



Development of an antimicrobial urinary catheter to inhibit urinary catheter encrustation

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Abstract

Background: Encrustation of urinary catheters is a frequent problem in patients with long-term indwelling catheters colonised with urease-positive bacteria such as *Proteus mirabilis*. Catheter blockage may follow catheter encrustation, potentially leading to systemic infection. Prevention of encrustation is difficult and avoidance of recurrence often unsuccessful. One possible preventative strategy is to use a catheter with an antimicrobial surface and development and assessment of such a surface was the aim of this research.

Methods: Initial experiments assessed the antimicrobial activity of silicone impregnated with plant-derived antimicrobials and triclosan using agar diffusion. The longevity of activity of each antimicrobial silicone was examined over a period of 11 weeks following soaking individual pieces of antimicrobial silicone in an artificial urine solution before using agar diffusion to test remaining antimicrobial activity. Live/Dead staining of bacteria colonising the surface of each antimicrobial silicone was employed to determine the bactericidal properties of each antimicrobial silicone. Selected antimicrobial silicones were subsequently evaluated for their ability to prevent catheter encrustation in an *in vitro* bladder model.

Results: Results showed that antimicrobial activity was obtained using 1% triclosan-impregnated silicone and that this antimicrobial activity was long-lasting (up to 11 weeks). Use of a dip coat silicone formulation, containing 0.2% triclosan, proved effective at delaying catheter encrustation with *P. mirabilis* metabolites *in vitro*. In 8 out of 13 independent experiments using dip-coated catheters, no catheter blockage occurred over 7 days, whilst all control catheters blocked during this period. Only on one occasion was delayed encrustation not evident with the treated catheters.

Conclusions: In summary, a dip-coat silicone containing triclosan proved effective in preventing *in vitro* catheter encrustation caused by *P. mirabilis* infection. Further studies with triclosan silicone dip coat formulation are warranted, including those that investigate potential host cell toxicity and long-term benefits following its application to indwelling urinary catheters in clinical settings.

Keywords: *Proteus mirabilis*, catheter associated urinary tract infection, triclosan, eugenol, terpinen-4-ol

Introduction

Catheter associated-urinary tract infections (CA-UTIs) are the most frequently encountered hospital acquired infections, with 70-80% involving an indwelling urinary catheter [1]. The widely used Foley catheter predisposes patients to CA-UTIs as it disrupts the normal protective effect of urinary flow and provides a conduit for pathogens to the bladder that 'by-passes' the natural antimicrobial mechanisms of the urethral mucosa.

Once the bladder is colonised, the inflated catheter retention balloon ensures that the bladder does not completely empty, resulting in the retention of contaminated urine in the bladder [2].

Potential consequences of CA-UTI are numerous, and include pyelonephritis, septicaemia, bladder stone development, bacteraemia, endotoxic shock, and catheter encrustation [3]. Several microbial species, including *Escherichia coli* and

Pseudomonas aeruginosa can cause CA-UTIs, although it is infection by urease producing bacteria and particularly *Proteus mirabilis* that are frequently most problematic [4]. *Proteus mirabilis* produces a potent urease that hydrolyses urea leading to formation of ammonium and carbonate ions, which increase urinary pH. In alkaline urine, magnesium and calcium phosphates precipitate and impede urinary flow through the catheter [5]. Management of urinary catheter encrustation in long-term indwelling catheters is difficult, and no single effective prevention strategy is currently recognised [6].

The emergence and spread of antibiotic resistant microorganisms had driven the need to find new antimicrobial agents and in recent years, this has led to considerable interest in the use of natural antimicrobials, which, by often targeting multiple microbial sites, are associated with reduced incidence of resistance [7]. Recently we have identified several plant-derived antimicrobial agents with activity against *P. mirabilis* [8]. These studies highlighted the antimicrobial effects of eugenol (an essential oil extracted from clove oil), terpinen-4-ol and cineole (components of tea tree oil) against *P. mirabilis*. Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether), whilst not a natural antimicrobial agent, has been used as a biocide in numerous industrial and household products [9] and importantly, this agent is also highly effective against *P. mirabilis* [10] and as such triclosan was also evaluated in this investigation.

