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REVIEW

The encrustation and blockage of long-term indwelling bladder catheters: a way forward in prevention and control

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Objectives: To review the literature showing that understanding how Foley catheters become encrusted and blocked by crystalline bacterial biofilms has led to strategies for the control of this complication in the care of patients undergoing long-term indwelling bladder catheterization.
Methods: A comprehensive PubMed search of the literature published between 1980 and December 2009 was made for relevant articles using the Medical Subject Heading terms 'biofilms', 'urinary catheterization', 'catheter-associated urinary tract infection' and 'urolithiasis'. Papers on catheter-associated urinary tract infections and bacterial biofilms collected during 40 years of working in the field were also reviewed.
Results: There is strong experimental and epidemiological evidence that infection by *Proteus mirabilis* is the main cause of the crystalline biofilms that encrust and block Foley catheters. The ability of *P. mirabilis* to generate alkaline urine and to colonize all available types of indwelling catheters allows it to take up stable residence in the catheterized tract in bladder stones and cause recurrent catheter blockage.
Conclusion: The elimination of *P. mirabilis* by antibiotic therapy as soon as it appears in the catheterized urinary tract could improve the quality of life for many patients and reduce the current expenditure of resources when managing the complications of catheter encrustation and blockage. For patients who are already chronic blockers and stone formers, antibiotic treatment is unlikely to be effective owing to the resistance of cells in the crystalline biofilms. Strategies such as increasing fluid intake with citrated drinks could control the problem until bladder stone removal can be organized.
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Keywords: Foley catheters; *Proteus mirabilis*; bacterial biofilms; catheter-associated infections; urolithiasis; catheter encrustation

Introduction

Encrustation of Foley catheters remains a major problem in the care of patients undergoing long-term indwelling bladder catheterization. Crystalline deposits obstruct the catheter lumen (Figure 1), so that urine is either retained in the bladder causing distension and reflux to the upper tract or leaks around the outside of the catheter. If these blocked catheters are not changed, serious symptomatic episodes of pyelonephritis, septicaemia and endotoxic shock can arise.[1,2] All available catheter types are vulnerable to this problem and currently no effective methods are available for its prevention or control.[3–5] In many cases, the replacement catheters block repeatedly and the patients are classified as 'blockers'.[6] Up to 50% of the patients undergoing long-term catheterization will experience catheter encrustation and blockage.[7] An insight into the prevalence of the complication was given by the observations of Kohler-Ockmore and Feneley.[8] They followed 457 long-term catheterized patients in community care in the Bristol area over a 6-month period and recorded 506 emergency referrals, mostly to deal with catheter blockage. The problem thus puts the health of many patients at risk and makes substantial demands on the resources of a health service.

Nature of encrustation

Analysis of the crystalline deposits on catheters generally shows the presence of two main types of crystals, struvite and apatite. Struvite (magnesium ammonium phosphate) forms large commonly coffin-shaped crystals and apatite (a hydroxylated form of calcium phosphate in which some of the phosphate ions are replaced by carbonate) appears as microcrystalline aggregations. Scanning electron microscopy has revealed that large numbers of bacilli are associated with the crystalline formations[9] (Figure 2). Culture techniques have confirmed the consistent presence of bacteria. Significantly, species capable of producing the enzyme urease are predominant.[10]

