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Polymer-Coated Urinary Catheter Reduces Biofilm Formation and Biomineralization: A First-in-Man, Prospective Pilot Study

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Purpose: Biofilm formation and biomineralization on urinary catheters may cause severe complications including infection and obstruction. Here, we describe an in vitro evaluation and prospective pilot clinical study of a silicone catheter coated with a biofilm-resistant polymer.

Materials and Methods: Biofilm biomass and biomineralization on uncoated and coated catheters were quantified by confocal microscopy using fluorescently tagged bacteria or stained for biofilm and minerals. Biomineral identity was determined using scanning electron microscopy and X-ray spectroscopy. Biofilm formation and biomineralization were evaluated in vitro using uropathogens *Proteus mirabilis* and *Pseudomonas aeruginosa* and on catheters recovered from hospitalized patients. Fibrinogen in patient urine and on catheters was quantified using an immunofluorescence assay.

Results: In vitro *P. mirabilis* and *P. aeruginosa* formed significantly less biofilm and biomineral and failed to block coated compared with uncoated catheters in a bladder model after 89 h. Biofilm-resistant polymer-coated catheters (n = 83) recovered from hospitalized patients exhibited significantly lower biofilm biomass and biomineralization compared with uncoated silicone catheters (n = 78). Electron microscopy with elemental analysis of recovered catheters revealed calcium oxalate crystals on coated compared with the struvite and apatite crystals on uncoated catheters associated with catheter blockage. Lower levels of biofilm-promoting fibrinogen in postcatheterization urine and on catheters from patients receiving coated catheters was observed compared with those receiving uncoated catheters indicative of a reduced inflammatory response.

Conclusions: These data provide evidence that polymer-coated urinary catheters exhibit enhanced resistance to fibrinogen deposition, biofilm formation, and encrustation, reducing the risks associated with catheter-associated urinary tract infections and obstruction.

Key Words: urinary catheters, polymer coating, urinary tract infections, biofilms, biomineralization, fibrinogen

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INTRODUCTION

Catheter-associated urinary tract infections (CAUTIs) carry an estimated annual economic burden estimated at $1.7 billion in the United States alone.[1] Although catheter colonization frequently results in asymptomatic bacteriuria, bacterial biofilm formation on catheter surfaces has been linked to symptomatic CAUTI episodes including urolithiasis, pyelonephritis, and septicemia.[2,3]

Biofilms consisting of bacterial communities encased within a self-produced extracellular matrix (ECM) readily form on urinary catheter surfaces and are notoriously difficult to prevent or eradicate.[4,5] Severe complications can arise from crystalline biofilm formation by urease producers such as *Proteus*.[3,6] Ureases hydrolyze urea-releasing ammonia raising urinary pH and leading to formation of struvite and apatite biomineral crystals that become incorporated into the biofilm ECM.[3,7] This leads to encrustation and catheter blockage causing significant patient pain and discomfort. Catheter blockages occur as early as 2 days postcatheterization with up to 50% of individuals undergoing long-term catheterization (> 0 days) likely to experience a catheter blockage event.[8-10]

Urinary catheters are primarily manufactured from polymers such as polyurethane and silicone.[11] These were generally selected for their biocompatibility, mechanical properties, ease of manufacture, and low cost but with little consideration of CAUTIs. These can be reduced using the correct catheterization technique, optimization of closed drainage systems, and ensuring good hygiene practice.[12,13] However, impregnation of urinary catheters with antimicrobials or silver has generally been ineffective in preventing CAUTIs.[3,11] More recent strategies have focused on discovering biomaterials that intrinsically inhibit biofilm formation.[14-16] The first of a new class of biofilm-resistant acrylate polymers (Bactigon) also offers the mechanical and lubricating properties desirable for a flexible catheter coating.[17] Bactigon is a nontoxic copolymer of ethylene glycol dicyclopentenyl ether acrylate and diethylene glycol ethyl ether methacrylate.[17] Foley silicone catheters dip-coated[17] with Bactigon are manufactured by Camstent Ltd. They have received regulatory approval for human use in Europe. Here, we describe an investigation of biofilm formation, biomineralization, and fibrinogen (Fg)[18,19] deposition on the polymer-coated urinary catheters in vitro and in a first-in-man, prospective pilot clinical study.

METHODS

Bacterial Strains and Growth Conditions

P. mirabilis Hauser 1885 and *Ps. aeruginosa* PAO1 and *Staphylococcus aureus* SH1000 were routinely grown at 37°C in lysogeny broth with shaking at 200 rpm. Where required, bacteria were tagged with plasmids constitutively expressing fluorescent proteins dsRed (pBK-miniTn7-dsred),[20] mTurquoise (pSW002-Pc-mTurquoise),[21] or mTagBFP2.[22] For in vitro biofilm experiments, bacteria were cultured in artificial urine (AU)[23] of pH 6.5.

Biofilm Formation In Vitro

Sterile uncoated silicone or polymer-coated 1-cm catheter segments were placed in 6-well plates containing 6 ml of AU and inoculated with dsRed-tagged *P. mirabilis* or mTagBFP2-tagged *Ps. aeruginosa* or with a mixed 1:1 inoculum. These samples were incubated at 37 °C with shaking at 60 rpm for 48 hours.

