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Reduced Susceptibility of *Proteus mirabilis* to Triclosan[▽]

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Clinical isolates of *Proteus mirabilis* causing catheter encrustation and blockage are susceptible to the biocide triclosan (MICs of 0.2 mg/liter). Studies with laboratory models of the bladder have demonstrated that the inflation of catheter retention balloons with triclosan solutions rather than water results in the diffusion of triclosan from the balloons into the surrounding urine and the inhibition of catheter encrustation by *P. mirabilis*. The aim of this study was to test whether the exposure of *P. mirabilis* to triclosan under laboratory conditions resulted in the selection of strains with reduced susceptibilities to this biocide. Exposure to triclosan in agar was shown to select mutants with MICs elevated from 0.2 mg/liter up to 80 mg/liter. In a selection of 14 of these strains, the decreased susceptibility was found to be stable and not associated with increased resistance to antibiotics. Experiments with the laboratory models demonstrated that inflation of the catheter balloons with triclosan (10 mg/ml) prevented encrustation and blockage by the parent strain *P. mirabilis* B2 (MIC, 0.2 mg/liter) and the mutant strain M48 (MIC, 2.0 mg/liter) but had no effect on crystalline biofilm formation by strain M55 (MIC, 40 mg/liter). These results suggest that, in any clinical trial or subsequent clinical use of the strategy, it will be important to monitor the urinary flora of the catheterized patients for *P. mirabilis* strains with reduced susceptibility to triclosan. The emergence of these strains could undermine the ability of the triclosan strategy to control catheter encrustation.

Several studies have reported that the care of half of the many patients undergoing long-term bladder catheterization is compromised when the flow of urine through the catheter is blocked by encrustation (11, 13, 27). The problem stems from infection by urease-producing bacteria, particularly *Proteus mirabilis* (7, 12, 19). These organisms colonize catheters, producing biofilm communities embedded in a polysaccharide gel matrix. The urease they produce hydrolyzes urea to ammonia, elevating the pH of the urine and the biofilm. Under the resulting alkaline conditions, crystals of calcium and magnesium phosphates form in the urine and a crystalline biofilm develops on the catheter (20). This material can block the eyehole and lumen of the catheter, preventing the flow of urine from the bladder and putting the health and welfare of the patient at risk. All types of urinary catheters are vulnerable to encrustation, and currently there are no effective methods available to clinical staff to control the problem (13, 21).

Strains of *P. mirabilis* causing catheter encrustation have been shown to be very sensitive to the biocide triclosan, with MICs of 0.2 mg/liter (9). A strategy to control catheter encrustation has been developed in which triclosan can be delivered directly into the residual urine in the catheterized bladder (25). Laboratory studies with models of the catheterized bladder inoculated with *P. mirabilis* demonstrated that when the retention balloons of either silicone or latex-based catheters are inflated with solutions of triclosan rather than water, the biocide can diffuse through the balloon membranes into the urine. The population of *P. mirabilis* bacteria in the urine is then reduced, the pH of the urine remains acid, and the crystalline biofilm does not form on the catheter. Under experimental conditions where control catheters were blocked within 24 h, catheters inflated with triclosan (10 mg/ml) drained freely for 7 days and at the end of the test period showed little sign of encrustation (9, 25). The efficacy of such a strategy for dealing with the problem of catheter blockage and encrustation could of course be undermined if the strains of *P. mirabilis* causing urinary tract infections in catheterized patients developed a degree of resistance to triclosan. The aims of this study were (i) to test whether the exposure of *P. mirabilis* to triclosan under laboratory conditions might result in the selection of strains with a reduced susceptibility to this biocide and (ii) to test the hypothesis that the selection of a triclosan-tolerant strain would reduce the efficacy of a triclosan-based strategy in preventing *P. mirabilis*-mediated encrustation of catheters.