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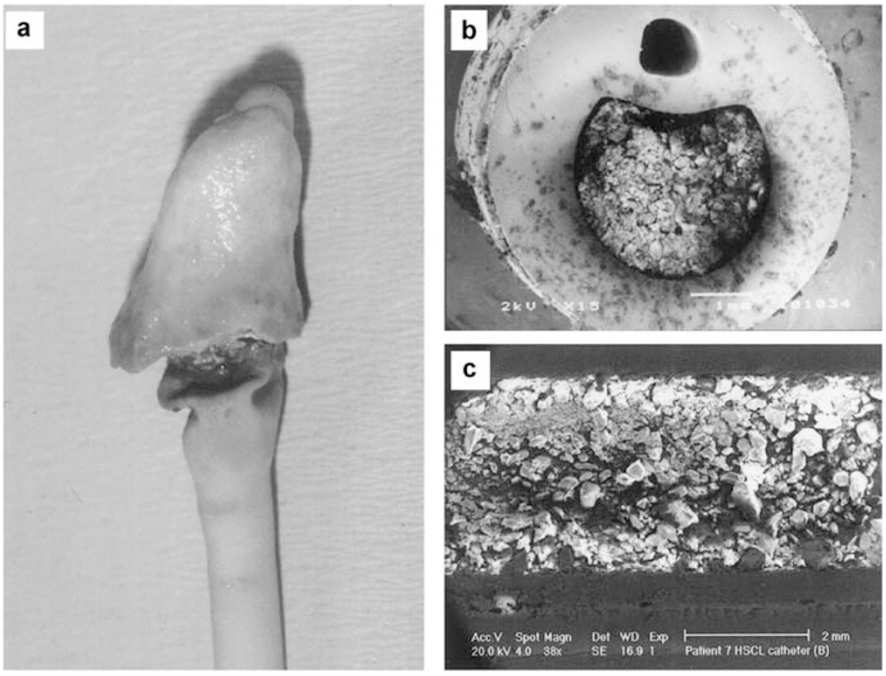

Figure 1 Examples of crystalline biofilms on blocked catheters removed from patients. Panel (**a**) shows a catheter that had been indwelling suprapubically for 6 months. It was removed surgically as crystalline material had completely covered the eyehole. (**b**) A cross-section of a silicone catheter that had been *in situ* for 8 weeks. (**c**) A longitudinal section of a silver/hydrogel-coated latex catheter that had blocked after 11 days *in situ*.[25]

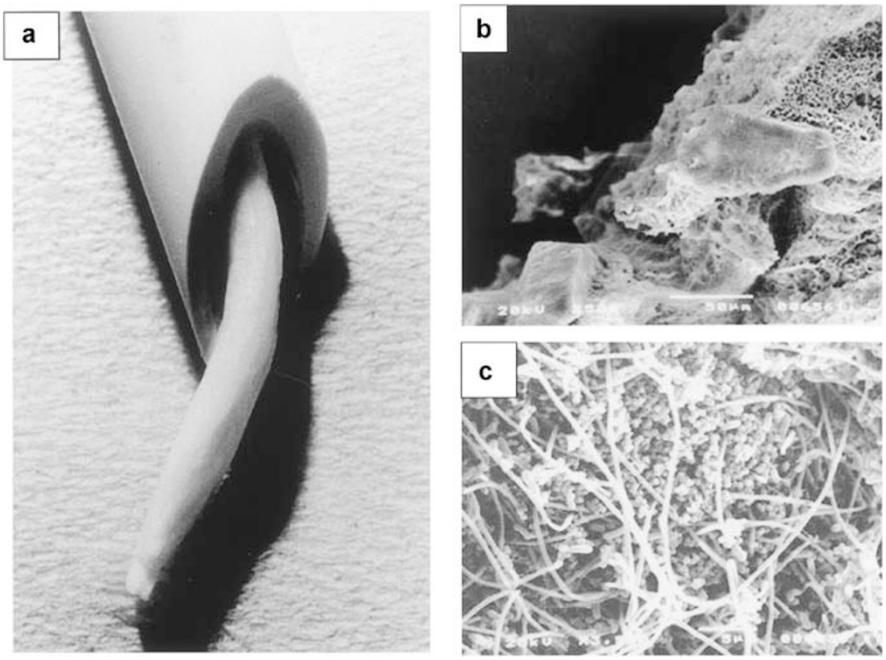

Figure 2 Scanning electron micrographs of the crystalline material that blocked a patient's catheter just after 4 days (**a**). The large coffin-shaped crystals were shown by X-ray microanalysis to be a form of magnesium phosphate (struvite) and the microcrystalline aggregates were shown to be calcium phosphate (apatite) (**b**). Large numbers of cocci and bacilli (**c**) were also observed and the culture revealed the presence of *Enterococcus faecalis*, *Escherichia coli*, *P. aeruginosa* and *P. mirabilis* among the crystalline formations.[23]

Urease is the catalyst that generates the crystals, hydrolyzing urea in the residual bladder urine to produce two molecules of ammonia to every molecule of carbon dioxide causing a rise in pH. As the urine becomes alkaline, crystallization of the magnesium and calcium phosphates is induced. In the meantime, the bacteria colonize the catheter surfaces forming bacterial biofilm. Aggregation of the crystalline material then occurs in the urine and in the

developing catheter bacterial biofilm.[11] This process continues until the accumulating crystalline deposits block the flow of urine through the catheter. Potentially distressing consequences can follow for patients, particularly for those in community care where professional help is not immediately available.