Bladder Catheterization In Vitro Model

The bladder catheterization model described by Milo et al[24] was used. Whole silicone (uncoated) or polymer-coated urethral catheters (Camstent Ltd, Bedford) were inserted into a double chambered glass vessel representing the bladder, and the closed drainage system was assembled by attaching a catheter drainage bag. A peristaltic pump supplied AU at 37 °C and a flow rate of 0.75 mL/min for up to 89 hours. The glass vessel was inoculated with either mTurquoise-tagged *Ps. aeruginosa* or dsRed-tagged *P. mirabilis* or with a mixed inoculum (10^8 CFU per mL). Catheter blockage times were determined by monitoring the flow of AU.

Patient Urinary Catheter and Urine Sample Collection

A total of 161 patients were recruited preoperatively from 5 UK hospitals where they received either a coated or an uncoated silicone urinary catheter. All patients received postcatheterization, preoperative antibiotics before surgery (Table S1, http://links.lww.com/JU9/A52). Catheters were recovered from patients consenting to the study at Queen's Medical Centre, Nottingham; Westmoreland St. Hospital, London; University Hospital Southampton; James Cook University Hospital, Middlesborough; and University Hospital of Wales, Cardiff. For Camstent catheters, a maximum of 30 days indwelling was permitted unless there was a clinical need to extend this time. Recovered catheters were placed in sterile containers and stored for up to 7 days at 4 °C before processing. Precatheterization and postcatheterization urine samples and the corresponding catheters were also obtained from 10 patients (5 with coated, 5 uncoated) at Queens Medical Centre. The study was approved by the respective Research Ethics Committees, under the UK National Health Service Integrated Research Application System project IDs 232293 and 242341 and UK clinical trial IDs NCTC05513677 and NCTC05719753.

Catheter Biofilm Analysis

After removal of tips and drainage funnels, catheters were cut into 7 × 5 cm segments. Quantification of biofilm biomass and biomineralization was achieved using confocal laser scanning microscopy (CLSM; Zeiss 700) and image analysis (Comstat2/ImageJ).[25] Patient catheter samples were stained for biofilms with the cell permeant DNA stain, Syto 64 (Thermofisher) and minerals with calcein (Thermofisher). For each catheter segment (at

least 3 per catheter), five Z-stacked (2.5 mm × 2.5 mm) images were quantified.

Scanning Electron Microscopy and Energy Dispersive X-ray Spectroscopy

Catheter sections were vapor-fixed for 16 hours using 4% (v/v) formaldehyde and imaged by environmental scanning electron microscopy (ESEM) coupled with energy dispersive X-ray spectroscopy (EDS). Mineral elemental composition was determined from the EDS spectra for Ca, Mg, N (nitrogen), and P (phosphorous) content that relate to struvite (magnesium ammonium phosphate; $NH_4MgPO_4 \cdot 6H_2O$) and apatite (calcium phosphate; $Ca_5(PO_4)_3(F,Cl,OH)$). N content was selected as representative of biofilm formation because it is associated with proteins and nucleic acids. For scanning electron microscopy (SEM), catheter sections were perfusion-fixed with 2.5% (v/v) glutaraldehyde in 0.05 M sodium cacodylate, subjected to 1% osmium tetroxide for 1 hour postfixation and dehydrated with ethanol. Catheter sections were subjected to SEM after gold-sputter coating.

Calcium Oxalate Quantification

Calcium oxalate was extracted from catheters recovered from patients with high levels of catheter mineral accumulation by treating with HCl (5M) and quantified using an oxalate colorimetric assay kit (Sigma-Aldrich).

Fibrinogen Quantification

The Fg content of precatheterization and postcatheterization urine samples was determined using a human Fg ELISA kit (Abcam). The in vitro deposition of human plasma Fg