The aim of this present study was to use the natural antimicrobials, eugenol and terpinen-4-ol, in addition to triclosan, to develop novel antimicrobial silicone formulations that could prevent catheter encrustation. Constructed antimicrobial silicones were applied as a material insert or a 'dip coat' to Foley catheters and assessed for their ability to delay or prevent *in vitro* catheter encrustation following *P. mirabilis* infection. This study found that a dip coat silicone containing 0.2% triclosan was effective at preventing catheter encrustation in all but one test catheter and as such, further investigation, including host cell toxicity and effectiveness in a clinical setting is warranted.

Materials and methods

Bacterial strains and culture conditions

Bacterial isolates associated with urinary tract infection (Table 1) were cultured on Cysteine Lactose Electrolyte Deficient (CLED; Oxoid, Basingstoke, United Kingdom) agar at 37°C. Artificial urine was used as a liquid culture medium, as previously described with incorporation of Tryptone Soya Broth (TSB) at 1 g/L [20,21]. Mueller-Hinton Broth (MHB; Oxoid) and Iso-Sensitest Agar (ISO; Oxoid) were used for antimicrobial assessment by zone of inhibition testing.

Manufacture of antimicrobial silicone material

Stock antimicrobial solutions were 10% (w/w) triclosan (Sigma-Aldrich, Poole, United Kingdom) in 2-propanol (Sigma-Aldrich), 10% (w/w) eugenol (Sigma-Aldrich) and 5% (w/w) terpinen-4-ol (Sigma-Aldrich), both in acetone. Solvent only controls

Table 1. Bacterial species and strains used in this study.

Isolate	Original source of isolate	Reference
<i>Proteus mirabilis</i> NCTC 11938*	Putrefied meat	[11]
<i>P. mirabilis</i> B2	Catheter biofilm	[12]
<i>P. mirabilis</i> RB6	Catheter biofilm	[13]
<i>P. mirabilis</i> NSM6	Clinical isolate of an encrusted catheter of a patient undergoing long term catheterisation	[14]
<i>P. mirabilis</i> NCTC 13376/ATCC [®] 14153 [™]	Reference strain	n/a
<i>P. mirabilis</i> HI4320-wild type	Urine of a long-term-catheterised elderly patient with significant bacteriuria	[15,16]
<i>P. mirabilis</i> NP6	Urine of a patient at a nursing home	[17]
<i>P. mirabilis</i> RB22	Clinical isolate	n/a
<i>P. mirabilis</i> urease neg 2	Clinical isolate	n/a
<i>Proteus vulgaris</i> H2V	Clinical isolate	n/a
<i>P. vulgaris</i> NSM19	Clinical isolate	[18]
<i>P. vulgaris</i> SDM2	Catheter biofilm	[13]
<i>Providencia rettgeri</i> SDM1	Catheter biofilm	[13]
<i>Providencia stuartii</i> NSM40	Indwelling catheter of long term catheterised patient	[19]
<i>Escherichia coli</i> NCTC 12923	Reference strain	n/a
<i>Pseudomonas aeruginosa</i> SDM5	Clinical isolate	n/a
<i>Ps. aeruginosa</i> NCTC 10662	Reference strain	n/a
<i>Staphylococcus aureus</i> P10 6/9	Catheter biofilm	[13]

*Type strain

were also tested. Polydimethylsiloxanes of various molecular weight (Silanes & Silicones Ltd., Manchester, United Kingdom), silica filler (hydrophobic Gelest filler; Silanes & Silicones Ltd.) and hydrophilic Cabosil filler (Sigma-Aldrich) were mixed for at least 1 h. The developed 'Base' was then used to prepare two component parts (parts A and B). Part A consisted of Base, platinum catalyst (Silanes & Silicones Ltd.) and either the test antimicrobial or its control solvent. Part B consisted of Base, cross linker (Silanes & Silicones Ltd.) and either antimicrobial agent or control solvent. Equal quantities of parts A and B were mixed and cured for 10-15 min at 90°C in an appropriate mould, resulting in a final concentration of 1% triclosan, 1% eugenol or 0.5% terpinen-4-ol solution in the cured silicone. Once cooled, the biomaterial was cut into 1-cm² squares and autoclaved. In addition, a triclosan containing silicone dip coat was also prepared using parts A and B. Parts A and B were

diluted separately at a ratio of 20% solid silicone formulation to 80% 1 cst fluid (diluent) before equal amounts of diluted parts A and B were mixed resulting in a final concentration of 0.2% triclosan in the silicone dip coat. This silicone dip was used to coat all-silicone (100%) Foley catheters (size 14 Ch; C. R. Bard, Inc., Crawley, United Kingdom) by immersion in the formulation for 5 min, before air-drying for 12 h.