Several species commonly found in catheter-associated urinary tract infections produce urease.[12,13] In laboratory tests, the enzyme can be detected in *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus* species together with some *Providencia* species, and in some strains of *Staphylococcus aureus* and coagulase-negative staphylococci. Of these, *Proteus mirabilis* is most commonly isolated from the urine of patients suffering from recurrent catheter encrustation and blockage.[13,14] It is also the species most commonly recovered from patient's encrusted catheters.[10] The urease of *P. mirabilis* is a potent enzyme, being able to hydrolyze urea several times faster than those produced by other species.[15] Experimental study in laboratory models of the catheterized bladder demonstrated that species such as *M. morganii*, *K. pneumoniae* and *P. aeruginosa* failed to produce alkaline urine and generate appreciable encrustation on catheters.[5,16] The only species capable of producing alkaline urine and causing extensive encrustation were *P. mirabilis*, *P. vulgaris* and *Providencia rettgeri*. The latter two organisms are only found in about 5–10% of catheter biofilms.[17] There is thus strong epidemiological and experimental evidence that *P. mirabilis* is mainly responsible for the formation of crystalline biofilms on catheters.

P. mirabilis as the cause of catheter encrustation

P. mirabilis is an extraordinary microbe. It was named *Proteus* after an elusive character in Homer's Odyssey who escaped capture by changing form. Its natural habitat is the intestinal tract where it forms part of the faecal flora. In individuals with normally functioning urinary tracts, it rarely causes infection. In patients whose urinary tracts are subjected to chronic inflammatory changes from procedures such as long-term catheterization, however, it becomes a significant pathogen. Many properties make it ideally suited to life in the catheterized urinary tract.[18] It is a very sticky bacillus having at least four different adhesins that mediate its attachment to tissue and catheter surfaces. An exopolysaccharide capsule protects it against host's defences and helps it to consolidate its attachment to surfaces. It secretes a haemolysin, an iron-scavenging protein, proteases and amino acid deaminases, all of which are essential for extracting important nutrients from host tissues and fluids. It produces a specific IgA protease that is capable of degrading the predominant immunoglobulin in the mucus secreted from epithelial surfaces. Finally, it has two signature features that are particularly important in the catheterized urinary tract. Along with its ability to produce a potent urease, it can migrate rapidly over solid surfaces.

Microscopic examination of samples of urine infected with *P. mirabilis* will reveal the presence of small Gram-negative bacilli about 2 μm in length. They swim around quite actively being propelled by the action of a small number (1–10) of flagella. When these cells attach to a surface, however, spectacular changes can occur that transform them into cells that can be up to 80 μm long. These elongated cells can produce hundreds of flagella per cell and organize themselves into parallel groups tied together by the helical binding of the flagella around adjacent cells (Figure 3). These rafts of cells are then capable of moving off rapidly in a co-ordinated manner (swarming) over solid surfaces.[19,20] In this way they can spread over surfaces and colonize new locations.

P. mirabilis can swarm rapidly over all-silicone, silicone-coated latex, hydrogel-coated latex and hydrogel/silver-coated latex catheters (Figure 4).[21] Migration was shown to be significantly more rapid over the two hydrogel-coated catheters. A subsequent study showed that *P. mirabilis* was able to migrate over all the basic types of catheter more effectively than any other urinary tract pathogen.[22] Electron microscopy revealed the presence of the rafts of elongated swarmer cells on catheter surfaces.[23] Mutants lacking the ability to swarm failed to migrate over catheters.[20] The evidence thus indicates that swarming may well have a role in the initiation of catheter-associated UTI by facilitating the movement of *P. mirabilis* from the skin at the catheter-insertion site, along the outside of the catheter into the bladder.