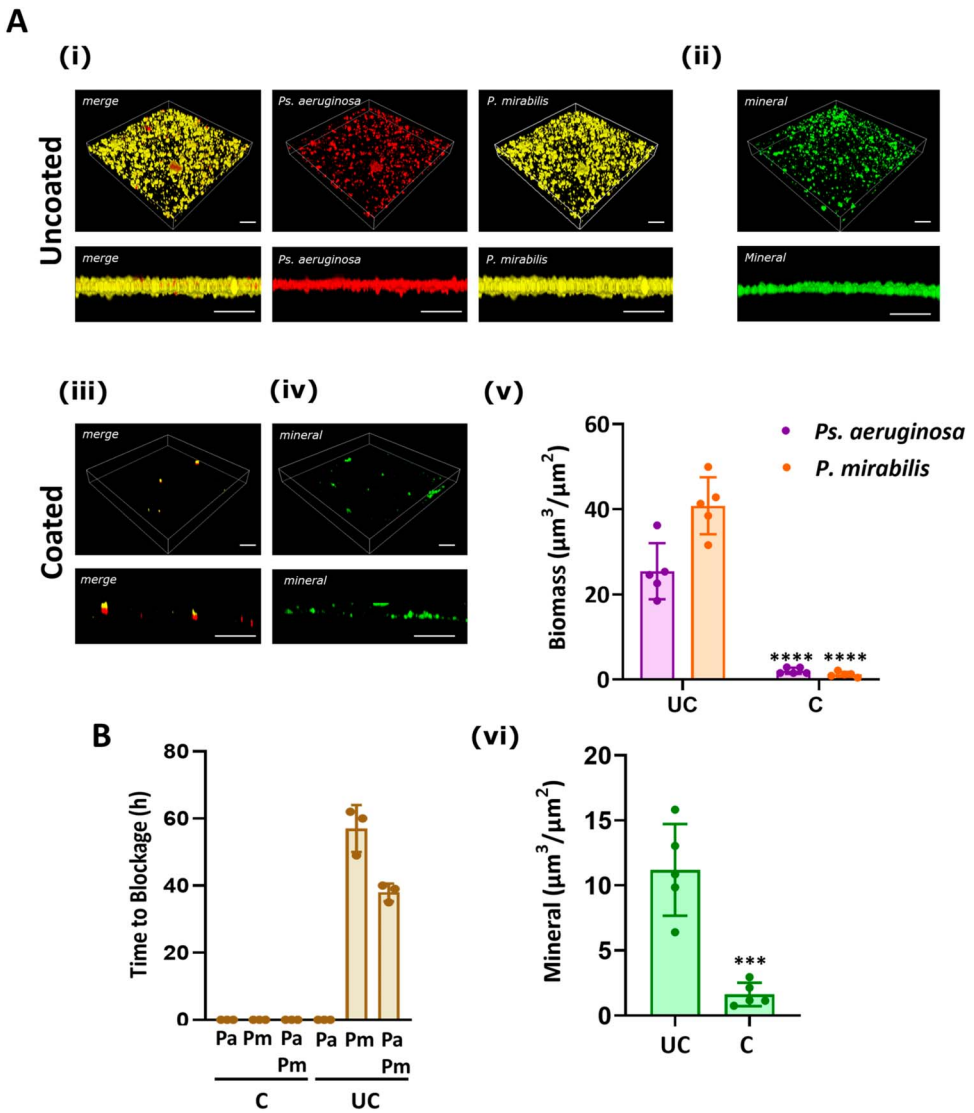

Figure 1. Biofilm accumulation, mineralization, and blockage of UC and coated (C) catheters. **A**, Biofilm biomass (i and iii) and biomineral deposition (ii and iv) by a mixed inoculum of *P. mirabilis* (yellow) and *Ps. aeruginosa* (red) on catheter segments in vitro. Scale bars, 50 µm. The corresponding quantitative data for biofilm biomass and mineralization are shown in (v) and (vi). Error bars represent standard deviations. **B**, The mean time taken to block UC or coated catheters in the bladder infection model, following inoculation with *P. mirabilis* (Pm) or *Ps. aeruginosa* (Pa) or a mixed culture of the 2 species (PA/Pm). Error bars represent standard deviations. UC, uncoated.

(Sigma-Aldrich) on catheter segments (1 cm) was quantified using CLSM after incubation with 0, 0.1 μg/ml, or 10 mg/ml Fg in PBS pH 7.4 for 16 hours, blocking with 10% (v/v) fetal bovine serum before incubation with antibodies to human Fg (ThermoFisher), followed by a goat anti-rabbit IgG Alexa Fluor 555 conjugate. Biofilm formation by *S. aureus* on Fg-conditioned catheter segments was quantified using CLSM after 72 hours of growth in AU. Surface Fg deposition on catheters recovered from 10 patients was quantified as above.

Statistical Analysis

The statistical software SPSS was used to check for data normality (IBM Corp) and GraphPad Prism 7 (GraphPad Inc, CA) for calculating statistically significant differences between coated and uncoated catheters by carrying out a Student *t* test or Mann-Whitney *U* test based on the initial data set normality checks. $P < .05$ (2-tailed) was considered statistically significant.

RESULTS

Polymer Coating Reduces Biofilm Biomass, Biomineralization, and Blockage In Vitro

Biofilm formation and biomineralization on coated and uncoated catheter segments was evaluated in vitro after incubation with either *P. mirabilis* or *Ps. aeruginosa* or a mixed (1:1) inoculum in AU. These uropathogens were chosen because they are urease producers and commonly form biofilms in CAUTIs.[26] In contrast to uncoated silicone, very little biofilm or biomineralization was apparent on the coated catheter for mixed (Figure 1) or single species (Figure S1, http://links.lww.com/JU9/A52).

Blockage times and biomineral deposition on intact catheters were investigated in the in vitro bladder catheterization model. Silicone catheters were blocked by *P. mirabilis* 57 ± 7 hours after inoculation, a time that reduced to 38 ± 2.6 hours after coinoculation with *Ps. aeruginosa* (Figure 1B). No blockage of the coated catheters was observed after a maximum of 89 hours incubation for either pathogen, alone or when coinoculated (Figure 1B).

