis) over this period. The inhibition zone for E. faecalis fell steeply and declined to zero on Day 22. No resistance was seen with any test bacterium in this assay. For the tK100 assay, we applied a urinary protein conditioning film. X-ray Photoelectron Spectroscopy (XPS), used to verify the deposition of a conditioning film, showed an increase in carbon and nitrogen with a decrease in silicon signal, indicating deposition of C + N rich material on the silicone surface (Fig. 5b). No viable S. saprophyticus, S. aureus or K. pneumoniae was found after 24 h. All E. coli were killed by 48 h and all E. faecalis by 72 h. In the case of P. mirabilis, <25 cfu/mL remained at 72 h compared to \(10^5\) cfu/mL from plain controls indicating a >99.9% reduction (Fig. 5c and d). In the flow challenge test, on each challenge, all the control catheters became colonized by Day 1 and remained so until removed (Table 1).

No colonies were observed for S. aureus and E. coli, including the ESBL strain in effluents for the 84-day duration of the challenge test. Those challenged with P. mirabilis became colonized on Days 57, 78 and 85. The processed catheters failed to prevent colonization by E. faecalis beyond Day 15. Repeat MIC determination on isolates from failed catheters showed slight increases for P. mirabilis but still within the susceptible range, and no change for E. faecalis, suggesting that in each case failure to prevent colonization was not due to the development of resistance. Resistance development was not seen after prolonged exposure of test bacteria to the catheters in the Serial Plate Transfer Test or in the Serial Challenge Flow Test. Concerns regarding resistance strains appearing as a result of use of antimicrobial catheters are entirely justified and this is why we used these combinations of antimicrobials, which according to the Dual Drug Principle [29] would significantly reduce the likelihood of mutational resistance. Also, when much higher inocula of P. mirabilis (\(10^6\) cfu/mL) have been exposed to triclosan alone on agar surfaces they have shown evidence of mutational resistance, as expected [30]. However, those mutants showing MICs of 2 mg/L were still prevented from colonizing urinary catheters in a laboratory model [30]. In most cases reduction of viable bacteria was below the detectable levels, at least a five-log reduction (Table 1: in vitro challenge, and Fig. 5c and d, tK100). Overall, the test catheters were able to delay colonization by CAUTI pathogens between 7 and 12 weeks, with the exception of E. faecalis. The spectrum of activity therefore extends to most of the CAUTI uropathogens, the exceptions being P. aeruginosa, Candida and, except for the first two weeks, enterococci. However, most CAUTI is caused by enterobacteria (E. coli, K. pneumoniae, P. mirabilis) with a minority due to P. aeruginosa or Candida in most studies [31].

Long-term urinary catheters have also been identified as reservoirs for S. aureus including MRSA [32] and our catheter also showed a strong activity against these bacteria. As well as reducing CAUTI due to staphylococci, the catheter promises to reduce spread of S. aureus and MRSA, contributing to infection control measures. The results suggest that this might similarly be the case for multi-resistant ESBL E. coli, reducing the spread of these bacteria to the environment, to healthcare workers and to other patients.
3.3. Effect of processing on mechanical properties of the catheter and balloon

The results show that neither the process itself nor the presence of the antimicrobials affects the mechanical properties of the material. Impregnating the catheter and balloon with antimicrobial agents caused no adverse effects to the mechanical performance (Fig. 6b, c).

Despite a load of 60–70 N applied at 100 mm/min, resulting in an elongation of 377% (instrument limit) for all catheters, none was fractured. There were no statistically significant differences (2 tailed homoscedastic Student’s t-test) between control and impregnated catheters in their unused state with regard to load (p = 0.168), tensile strength (p = 0.111), and modulus (p = 0.054) or between control and impregnated catheters after soaking in artificial urine for load (p = 0.993), tensile strength (p = 0.994) and modulus (p = 0.381) (Fig. 6c). All control and impregnated balloons, before and after soaking, passed the test. No leakage was seen from control or impregnated balloons, and in all cases the balloons deflated fully at the end of the test (Supplementary Table 1), an essential requirement in clinical use to allow free removal of the catheter from the bladder. Impregnating the catheter and balloon with antimicrobial agents therefore caused no adverse effects to the mechanical performance. The processing and impregnation did not change the surface roughness of the catheters. There was no significant difference (2 tailed homoscedastic Student’s t-test) in Rq values between control and impregnated catheters before soaking (p = 0.240), but after soaking the impregnated catheters showed an increase in the Rq value (9.57 nm ± 1.35 s.d. vs 22.72 nm ± 4.33 s.d., p = 1.628 × 10⁻¹⁵), presumably due to the release of antimicrobials during soaking (Fig. 6d). This nm increase in surface roughness would be unlikely to cause patient discomfort, or act to promote bacterial colonization or mineral encrustation, though further testing of mineral encrustation propensity would be required to exclude this possibility.
4. Conclusions

Currently available “antimicrobial” urinary catheters have been shown not to be effective in laboratory and clinical studies, and there is no catheter available for either short-term or long-term catheter users, leaving them with the problem of recurring infection and obstruction leading to painful catheter changes. If the antimicrobial catheter were to prove to be effective in clinical use then a considerable saving in hospital time and treatment and vastly improved quality of life for patients could be achieved. The results suggest that the impregnated catheters might reduce CAUTI in both short-term and long-term urinary catheter use. Though this reduction is difficult to quantify at this stage, it is likely that, if CAUTI could be prevented or significantly delayed in a new catheter user, the concomitant reduction in antibiotic use might also avoid progression to infection by *Pseudomonas* or *Candida*, and in any case would contribute considerably to the drive to reduce antibiotic resistance.

Further studies on the antimicrobial catheter will include an evaluation of its ability to reduce or prevent mineral encrustation, before a Phase 1 study followed by a full Phase 2 clinical efficacy trial.

Contributions

RB and LEF conceived and designed the experiments. LEF, ALH, WA, RB, AY, DAB, DJS, XC, MF, EFS and CDJP carried out the experiments and supplied specialist expertise. RP gave specialist urological advice. LEF, RB and ALH wrote the paper and all authors reviewed the draft.

Competing financial interests

RB has filed a patent application, approved in several countries, on the impregnation technology. No other author has any competing financial interest.

#### Table 1

<table>
<thead>
<tr>
<th>Test bacterium</th>
<th>Day of failure</th>
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<tr>
<td><em>Staphylococcus aureus</em> MRSA</td>
<td>&gt;84</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>15</td>
</tr>
<tr>
<td><em>Escherichia coli</em> ESBL</td>
<td>&gt;84</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>57, 78, 84</td>
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#### Fig. 6

Mechanical characterization of impregnated catheters. (a) Image of the setup used to assess the load, tensile strength and modulus of catheters. (b) Image of impregnated (left) and untreated (right) catheters with the balloon inflated. (c) Table of the mechanical measurements taken for untreated and impregnated catheters before and after elution. (d) AFM characterization of untreated and impregnated catheters before (left) and after (right) elution, showing both the topographical images and RMS (Root Mean Square) roughness ($R_q$). Images were acquired from an area of 5 μm - 5 μm.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jconrel.2015.01.037.

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