Mechanisms of crystalline biofilm formation

P. mirabilis is an ingenious organism that can initiate the formation of crystalline biofilms in several ways[24] on all types of indwelling catheters including those with silver and nitrofurazone coatings.[4,25] To deal with the complication more effectively, it is important to understand the precise mechanisms *P. mirabilis* uses to colonize, encrust and block catheters. The primary stage in the formation of biofilms on implanted medical devices usually involves their rapid coating by a conditioning film of proteins from body fluids. These proteins provide receptor sites for bacterial attachment through the fine hair-like fimbriae (adhesins) that protrude from their cell walls.[26] Several such adhesins have been identified on *P. mirabilis* cells[18] and protein coatings have been found on catheters removed from patients after short periods.[27] Although *P. mirabilis* can probably attach to conditioning films, in this way they can also bind directly to silicone surfaces.[28]

Powerful physical forces can also initiate crystalline biofilm formation. The irregular nature of catheter surfaces, especially latex-based catheters, has been revealed by scanning electron microscopy.[29,30] The techniques used to produce drainage eyeholes tear through the latex-producing surfaces that appear in micrographs like rocky landscapes of craters and crevices. The unevenness of the lumenal surfaces of these catheters is exacerbated by the common presence of embedded diatom skeletons. These come from the diatomaceous earth used to prevent the latex sticking to the metal formers on which the catheters are manufactured. Silicone-based catheters have rather smoother surfaces but

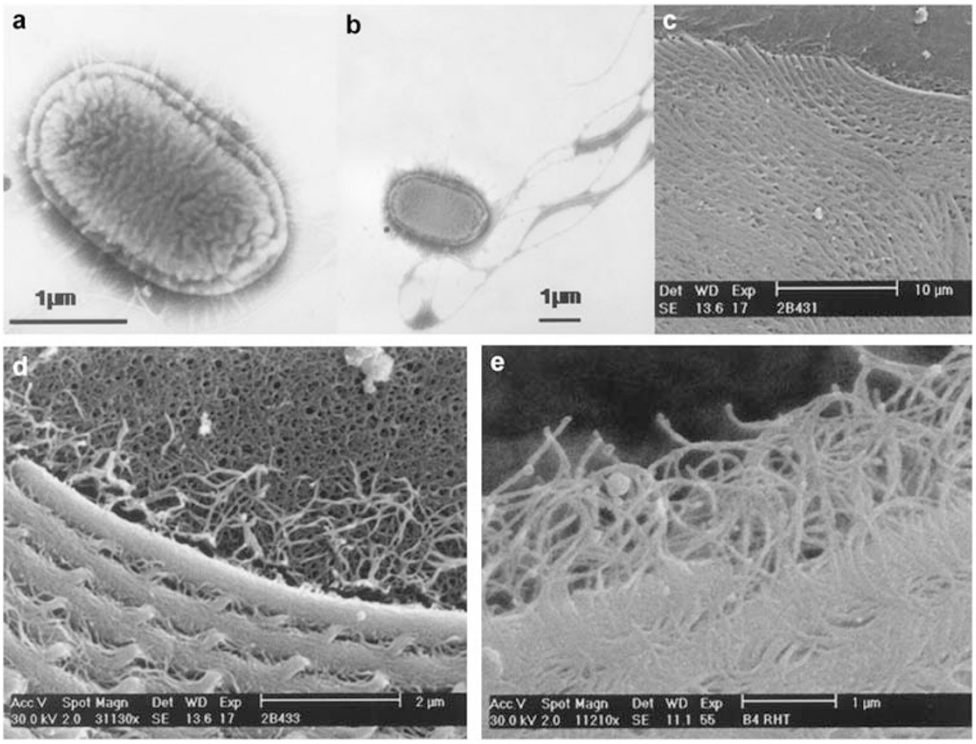

Figure 3 Electron micrographs of *P. mirabilis* showing the normal cells swimming in urine (**a**, **b**). The short hair-like structures visible in (**a**) are fimbrial adhesins. The cells are motile owing to the action of a small number of flagella (**b**). The leading edge of a swarming front on agar is shown in panel (**c**). It can be seen that on a surface, the organism has transformed itself into long multi-flagellate cells arranged in parallel masses. In (**d**) and (**e**) the swarmer cells are shown to be tied together by the helical binding of flagella around adjacent cells.[51]