To determine the morphology and elemental composition of minerals, catheter segments recovered from the bladder model were subjected to ESEM-EDS[7] (Figure 2). On the blocked, uncoated catheters, an abundance of large crystals identified as struvite (Figure S2, http://links.lww.com/JU9/A52) was apparent when *P. mirabilis* was present either alone or with *Ps. aeruginosa* (Figures 2B and 2C). On coated catheters (Figures 2A-2C), the mineral deposition was very different from that observed on uncoated catheters (Figures 2D-2F). Although no struvite formation was observed on the coated catheters, small crystals of apatite were detected (Figure S3, http://links.lww.com/JU9/A52).

Biofilm Biomass and Mineralization on Coated Catheters Recovered From Patients Are Reduced

One hundred sixty-one catheters (83 coated; 78 uncoated) were recovered from 140 male and 21 female

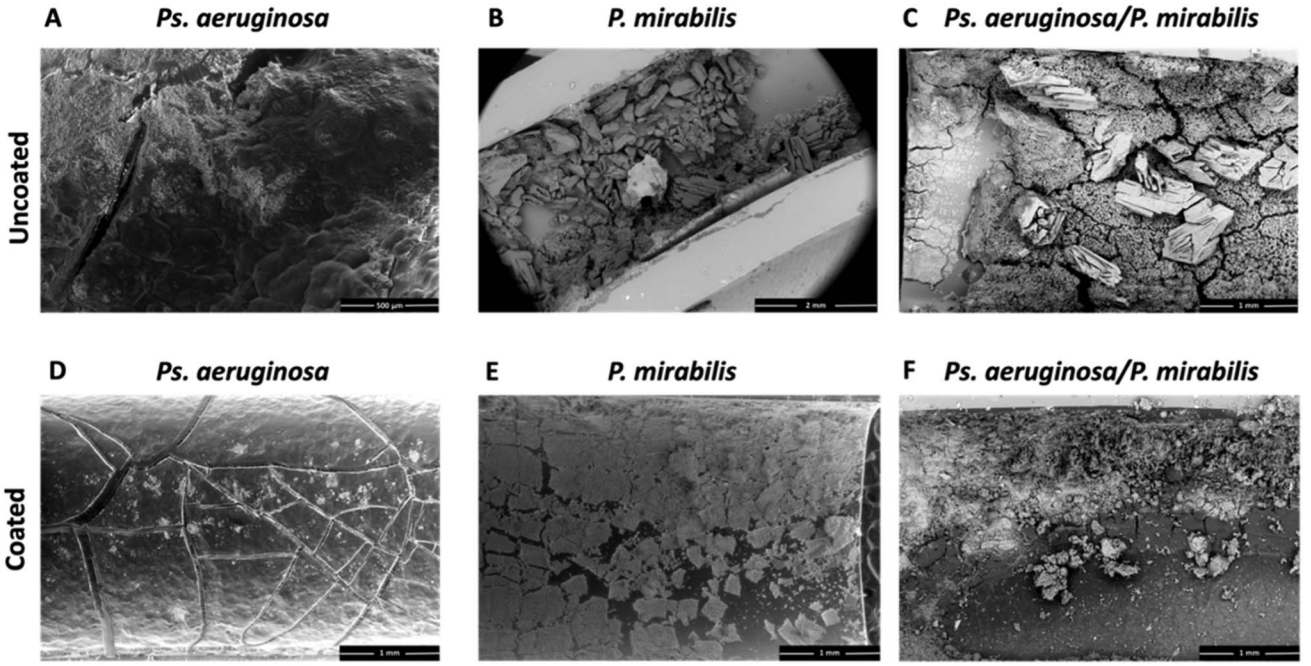

Figure 2. Representative environmental scanning electron microscopy micrographs of biofilms and biomineralization on catheters from the in vitro bladder catheterization model. Morphology of biofilms/biomineralization on uncoated (**A**-**C**) and coated (**D**-**F**) catheter segments formed by *Ps. aeruginosa* (**A** and **D**), *P. mirabilis* (**B** and **E**), and dual species *Ps. aeruginosa/P. mirabilis* (**C** and **F**) recovered from the in vitro bladder model. Scale bars: **A**, 500 μm; **B**, 2 mm; **C**-**F**, 1 mm.