MATERIALS AND METHODS

Bacterial strains and media. The strains of *P. mirabilis* used in this study were clinical isolates from the indwelling catheters of patients undergoing long-term catheterization. The media used were purchased from Oxoid Ltd. (Basingstoke, United Kingdom). Cysteine-lactose-electrolyte-deficient agar was used to culture strains from stocks maintained at −80°C and for the enumeration of the viable cell populations of urine samples. Tryptone soya agar (TSA) was used for determining the MICs of triclosan to the test organisms. Iso-sensitest agar was used to test the susceptibility of strains to antibiotics. Tryptone soya broth (TSB) was used to grow cultures for experimental purposes. The composition and method of sterilization of the artificial urine supplied to the bladder models have been described previously (26). The pH of the urine was 6.1.

MIC determinations. Stock solutions of triclosan (Ciba, Basel, Switzerland) were prepared in dimethyl sulfoxide (Fisher Scientific, Ltd., Loughborough, United Kingdom) and were added to molten TSA to produce plates containing a range of triclosan concentrations. Plates with TSA alone and TSA containing the maximum dimethyl sulfoxide concentration were used as controls. Aliquots (1 μl) of overnight cultures of test organisms in TSB were applied to the agar plates by using the Denley multipoint inoculator (Denley Instruments Ltd., Billinghurst, United Kingdom). Each strain was inoculated onto three plates of each concentration of triclosan and the control plates. The plates were incubated at 37°C for 18 h and examined for growth the following day. The MICs of ampicillin, ciprofloxacin, gentamicin, nalidixic acid, nitrofurantoin, trimethoprim, cephalexin,

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TABLE 1. MICs of eight antibiotics for the *P. mirabilis* parental isolates and mutants exhibiting reduced susceptibility to triclosan

Parental strain and mutant	MIC (mg/liter) range for[a]:								
	Triclosan	Trimethoprim	Ampicillin	Ciprofloxacin	Nitrofurantoin	Norfloxacin	Cephalexin	Nalidixic acid	Gentamicin
E. coli 10418	0.2	0.03–0.05	0.5–0.75	0.004	2–3	0.02	2–3	0.38–0.58	0.09
P. mirabilis B2	0.2	R	R	0.02–0.03	64–96	0.05	6	2–3	0.38
M 44	40	R	R	0.03	32–48	0.05	4–6	1.5–2	0.38
M 48	2	R	R	0.02	24–48	0.05	3–4	1.5–2	0.25–0.38
M 55	40	R	R	0.02–0.03	48	0.05	4	1.5	0.38–0.5
P. mirabilis NP14	0.2	R	16	0.06	32–48	0.25	3	3	0.13–0.25
M 19	40–60	R	12–16	0.05–0.06	32–48	0.19–0.25	4	2–3	0.13–0.19
M 21	5	R	16	0.05–0.06	48	0.19–0.25	3–4	3	0.13–0.19
M 23	5–10	R	12–16	0.05–0.06	32–48	0.19–0.25	3	2–4	0.09–0.13
P. mirabilis NP37	0.1	R	R	0.02	24	0.05–0.06	4–24	4–12	0.38–0.4
M 26	20	R	R	0.012	24–32	0.03	3	1.5–2	0.13–0.19
M 29	10	R	R	0.008–0.012	16–24	0.03–0.05	2–4	2–3	0.19–1
M 31	5	R	R	0.008–0.012	24	0.02–0.03	3–12	1.5–2	0.13–0.25
P. mirabilis NP43	0.2	0.4	0.4–0.5	0.01	48	0.05	4	2	0.1
M 12	40–60	0.19–0.25	0.13–0.19	0.006–0.008	12–32	0.02	1.5–2	1.5–2	0.06–0.09
M 17	40–60	0.25–0.4	0.19–0.25	0.006–0.012	12–32	0.02	1–2	2	0.06–0.09
P. mirabilis NP55	0.2	R	R	0.016	64–96	0.05–0.06	4–6	3	0.1–0.25
M 35	40	R	R	0.016–0.02	32–96	0.03–0.05	3	2–3	0.25
M 40	40–60	R	R	0.012–0.02	64	0.03–0.05	3–6	1.5–2	0.13–0.19
M 42	0.8–5	R	R	0.016	48–64	0.03	4	2–3	0.25

[a] Results were obtained from triplicate determinations. R indicates that the Etest gave values of >256 μg/ml for ampicillin and >32 μg/ml for trimethoprim.

and norfloxacin for a range of test organisms were determined using Etest strips (AB Biodisk, Sweden) according to the method described by Brown and Brown (3).