irregularities commonly occur around the eyeholes and where the extrusion production techniques have generated striations on the lumenal surfaces. As contaminated urine flows over these surfaces, bacteria become entrapped in the irregularities, particularly those around the drainage eyelets. Experiments in laboratory models[30] have shown that, within 2 h of incubation, *P. mirabilis* cells were present in the surface crevices and depressions. After 4 h, microcolonies had developed from these pioneer cells, and by 6 h with the rising pH of the urine, crystals appeared in the developing biofilm. Continued development led to the spread of extensive crystalline biofilms over the catheter surfaces. The silica skeletons of diatoms were also attractive sites for bacterial attachment.[25] Finally, the catheter eyehole or the central lumen in the balloon region became totally blocked.

Other *in vitro* studies have demonstrated that when urine flows over smooth polymer films, the pH of the urine can be a major factor in determining bacterial adhesion. Some polymers with strong electron-donating hydrophilic surfaces will resist colonization at pH 6. However, if the pH rises, calcium and magnesium phosphates come out of solution, macroscopic aggregates of crystals and cells form in the urine, settle on the surface and initiate crystalline biofilm formation.[31]

The normal practice in the care of patients enduring recurrent catheter encrustation is to replace the blocked catheter. The new catheters are thus placed directly into urine cultures of *P. mirabilis* at alkaline pH containing aggregates of microcrystals. An investigation of the early stages of biofilm formation under these conditions revealed that the catheter surfaces were rapidly covered by a microcrystalline layer, which was confirmed as calcium phosphate by X-ray microanalysis. Bacterial colonization of this crystalline foundation layer then led to mature crystalline biofilm formation.[25,32]

These observations that crystalline biofilms of *P. mirabilis* can form in several distinct ways under various conditions have important implications for the development of encrustation-resistant catheters. It is clear that trying to inhibit bacterial attachment and crystalline biofilm formation by immobilizing an antibacterial in the catheter is unlikely to prevent the problem in patients infected with *P. mirabilis*. For example, in the case of the silver-coated catheters, deposition of the crystalline foundation layer allows cells to attach and multiply, protected from contact with the underlying silver. Thus, if antibacterials are to be incorporated into catheters to stop encrustation, they should diffuse out from the catheter surface and prevent bacteria from elevating the urinary pH. Unfortunately, this does not happen with the currently available antimicrobial catheters.[25,32]

Controlling the rate of crystalline biofilm formation

Clinicians recognize that patients experiencing recurrent catheter blockage show considerable variation in catheter