Table. *Summary of Patient Cohorts, Catheter Indwelling Times, Urinary Tract Infections, and Catheter Blockages*

	Catheters		Mean indwelling Time (d)		Median indwelling Time (d)			Confirmed UTIs (postcatheterization)		Catheter blockages	
Cohort	Bactigon	Control	Bactigon	Control	Bactigon	Control	Surgery	Bactigon	Control	Bactigon	Control
1	20	20	6	7	5	4	GI	0	0	0	1
2	35	35	12	10	10	10	Urinary	0	0	0	0
3	28	23	19	27	18	14	Urinary	1	2	0	2

UTIs, urinary tract infections.

patients. These were grouped (Table) into 3 cohorts defined by their mean catheter indwelling times thus—cohort 1 (colorectal; 6.5 days), cohort 2 (urological; 11 days), and cohort 3 (urological; 23 days). Figure S4 (http://links.lww.com/JU9/A52) summarizes the distribution of indwelling times for all catheters ranging from 1 to 92 days. Five patients receiving coated and 7 receiving uncoated catheters had indwelling times of >30 days. Three patients with confirmed UTIs postcatheterization (2 uncoated; 1 coated) and three blocked catheters (all uncoated) were recovered (Table 1). For 21 patients, postcatheterization, preoperative urine samples yielded positive cultures, 6 of which presented as unidentified mixed microbial growth. Of these culture-positive patients (Table S2, http://links.lww.com/JU9/A52), 12 had received uncoated and 9 received coated catheters.

To quantify biofilm biomass and biomineralization, recovered catheters were cut into segments to provide proximal (closest to bladder), middle, and distal sections (nearest to drainage port). The data for each segment were combined and given the

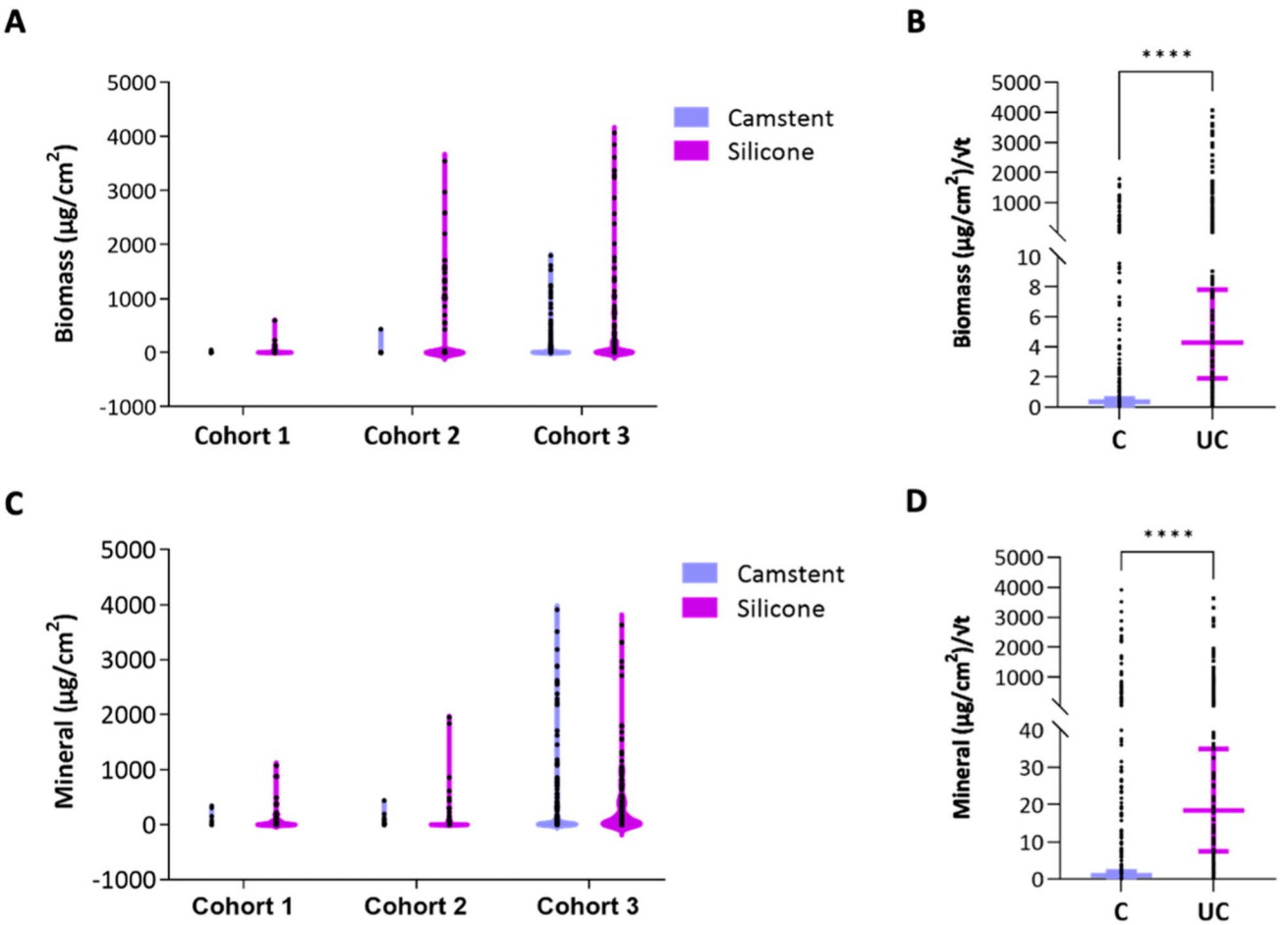

Figure 3. Biofilm biomass (**A** and **B**) and biomineral accumulation (**C** and **D**). Catheters were recovered from 161 patients divided into three clinical cohorts (Table 1) and presented in **A** and **C** as violin plots for each cohort. **B** and **D**, show the combined biofilm and biomineralization data for all 3 cohorts where C is coated and UC is uncoated catheters. The data were normalized by dividing biofilm and mineral biomass values for each catheter sample by the square root of their respective indwelling times. Error bars represent the 95% confidence intervals of the median values (statistical analysis using the Mann-Whitney *U* test; ****$P \leq .0001$).