Bladder model. The bladder model has been described previously (26). It consists of a glass chamber maintained at 37°C by a water jacket. Each model was sterilized by autoclaving, and then a size 14 all-silicone catheter (Bard Ltd., Crawley, United Kingdom) was inserted into the chamber through an outlet at the base. The catheter retention balloons were inflated with 10 ml of water or 10 mg/ml triclosan in 5% (wt/vol) polyethylene glycol (Sigma Chemicals, Poole, United Kingdom). The triclosan mixture was stirred overnight and heated to 70°C to produce a stable white colloidal suspension. The catheters were connected to drainage bags in the normal way. Sterile artificial urine was pumped into the chambers at 0.5 ml/min so that residual volumes collected below the catheter eyeholes before flowing through the drainage tube to the collecting bags.

Experimental protocol. Pairs of models were assembled and supplied with artificial urine up to the level of the catheter eyeholes. Control models were fitted with catheters inflated with water; test models were fitted with catheters inflated with triclosan. The urine supply was then switched off, and 10 ml of the artificial urine was removed from the bladder chamber and replaced with an artificial urine culture (10 ml) of one of the test strains of *P. mirabilis* that had been incubated at 37°C for 4 h. The organisms were left for an hour to establish themselves in the model; the urine supply was then resumed for a total of 48 h or until catheter blockage. The time taken for the catheters to block was recorded. The urinary pH and the numbers of viable cells in the residual bladder urine at 48 h or at the time of blockage were also determined.

Chemical estimation of catheter encrustation. Catheters were removed from the models and cut into 2-cm sections that were then soaked in nitric acid (4% [vol/vol]). These samples were then sonicated at 35 kHz for 5 min in a sonic cleaning bath to facilitate the dissolution of the crystals embedded in the catheter biofilm. The resulting solution was assayed for calcium and magnesium by using atomic absorption spectrophotometry.

Statistical analysis. One-way analysis of variance carried out at a 95% confidence interval was the statistical test of choice for all the experiments. This was carried out using Minitab release 13 software (Minitab, Inc., PA). If the assumptions required to perform analysis of variance were violated, the Kruskal-Wallis test was performed at a 95% confidence interval.

RESULTS AND DISCUSSION

Isolation of *P. mirabilis* mutants with decreased sensitivity to triclosan. Five strains of *P. mirabilis* having MICs of 0.1 to 0.2 mg/liter to triclosan were selected for study. Aliquots (100 μl) of cultures of the test strains (2×10^8 CFU/ml) that had been grown in TSB at 37°C for 4 h were spread over the surface of TSA plates containing triclosan at concentrations ranging from 0.5 to 10 mg/liter. After incubation at 37°C for up to 5 days, colonies growing on these agar plates were subcultured onto cysteine-lactose-electrolyte-deficient agar. Their identities as *P. mirabilis* were confirmed by Gram staining and using the appropriate BBL Crystal identification kits (Becton Dickinson, Oxford, United Kingdom). The MICs of triclosan for 54 of these isolates ranged from 0.3 to 80 mg/ml. A selection of 14 mutants was subcultured daily for 15 days in the absence of triclosan. Each day, their MICs of triclosan were tested and no significant changes were found, confirming the stability of the mutations.

Have the triclosan-resistant strains also gained resistance to antibiotics? The parental strains and the 14 mutants in which the reduced susceptibility to triclosan had been shown to be stable were tested for their susceptibility to eight antibiotics that are used to treat urinary tract infections. The results of the Etests on these organisms (Table 1) demonstrate that none of these mutants had gained resistance to any of the eight antibiotics tested.