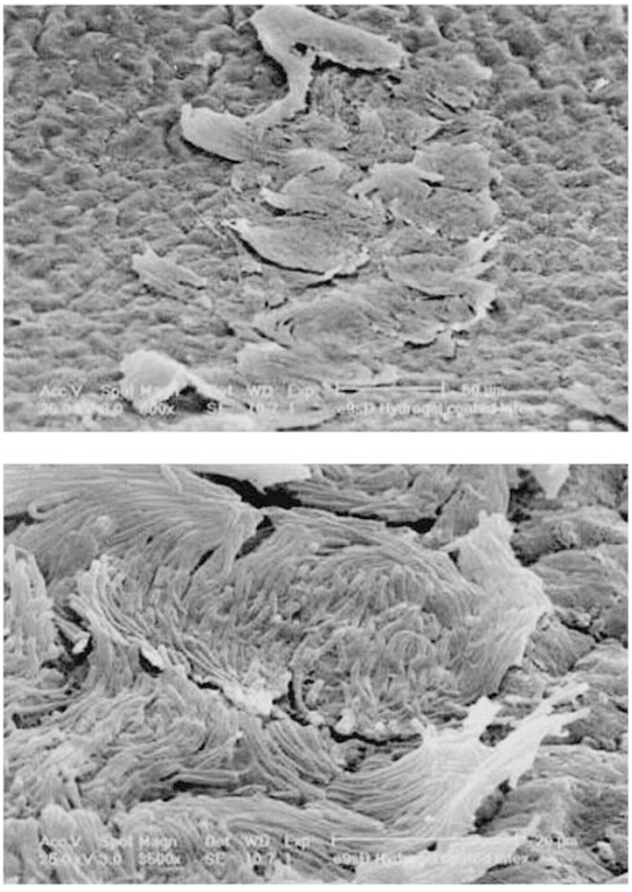

Figure 4 Scanning electron micrographs showing rafts of *P. mirabilis* swarmers migrating from left to right over the irregular surface of a hydrogel-coated latex catheter.[23]

lifespan. In a prospective study of catheterized patients infected with *P. mirabilis*, Mathur *et al*.[33] found that the time taken for catheters to block varied from 2 to 98 days. In these patients, the important factor in determining the rate of catheter encrustation and blockage was identified as the nucleation pH (pHn) of the urine. This is defined as the pH at which crystals form in urine as it becomes alkaline and is characteristic for any sample of urine.[34] Mathur *et al*.[33,35] showed that in patients infected with *P. mirabilis*, the higher the mean pHn of a patient's urine, the slower the rate of encrustation and the longer the catheters took to block. It was also found that the urinary pHn of a patient could vary considerably from week to week. These observations suggested that manipulation of the pHn could form the basis for a strategy to prevent catheter encrustation. A study using healthy volunteers demonstrated that simply by increasing fluid and citrate intake, the pHn of urine could be elevated to pH values that are rarely achieved, even in *P. mirabilis*-infected urine.[36] Subsequent experiments[37] in a laboratory model infected with *P. mirabilis* confirmed that when models were supplied with dilute citrate containing urine with a pHn >8.3, crystalline biofilms did not form.

The advice of Burr and Nuseibeh[38] to patients to increase their fluid intake by drinking steadily throughout the day clearly has a sound basis in physiology and physical chemistry. The dilution of urine resulting from an increased fluid intake will elevate its nucleation pH and slow down the rate of catheter encrustation. If the citrate content of urine can also be elevated by encouraging patients to take lemon-based drinks for example, the rate of crystal formation should reduce further.

Epidemiology and pathogenesis of *P. mirabilis* infections

P. mirabilis is not generally among the pioneer colonizers of the catheterized urinary tract, nor it is commonly found infecting patients undergoing short-term catheterization.[39] However, the longer the catheter is *in situ*, the more likely *P. mirabilis* is to colonize the urine. In patients undergoing long-term catheterization, it has been isolated from 44% of urine samples.[40] It is also clear that in these patients, bacteriuria with *P. mirabilis* is associated with significant morbidity. Hung *et al*., for example,[41] after a retrospective chart review of a population with spinal cord injury concluded that the presence of *P. mirabilis* in the bladder is not a benign condition rather it is a good predictor of urological complications. To facilitate a better understanding of the epidemiology and pathogenesis of these *P. mirabilis* infections, Sabbuba *et al*.[42] developed a method for its genotyping. Pulsed-field gel electrophoresis of restriction enzyme digests of *P. mirabilis* DNA produced highly discriminatory genotype profiles. Application of this method established the remarkable stability of strains of *P. mirabilis* in the catheterized urinary tract. The same genotype was shown to persist in a patient's urinary tract despite many catheter changes, antibiotic treatment and even periods when the patient was not catheterized.

Patients undergoing chronic indwelling catheterization are at serious risk of developing bladder stones. Chen *et al*.,[43] for example, analysed the histories of a cohort of 1336 patients with spinal cord injury and reported that compared with those who were catheter-free with continent bladder control, users of indwelling urethral or suprapubic catheters had a ninefold increased risk of developing bladder stones in the first year after injury. Feneley *et al*.[44] using flexible cystoscopy found bladder stones in 38 of 61 (62%) of patients who were encrusting their catheters, and 90% of these stone formers had *P. mirabilis* infections. Subsequent genotyping of pairs of *P. mirabilis* isolates from the encrusted catheters and bladder stones of patients demonstrated that in each case the isolate from the stone was identical to that from the catheter.[45] The presence of *P. mirabilis* in the bladder stones thus ensures its stable residence in the catheterized tract. Although *P. mirabilis* is generally susceptible to antibiotics in laboratory tests, it is difficult to clear from the catheterized urinary tract by antibiotic treatment. The probable reason for this is that bacteria within the matrix of the bladder stones are protected from antibacterial agents. Flexible cystoscopy to detect and remove bladder stones becomes mandatory if the problems of recurrent catheter encrustation are to be resolved.[44]