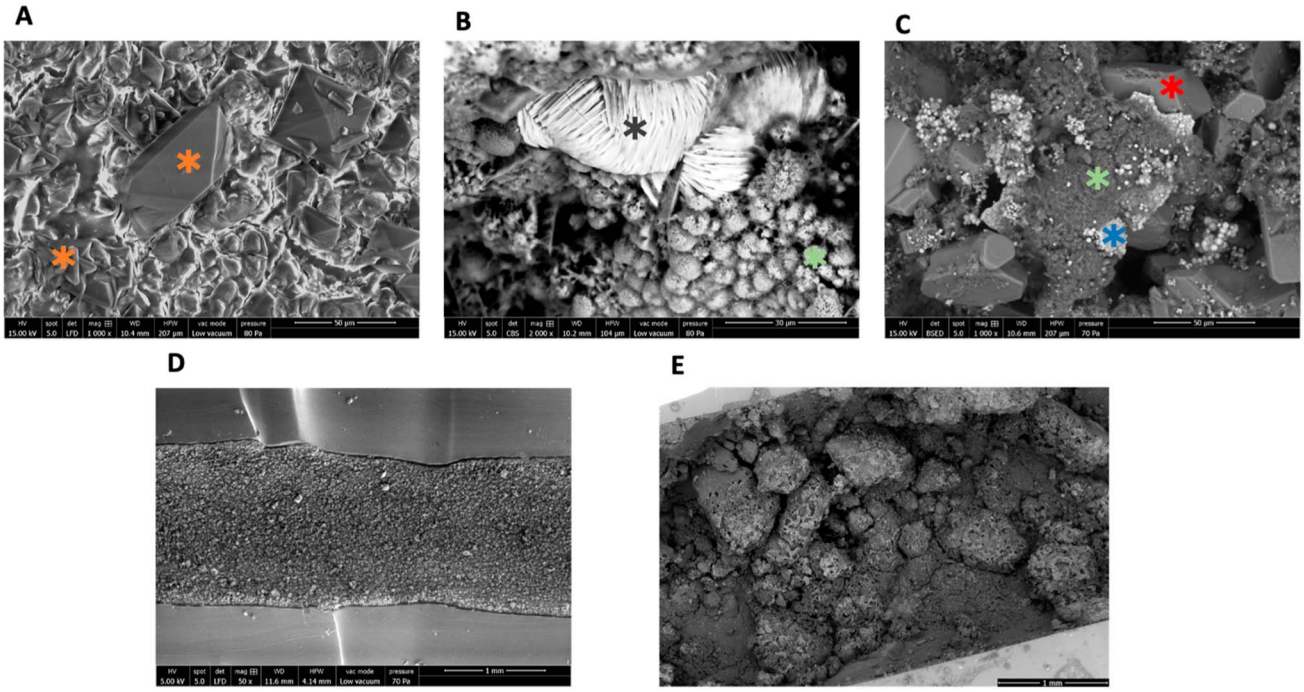

Figure 4. Environmental scanning electron microscopy-EDS analysis of the biofilms and biomineralization formed on the lumen of catheters recovered from patients. Representative morphologies of biofilm biomass and biomineral deposited on (**A**) coated catheter, patient #18 (indwelling time 22 days); scale bar 50 μm; (**B**) uncoated catheter, patient #15 (indwelling time 91 days), scale bar 30 μM; and (**C**) uncoated catheter, patient #30 (indwelling time 82 days) scale bar 50 μM. **D** and **E**, the uncoated catheter as in (**A**) and (**B**) but taken at a lower magnification (scale bar, 1 mm). *Calcium oxalate; *calcium carbonate *struvite, *apatite, and *biofilm. The corresponding EDS spectra are presented in the supplementary information, Figure S5 (http://links.lww.com/JU9/A52). EDS, energy dispersive X-ray spectroscopy.

skewed distribution of the catheter indwelling times, normalized by plotting biofilm and mineral biomass against the square root of the indwelling time. Figure 3 shows that both median biofilm accumulation and mineral deposition were significantly lower on coated compared with uncoated catheters across all three cohorts. The greatest biomasses were associated with cohort 3, which had the longest mean indwelling time (23 days). On uncoated catheters recovered from 2 patients with postcatheterization UTIs (#89, 5 days indwelling; #139, 7 days indwelling), the average biofilm and mineral biomasses were 1600 μg cm^{-2} and 869 μg cm^{-2}, respectively, compared with 9.6 μg cm^{-2} and 0.03 μg cm^{-2} for a patient with urinary tract infection who received a coated catheter (#75, 4 days indwelling).