Does inflation of the catheter balloon with triclosan stop crystalline biofilm formation by the mutant strains? Two of the mutant strains, M48 and M55, and their parental strain, *P. mirabilis* B2, were inoculated into bladder models that were

TABLE 2. Effect of triclosan on times to catheter blockage, rates of catheter encrustation, pHs, and viable cells in bladder models inoculated with the wild-type *P. mirabilis* B2 strain and its mutants[a]

Strain	MIC of triclosan (mg/liter)	Time to catheter blockage (h)		Rate of catheter encrustation (μg Ca + Mg deposited/catheter/h)		pH of residual urine at time of catheter blockage or 48 h		Viable cells in urine at time of catheter blockage or 48 h (CFU/ml)	
		Water in balloon	Triclosan in balloon	Water in balloon	Triclosan in balloon	Water in balloon	Triclosan in balloon	Water in balloon	Triclosan in balloon
B2 (wild type)	0.2	32	>48	426.25	3.22	8.75	6.28	7.17×10^7	2.07×10^3
M48	2.0	33	>48	602.31	22.58	8.68	6.51	7.36×10^7	5.44×10^5
M55	40.0	36	44	336.70	447.17	8.88	8.84	6.04×10^7	4.2×10^7

[a] The values shown are means calculated from three replicate experiments.

fitted with all-silicone catheters. Control models in which catheter balloons were inflated with sterile water and test models with catheters primed with triclosan (10 mg/ml in 5% polyethylene glycol) in the retention balloons were set up for each mutant and the wild type. The urine was supplied to the models until the catheters became blocked or for a maximum of 48 h. The times to blockage of the catheters recorded from triplicate experiments are shown in Table 2. It is clear that triclosan prevented catheter blockage by the wild type and strain M48. In the case of strain M55, however, triclosan failed to inhibit encrustation and catheter blockage. The mean times to blockage of 36 h for control catheters and 44 h for test catheters were not significantly different ($P > 0.05$).

The pHs and the viable cell populations of the residual urine samples in the models at the time of blockage or at 48 h are presented in Table 2. The mean pHs in the test models inoculated with strains B2 and M48 were significantly lower ($P < 0.05$) than those in all the other test and control models. The mean pHs of and viable cell populations in the urine in the test models inoculated with M55, however, were not significantly different from those in the control models ($P > 0.05$).

Calcium and magnesium analyses were performed on the catheters removed from models at the time of blockage or at 48 h. The rates of encrustation on the control and test catheters were calculated and are summarized in Table 2. Triclosan significantly reduced the encrustation rates for B2 and M48 ($P < 0.05$) but not for M55. The MIC of triclosan for M55 was 40 μg/ml, compared to 2 μg/ml for M48. At first sight, it might seem strange that urinary concentrations of triclosan around 0.1 mg/liter inhibit catheter encrustation by a strain with an MIC of 2.0 mg/liter. A possible explanation, however, is that as the catheterized bladder is a continuous culture system, a concentration of an antibacterial agent that merely decreases the growth rate could be sufficient to ensure a significant reduction in the bacterial population and pH of the residual urine.

Triclosan is a widely used antibacterial agent that has been incorporated into an extensive range of health care and consumer products. Concern has been expressed that the scale of its exploitation might result in the selection of resistant organisms (23). These concerns have been compounded by suggestions that resistance to triclosan might be linked to cross-resistance to antibiotics (15).