Assessment of antimicrobial activity of developed silicone

Bacteria maintained on CLED agar were sub-cultured in 10 ml of MHB and cultured for 16 h at 37°C with gentle rotation (100 rev/min). Test bacteria were spread-plated on ISO agar and incubated for 3.5 h at 37°C. A silicone square (1 cm²) containing test antimicrobial or solvent control was placed in the centre of the agar. After incubation at 37°C for 16 h, zones of growth inhibition were measured. Each antimicrobial material was tested in triplicate. Data from the zone of inhibition experiments were correlated and graphically depicted using GraphPad Prism[®] Software Version 4.00 (GraphPad Software Inc., La Jolla, USA).

To determine persistence of antimicrobial activity, silicone squares (10 mm×10 mm×5 mm containing 1% triclosan) were immersed in 1 L of artificial urine at 37°C. At weekly intervals, specimens were removed and tested for antimicrobial activity against *P. mirabilis* NCTC 11938 using zone of inhibition testing. The artificial urine was replenished weekly for 11 weeks.

Live/Dead staining of bacteria on antimicrobial biomaterials

Proteus mirabilis NCTC 11938 was cultured for 4 h at 37°C in artificial urine. A portion of the culture was stained using LIVE/DEAD[®] BacLight[™] Bacterial Viability Kit (Molecular Probes Europe BV, The Netherlands) according to the manufacturer's instructions. A 10- μ l volume of the stained bacteria was then deposited on the surface of the silicone and overlaid with a cover slip before being observed using time-lapse confocal microscopy over 24 h.

Prevention of urinary catheter encrustation by antimicrobial silicones

Cylinders (5 mm height) of solid silicone were constructed using cork-borers (Cole-Parmer Instrument Co. Ltd, United Kingdom). A single cylinder was located into the fluted part of the lumen of an all-silicone (100%) Foley catheter prior to autoclaving. Test solid silicone contained a final concentration of 1% triclosan and control catheters contained solvent alone (2-propanol). Additional catheters were coated, intra- and extra-luminally, using liquid silicone formulation containing a final concentration of 0.2% triclosan and control catheters contained solvent (2-propanol) alone.

Test catheters were located within an *in vitro* bladder model (Figure 1; [21]) and the retention balloon inflated with 10 mL of sterile water. The catheter was connected to a drainage tube and bag in the standard way. The distance from the bottom