ESEM-EDS Analysis Reveals Differences in Biofilm and Biomineral Architecture on Coated and Uncoated Catheters Recovered From Hospitalized Patients

Figure 4 shows ESEM images of catheters recovered from patients with the corresponding EDS spectra presented in Figure S5 (http://links.lww.com/JU9/A52). The presence and distribution of struvite and apatite crystals and biofilm are clearly apparent on a blocked uncoated catheter recovered from patient #30, 82 days after insertion (Figure 4C and Figure S5C, http://links.lww.com/JU9/A52). *P. mirabilis* was cultured from this catheter, and the biofilm architecture observed using ESEM was similar to that of *P. mirabilis* biofilms formed in the bladder model (Figure S6, http://links.lww.com/JU9/A52). Figure 4B and Figure S5B (http://links.lww.com/JU9/A52) show an example of a highly nitrogenous surface elemental composition indicative of biofilm formation on an uncoated catheter (patient #15; indwelling time 91 days) lacking in struvite and apatite but rich in calcium carbonate.

By contrast, a very different mineral composition was observed on the coated catheter recovered from patient #18 (Figures 4A and 4D). EDS identified the crystal deposits as calcium oxalate (Figure S5A, http://links.lww.com/JU9/A52). The lack of nitrogen in the EDS spectrum is consistent with the absence of biofilm on this coated catheter. To confirm these observations, we quantified using CLSM the calcium oxalate associated with 10 coated catheters showing the greatest mineral deposition (Figure S7, http://links.lww.com/JU9/A52). Linear regression analysis revealed a strong correlation (R^2 0.715) between the amount of calcium oxalate associated with the coated catheters and mineralization (Figure S7A, http://links.lww.com/JU9/A52). By

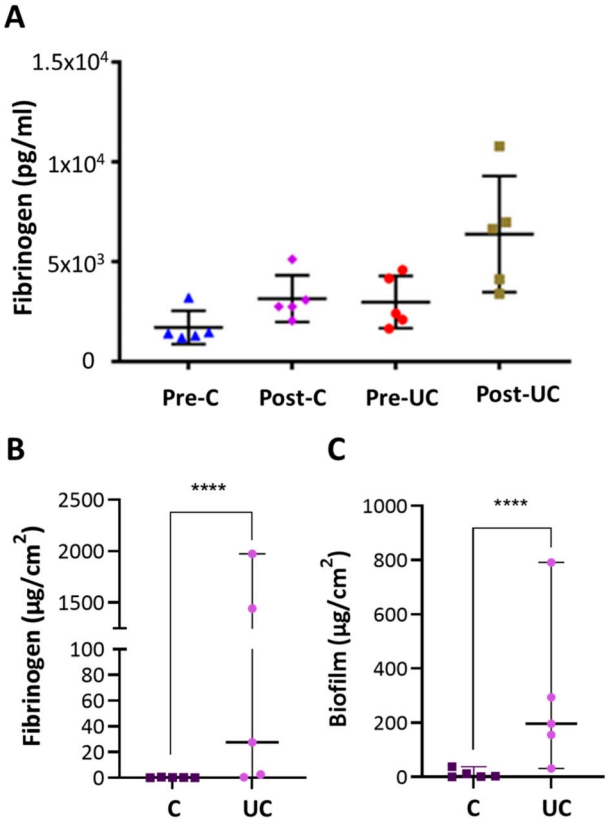

Figure 5. Fibrinogen (Fg) concentrations in patients' precatheterization and postcatheterization urine and deposited on catheters. **A**, Mean Fg concentrations in urine samples collected from patients precatheterization and postcatheterization receiving either coated (C; 5 patients) or uncoated (UC; 5 patients) catheters. **B**, Fg deposition and (**C**) biofilm biomass on coated (C; 5 patients) and uncoated (UC; 5 patients) catheters. Error bars represent the standard deviation of the mean values. Significance was determined by two-way ANOVA analysis using the Sidak multiple comparisons test. UC, uncoated.

comparison (Figure S7B, http://links.lww.com/JU9/A52), although calcium oxalate was present on the 10 uncoated catheter samples, no significant correlation was observed (R^2 0.377).

Polymer Coating Reduces Fibrinogen Release and Deposition Postcatheterization

Urinary tract catheterization induces mechanical stress and mucosal tissue damage increasing fibrinogen (Fg) release in the bladder which accumulates in urine and on the catheter.[17,18] This can potentiate infection by facilitating catheter surface attachment and subsequent biofilm formation by Fg-binding pathogens such as *S. aureus* and *Enterococcus faecalis*.[18,19] We, therefore, investigated whether the polymer coating was more refractory to Fg deposition and subsequent staphylococcal biofilm formation than silicone. Fig. S8A shows that less Fg accumulated in vitro on the coated catheter. This was reflected by the reduced *S. aureus* biofilm biomass observed on the Fg-exposed coated catheter (Figure S8B, http://links.lww.com/JU9/A52). To determine whether this reduction in Fg deposition occurred clinically, we obtained urine samples from 10 patients undergoing elective colorectal surgery, preinsertion and postinsertion of either a coated or an uncoated catheter where the mean indwelling time was 2.5 days. Figure 5A shows that higher levels of Fg were present in the postcatheterization compared with precatheterization urine of patients receiving uncoated catheters confirming previous studies.[18,19] Higher Fg levels (Figure 5B) and biofilm biomasses (Figure 5C) were present on the uncoated catheters recovered from the same patients.