There is certainly evidence that, under laboratory conditions, exposure to triclosan has resulted in the reduced susceptibility of some bacterial species to this biocide. The exposure of an *Escherichia coli* strain with an MIC of 0.8 mg/liter to triclosan has resulted in the selection of mutants with MICs ranging from 2 to 80 mg/liter (18). The repeated subculture in triclosan (0.01 mg/liter) of a *Staphylococcus aureus* strain with an MIC of 0.025 mg/liter selected for stable mutants with MICs of up to 1 mg/liter (28). The decreased susceptibility to triclosan was not associated, however, with an increase in resistance to any of six antibiotics. Ledder et al. (14) exposed a wide range of enteric, skin, and oral species to a total of 10 subcultures on agar containing gradients of triclosan. The results suggested that the selection of strains with increased tolerance to triclosan was not widespread, with most species showing no alteration in their MICs to triclosan. The exceptions were an *E. coli* strain for which the MIC increased from 0.00024 to 16 mg/liter and a *Klebsiella oxytoca* strain (from 0.00012 to 0.49 mg/liter). These strains exhibited no increase in MICs to antibiotics. In contrast, other studies have reported that *E. coli* and *Salmonella* variants that had acquired reduced susceptibility to triclosan in the laboratory had also gained cross-resistance to antibiotics (1). A recent study by Karatzas et al. (10), for example, reported that prolonged exposure of *Salmonella enterica* serovar Typhimurium to triclosan in the laboratory selected for strains having a 2,000-fold increase in their MICs (up to 64 mg/liter). These variants were also less susceptible to chloramphenicol, tetracycline, ampicillin, and acriflavine. Evidence was presented that resistance was due to the overexpression of an efflux pump. The results reported in Table 1 indicate that *P. mirabilis* can be added to the list of species that have developed elevated MICs to triclosan after exposure to the biocide under laboratory conditions. In this case, however, the decreased susceptibility to triclosan was not associated with changes in susceptibility to antibiotics.

Several groups have investigated whether the extensive use of triclosan in health care, dental, and domestic situations has resulted in the selection of resistant organisms. While strains of *S. aureus* with MICs of 2 to 4 mg/liter were isolated from patients who had daily baths with triclosan (4), the general picture is that acquired resistance to triclosan has rarely been found in organisms isolated from clinical sources (29). The extended use of triclosan in dental products has not led to decreased susceptibility to triclosan and other antibacterial agents (5, 6, 24). A large-scale double-blind randomized intervention trial showed that the use of triclosan-containing (0.2%) liquid hand-washing soap in households for periods of 12 months had no effect on the susceptibility of either gram-negative bacteria or staphylococci from the hands of occupants. Neither did the use of this antibacterial product lead to any significant increases in antibacterial drug resistance (2). A study of the effect of the exposure of domestic-drain biofilm

microcosms to low levels of triclosan showed no changes in antimicrobial susceptibility (17). Those authors concluded that the emergence of antibiotic resistance through the domestic use of triclosan is improbable (17).

It has been argued that there is no convincing evidence in the literature that the use of triclosan has resulted in the development of clinically significant levels of resistance or associated antibiotic resistance (22, 29). It is clear that the MICs recorded for "resistant" strains are orders of magnitude below the concentrations of triclosan used in practice (2 to 20 g/liter). Strains with elevated MICs have not been able to survive "in-use" concentrations of the biocide (4, 16, 28). In the case of the triclosan strategy to prevent catheter encrustation by *P. mirabilis*, however, this argument does not hold. Although triclosan at 10 mg/ml is used to inflate catheter balloons, the concentrations of the biocide diffusing into the residual bladder urine are around 0.1 mg/liter (8), very close to the MICs for this species. The strain with an MIC of 40 mg/liter that had been selected by prior exposure to triclosan did not respond to the strategy (Table 2). The possibility of the selection of strains resistant to triclosan in this context is thus of more concern.

We have not advocated the use of triclosan to prevent or control catheter-associated urinary tract infections. Indeed, pathogens such as *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Morganella morganii*, which infect the catheterized urinary tract, are not sensitive to triclosan and can form extensive biofilms on catheters that have been primed with triclosan (8). We have suggested that the strategy should be deployed only when encrustation of the catheters is being induced by *P. mirabilis*. All 118 clinical and environmental isolates of *P. mirabilis* that we have tested are uniformly susceptible to triclosan, with MICs ranging from 0.1 to 0.3 mg/liter (9). Concerns about the development of resistance to triclosan should not, therefore, currently preclude its use in the prevention of the complication of catheter encrustation. In view of the results presented here, however, in any clinical trial or subsequent clinical use of the strategy, it will be important to monitor the urinary flora of the catheterized patients for signs of the emergence of less susceptible strains or the selection of intrinsically resistant species that might coincidently also be resistant to antibiotics.

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