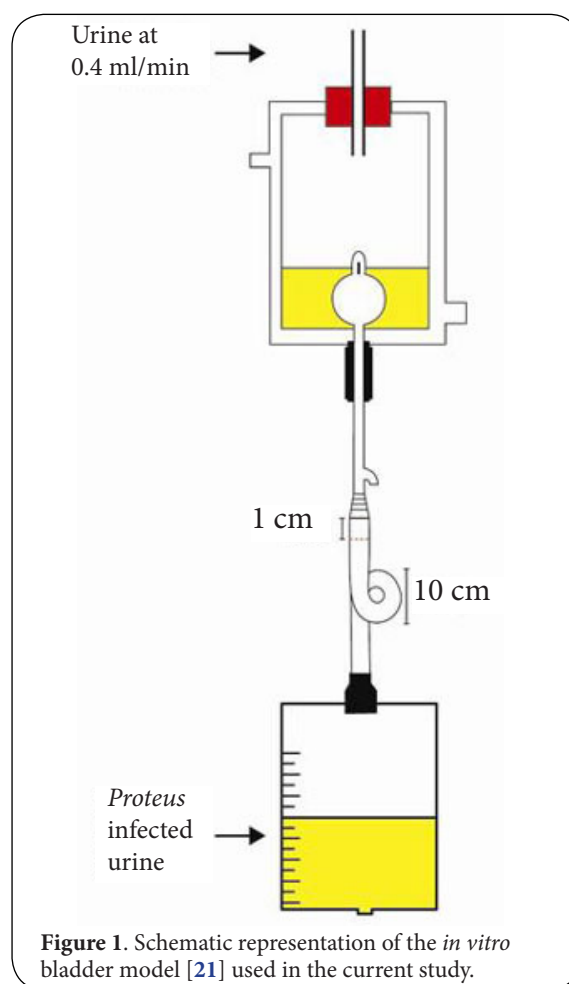


Figure 1. Schematic representation of the *in vitro* bladder model [21] used in the current study.

of the bladder chamber to the top of the drainage bag was 50 cm and a loop (outside radius 10 cm) was introduced into the drainage system.

Artificial urine was added to the bladder chamber at 0.4 ml/min via a peristaltic pump until it filled the bladder chamber to just below the catheter eyehole. Delivery of artificial urine to the bladder chamber was stopped and the drainage tube and bag completely emptied of artificial urine before inoculating the drainage bag (through the drainage tap) with 10 mL of a 4-h artificial urine culture of *P. mirabilis* NCTC 11938. Contamination events were performed four times per day and involved raising the drainage bag, to create a reverse flow of contaminated urine, to a defined level in the drainage tube and holding the contaminated urine at this level for 30 s. Where catheters contained a solid silicone insert, the contamination level in the drainage tube was defined as the base of the inserted silicone material. Where the catheters were dip coated, the contamination level was defined at a 1 cm mark on the drainage tube, below the connection point of the drainage tube and the catheter (Figure 1). Supply of artificial urine was recommenced after each contamination event.

The models were run for a maximum of 7 days, or until the

catheters blocked. Catheters were defined as blocked when artificial urine began to collect in the bladder chamber, above the level of the catheter eyehole. Time taken for catheters to block was determined based on volume of urine removed from the drainage bags. Each experiment comprised of 3 'test' catheters and two 'control' catheters. Experiments were repeated on five separate occasions.

Results

Antimicrobial activity of novel silicone materials

Inhibition of growth based on agar diffusion was evident only with 1% triclosan-containing silicone, which was effective against 15 of the 18 test isolates (*Providencia rettgeri* SDM1, *Pseudomonas aeruginosa* SDM5 and *Ps. aeruginosa* NCTC 10662 were not susceptible; **Figure 2**). No antimicrobial activity was evident using eugenol or terpinen-4-ol incorporated into silicone, despite having previously demonstrated activity outside silicone against these bacterial strains [8]. Eugenol, when tested in its acetone diluent and not in silicone, retained its previously shown antibacterial effect, however, terpinen-4-ol, in the presence of acetone

solvent, lost its antibacterial activity (results not shown).

Live/dead staining of *P. mirabilis* NCTC 11938 on antimicrobial silicones was undertaken to assess whether antimicrobial effects were associated with the silicone surface only, as previous zones of inhibition experiments would have required release of the agent into the agar. In these studies, the time to kill >95% of *P. mirabilis* NCTC 11938 deposited on the antimicrobial silicones was assessed in 24-h time course experiments. After 12 min, >95% of *P. mirabilis* NCTC 11938 were killed on silicone containing 1% triclosan. Conversely, after 24 h, >95% of *P. mirabilis* NCTC 11938 remained alive on eugenol- and terpinen-4-ol-containing silicone (**Figure 3**).