DISCUSSION

The data presented offer encouraging evidence that Bactigon reduces biofilm development and encrustation. Significantly lower median biofilm biomass and mineral deposition were observed in our clinical pilot study for the polymer-coated catheters with no blockages reported, consistent with the lack of encrustation observed in the in vitro bladder model. These findings suggest that on Bactigon not enough urease is being produced to alkalinize urine sufficiently for struvite formation to occur. Although planktonic urease-producing bacteria can still raise urinary pH, the absence of biofilm-creating chemical gradients near a surface would make it more difficult to reach the supersaturation state necessary for the formation and deposition of minerals such as struvite and apatite.

On polymer-coated catheters recovered from patients, although struvite and apatite were absent, fine calcium oxalate crystals were common. Oxalate is derived by host endogenous metabolic rather than bacterial processes.[27,28] Although a common component of urinary stones, thin crystals of calcium oxalate are known to form the first crystalline layer on ureteric stents.[29] In contrast to uncoated silicone, bacterial cells were not observed in the representative ESEM images of Bactigon-coated catheters. This may be a consequence of washing samples for processing for ESEM because bacterial cells only weakly adhere to Bactigon in vitro.[30] It is also possible that the oxalate on Bactigon catheter samples recovered from patients may adversely affect crystalline bacterial biofilm formation. These data highlight the potential of Bactigon for reducing the painful retention of urine or incontinence associated with encrustation[9,10,31] and for preventing blockage associated complications such as septicemia and pyelonephritis.[3]

Once introduced into the urinary tract, catheters are conditioned by host proteins such as Fg such that biofilm formation is enhanced.[18,19] Our in vitro experiments and analysis of patient urine and catheters demonstrated that Bactigon is more refractory to Fg binding than silicone. This is consistent with Andersen et al[14] who demonstrated that inhibiting

host protein deposition on implanted urethral catheters by pretreatment with a liquid-infused silicone reduced inflammation and bacterial colonization in a mouse CAUTI model. Given that the bladder is not sterile and that catheter insertion is a major source of contamination, it would be of interest to determine whether there is differential bacterial species colonization of coated compared with uncoated catheters.

Bactigon is a stable, biocompatible, nonbiodegradable polymer formulation that does not contain any leachable antimicrobials. It does not inhibit bacterial growth but blocks biofilm formation through a mechanism that prevents the transition from reversible to irreversible bacterial surface attachment that in turn depends on the intrinsic properties of the polymer.[15,31] Although current European regulatory approval limits indwelling times to $\leq$ 30 days, the coated catheter remained in place in three patients for 46, 49, and 55 days, respectively, without any reported adverse effects or obvious visual deterioration of the coating providing preliminary support for much longer-term usage. Apart from urinary catheters, Bactigon could, in future, be coated onto other silicone-based urological devices[17,32] including ureteric stents and nephrostomy tubes where infection and urolithiasis are responsible for significant morbidity.[33]

CONCLUSIONS

Although this prospective pilot study highlighted the potential of polymer-coated catheters, it was limited by a relatively small patient sample size, a restricted coated catheter indwelling time, and a lack of sample blinding and a focus on catheter biofouling rather than CAUTIs per se. In addition, the impact of prophylactic antibiotic therapy given to all patients in this pilot study irrespective of catheter type on biofilm formation is not known. Additional larger scale clinical studies with longer patient indwelling catheter periods ($>$ 30 days) will be required to demonstrate that the polymer coating prevents CAUTIs and the complications of catheter encrustation. Nevertheless, the significant reduction in Fg deposition, biofilm formation, and encrustation observed on coated catheters compared with silicone is likely to significantly reduce the risks associated with both CAUTIs and catheter blockage.

CLINICAL TRIAL

This study was approved by the respective Research Ethics Committees, under the UK National Health Service Integrated Research Application System (IRAS) project IDs 232293 and 242341 and UK clinical trial IDs NCTC05513677 and NCTC05719753.

FUNDING

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AUTHOR CONTRIBUTIONS

PW, DH, BB, and DA designed the study. KK, J-FD performed the in vitro experiments and data analysis supervised by PW, MRA, SH, and DJI. DA and BB together with NJ, CL-L carried out the patient recruitment and conducted the clinical work. All authors contributed to data interpretation. KK and PW drafted the manuscript, and all authors contributed and approved the manuscript before submission.

CONFLICTS OF INTEREST

PW and MRA have intellectual property in the Bactigon polymer which was licensed to Camstent Ltd for commercialization. KK, J-FD, CLL, NJ, SH, DJI, TJS, BB, DA, and DH have no conflicts of interest.

DATA AND MATERIALS AVAILABILITY

All data needed to evaluate the conclusions are present in the paper and Supplementary Information.

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