The results of the genotyping study suggested that most patients were infected with genetically distinct strains. There was little cross-infection with *P. mirabilis* especially between the community-based patients.[42,45] Subsequent analysis showed that pairs of faecal and catheter biofilm isolates from patients were identical.[46] The evidence thus indicates that most long-term catheterized patients who experience catheter encrustation acquire *P. mirabilis* from their own faecal flora. Once *P. mirabilis* is established in the catheterized urinary tract, there is progression to recurrent catheter blockage by crystalline biofilms and bladder stone formation. Prevention and control of these complications depend on breaking this sequence by the early detection of *P. mirabilis* infection followed by its elimination from the urinary flora by catheter change and appropriate antibiotic therapy.

Conclusions

Bacteriological analysis of urine from patients undergoing long-term catheterization is not routinely carried out, hence early infections with *P. mirabilis* are not detected and progression to chronic 'blocker' status results. Regular bacteriological screening of urine from these patients should be re-instated and followed by antibiotic susceptibility testing of any isolates of *P. mirabilis*. As many catheterized patients are in community care, regular urine sample collection can be problematic. An alternative would be the use of a simple sensor such as that which continually monitors for early stages of *P. mirabilis*-induced encrustation.[47,48] On detection and antibiotic susceptibility testing of *P. mirabilis*, treatment should be initiated and the catheter should be changed. For those patients in whom re-infection with *P. mirabilis* after antibiotic treatment becomes a problem, the strategy of increasing the fluid intake with citrate-containing drinks could be used. Although this will not eliminate the source of the complication, it should extend the lifespan of catheters and reduce the rate at which the bladder stones form.

Although the Foley catheter has been used extensively since its introduction in the 1930s, fundamental problems with its design remain unresolved.[49] The presence of an indwelling catheter undermines the bladder's chief mechanical defence against infection. The cyclic filling and emptying of the bladder is compromised, so any bacteria contaminating the urine or trying to ascend the urethra are no longer flushed out of the tract. A dynamic regularly flushed system is replaced by one which leaves a stagnant sump of infected residual urine within the bladder amounting to a volume of around 100 ml.[50] A continuous-culture system is thus established in which bacterial communities can flourish, and in case of *P. mirabilis* infections, provides urease with the opportunity to generate the alkaline conditions and precipitate the apatite and struvite crystals. Additional problems are caused by damage to the mucosal surface of the bladder by the catheter tip and balloon. The pressure exerted by the catheter on the urethra attenuates the blood supply and the stressed periurethral surfaces provide attractive sites for bacterial colonization. As Kunin[49] pointed out, the challenge is to produce a device that allows the bladder to retain its normal physiological activity permitting regular complete washing out of the bladder while preserving its antibacterial defence mechanisms.

While we wait for such improvements in catheter design and higher standards of manufacture, we need to instigate the *P. mirabilis* detection and elimination strategy.

For patients who have already become chronic blockers and stone formers, however, antibiotic treatment is unlikely to be effective owing to the resistance of cells in the crystalline biofilms. Increasing fluid intake with citrated drinks could control the problem until bladder stone removal by flexible cystoscopy could be organized. Antibiotic therapy and subsequent screening for any reappearance of *P. mirabilis* would then be appropriate.

The aggressive elimination of *P. mirabilis* by appropriate antibiotic therapy as soon as it appears in the catheterized urinary tract could improve the quality of life for many patients and reduce the current expenditure of resources on managing the complications of catheter encrustation and blockage.

Conflict of interest

Professor Feneley is Managing Director of Alternative Catheter Systems.

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