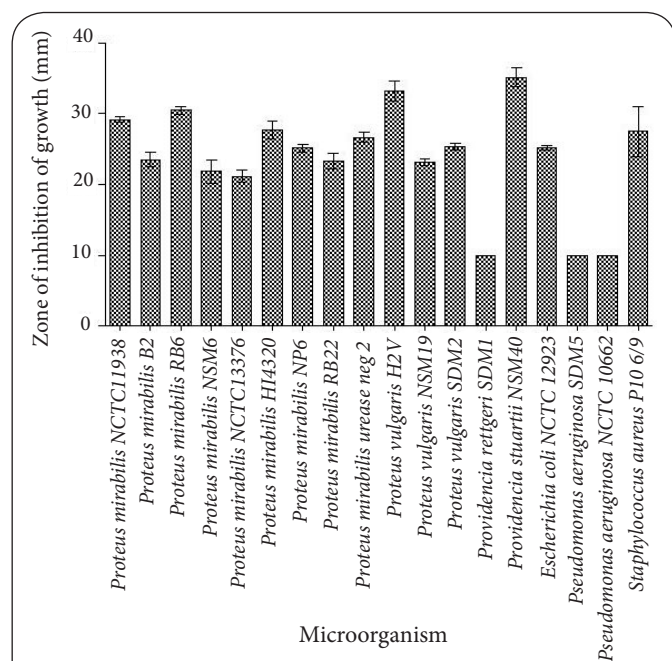


Figure 2. Antimicrobial activity of solid silicone containing triclosan against test bacterial strains.

Zones of inhibition of growth of selected bacterial strains involved in CA-UTI by a solid silicone formulation containing a final concentration of 1% triclosan. The zone of inhibition of growth of each isolate was measured in mm and the value shown above includes the 10 mm measurement of the silicone square. All isolates tested were susceptible to 1% triclosan in solid silicone formulation except *Providencia rettgeri* SDM1, *Pseudomonas aeruginosa* SDM5 and *Ps. aeruginosa* NCTC 10662. The graph represents the Mean and Standard Error of the Mean from duplicate readings taken when each antimicrobial material was tested in triplicate.

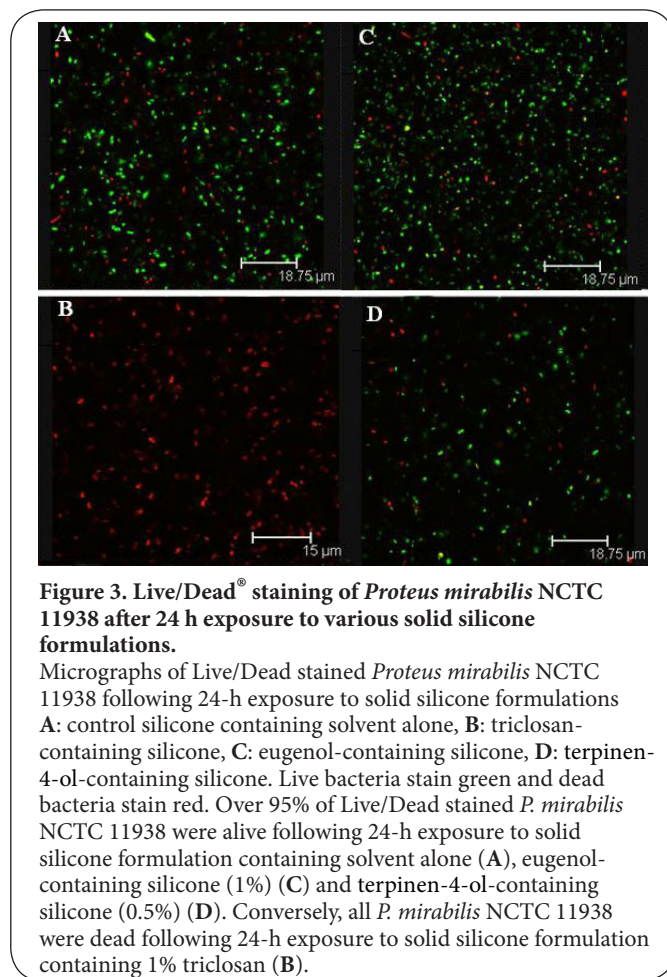


Figure 3. Live/Dead[®] staining of *Proteus mirabilis* NCTC 11938 after 24 h exposure to various solid silicone formulations.

Micrographs of Live/Dead stained *Proteus mirabilis* NCTC 11938 following 24-h exposure to solid silicone formulations **A**: control silicone containing solvent alone, **B**: triclosan-containing silicone, **C**: eugenol-containing silicone, **D**: terpinen-4-ol-containing silicone. Live bacteria stain green and dead bacteria stain red. Over 95% of Live/Dead stained *P. mirabilis* NCTC 11938 were alive following 24-h exposure to solid silicone formulation containing solvent alone (**A**), eugenol-containing silicone (1%) (**C**) and terpinen-4-ol-containing silicone (0.5%) (**D**). Conversely, all *P. mirabilis* NCTC 11938 were dead following 24-h exposure to solid silicone formulation containing 1% triclosan (**B**).

As catheters can remain in place for up to 11 weeks, persistence of antimicrobial activity of solid silicone containing 1% triclosan was determined by immersing samples (10 mm×10 mm×5 mm squares) in artificial urine, which was replaced at weekly intervals. The antimicrobial effect of the triclosan containing silicone was retained over this period, despite a gradual reduction in the size of the zone of inhibition of growth of *P. mirabilis* NCTC 11834 from week 0 (29 mm zone including 10 mm silicone square) to week 11 (15 mm zone including

10 mm silicone square) (Figure 4).

Prevention of urinary catheter encrustation by triclosan containing silicone

Where a solid triclosan silicone insert was used, out of 8 test catheters, only one showed delayed encrustation compared

to their controls and one test catheter did not block at all (data not shown). Importantly, however, using a triclosan containing liquid dip coat silicone formulation, a notable delay in time to blockage was evident compared with controls (dip coat containing solvent alone). In the case of 13 test catheters, 12 exhibited delayed encrustation compared to controls, and 8 of these did not block over the 7-day duration of the experiment (Table 2).

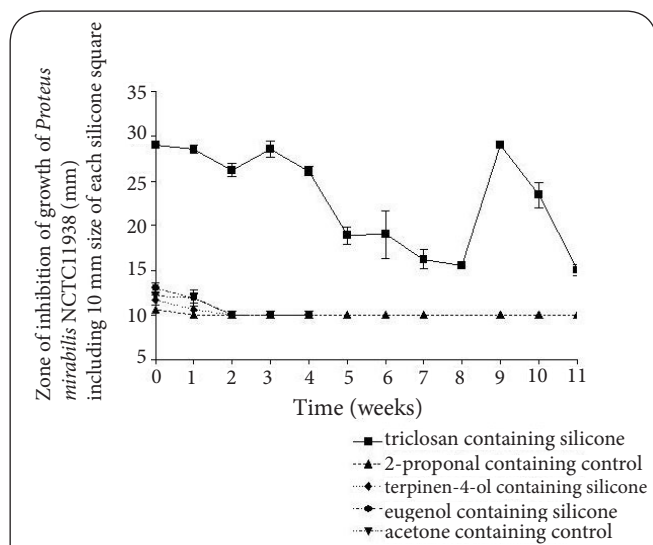


Figure 4. Antimicrobial activity of various solid silicone formulations against *Proteus mirabilis* NCTC11938 over a period of 11 weeks.

Three solid silicone squares (10 mm×10 mm×5 mm) of each silicone formulation were tested for antimicrobial activity at weekly intervals and results were recorded in duplicate for each solid silicone square. The diameter of the zone of inhibition of growth of *Proteus mirabilis* NCTC 11938 was measured in mm and included the width of the silicone square (10 mm). A decrease in the zone of inhibition can be seen for each silicone formulation except for triclosan containing silicone formulation where the zone of inhibition increased at week 9 and week 10. Testing of eugenol containing silicone formulation, terpinen-4-ol containing silicone formulation and the acetone containing control were discontinued after week 4 due to no zone of inhibition being observed from week 2 onwards.

Discussion

CA-UTIs are a major problem throughout the world. A key factor in individuals who have long-term indwelling catheters is contamination and infection by the urinary pathogen, *P. mirabilis*. *Proteus mirabilis* is not only able to rapidly migrate along the material of catheter surfaces to contaminate the bladder, it also generates a highly potent urease enzyme. Urease metabolises urea to produce ammonia, which, in a hydrated environment produces hydroxyl ions leading to elevated urine pH. The potential effect of alkaline urine is subsequent crystallisation of magnesium and calcium phosphates leading to encrustation and catheter blockage [5]. Catheter blockage is clinically important, as not only will the resulting bladder distension be painful for the patient, but a blocked catheter also increases the risk of serious clinical complications including septicaemia and pyelonephritis [3].

Management of urinary catheter encrustation is difficult, and occurrence is both unpredictable and extremely hard to prevent with existing strategies [6]. Most often, the approach used is catheter replacement once blockage has occurred [22]. Unfortunately, such treatment is often unsuccessful with frequent recurrence of blockage evident [23]. Prophylactic antibiotic use to prevent recurrence is not ideal due to the potential promotion of antibiotic resistance [24-26]. One possible approach is to employ catheter materials that incorporate an antimicrobial agent that is either gradually released to the surface to inhibit colonisation or is utilised as an external catheter coating.

Previously, we have demonstrated the effectiveness of several antimicrobial agents against urinary tract pathogens

Table 2. Time (h) to blockage of catheters with triclosan-containing silicone dip coat (test) or the relevant solvent (control).

Catheter type	Results of Experiment 1	Results of Experiment 2	Results of Experiment 3	Results of Experiment 4	Results of Experiment 5
Test	150	132	>168	160	140
Test	156	>168	>168	>168	>168
Test	No model	No model	>168	>168	>168
Control	108	138	105	59	112
Control	No model	No model	97	87	95

Five separate experiments containing 5 catheter models each were conducted to determine the time, in hours, to blockage of catheters dip-coated in liquid silicone formulation containing either triclosan (at a final concentration of 0.2%) (test), or solvent alone (control). In experiment 1 and 2, results for only three catheter models were recorded due to leakage of two of the bladder models meaning time to blockage could not be accurately determined. Results indicating >168 h, define dip-coated catheters that did not block for the duration for the experiment.

including *P. mirabilis*. These agents included natural compounds from plant extracts (tea tree oil, terpinen-4-ol, cineole, and eugenol [8]) and the widely used antimicrobial, triclosan [10]. Following this previous research, the aim of this study was to develop an antimicrobial insert or a coating that would theoretically prevent catheter encrustation caused by *P. mirabilis* infection.

Results showed that whilst several plant-derived antimicrobial agents had demonstrated previous *in vitro* activity against selected bacterial isolates [8], their incorporation into silicone or solvent, negated antimicrobial effects. Significantly, however, antimicrobial activity of triclosan was retained when incorporated into silicone as previous demonstrated [27,28]. Not only did this material show antibacterial activity using agar diffusion and Live/Dead assays, but there was also long-term (up to 11 weeks) persistence of antimicrobial activity.

It was initially envisaged that by incorporating a cylindrical section of this material into an existing Foley catheter, prevention of catheter encrustation by *P. mirabilis* (introduced below the point of material insertion) would follow. Unfortunately, this was not evident and may have been due to the design of the 'antimicrobial block' or to urinary flow over the surface of the cylinder allowing *P. mirabilis* to bypass the intended antimicrobial block. Significantly, however, use of triclosan within a dip coat silicone formulation resulted in a noticeable delay in catheter encrustation compared with controls. Indeed, over the 7-day period of running the *in vitro* bladder model, out of 13 repeated experiments delayed encrustation occurred in all but one occasion compared to controls. Furthermore, on 8 occasions there was no catheter blockage detected in any of the treated catheters over the duration of the experiment.

Conclusion

Use of such a dip coat has a number of advantages. Theoretically, it would be applicable to all commercially available silicone catheters without the need for modification in catheter design and application to the inner and outer luminal surfaces would provide potential protection against both routes of bladder contamination. Further studies with the triclosan silicone formulation are still warranted, including those that investigate potential host cell toxicity and long-term benefits following its application to indwelling urinary catheters in clinical settings.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	RPCJ	SM	MGW	DJS	DWW
Research concept and design	--	--	✓	✓	✓
Collection and/or assembly of data	✓	✓	--	--	--
Data analysis and interpretation	✓	--	--	--	--
Writing the article	✓	--	--	--	--
Critical revision of the article	--	✓	--	--	✓
Final approval of article	--	--	--	✓	✓
Statistical analysis	✓	--	--	--	--

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