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REVIEW

Greg L. Shaw · Simon K. Choong · Christopher Fry

# Encrustation of biomaterials in the urinary tract

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**Abstract** This review considers the problem of the encrustation of biomaterials used for urinary prostheses. After a general discussion of the problem it deals with exciting new developments which may prove to be clinically applicable in preventing this costly and resource consuming complication. The widespread use of use of in vitro models which accurately simulate the conditions found in the human urinary tract will allow appropriate preliminary studies. Perhaps then clinical evaluation will be warranted.

**Keywords** Biomaterials · Prostheses · Urinary tract · Encrustation

## Use of prostheses in the urinary tract

The use of biomaterials in urinary tract prostheses has been a subject of interest for millennia. They are most commonly used in urethral catheters and ureteric stents.

These prostheses are tubular and are functional whilst the lumen remains patent. Obstruction occurs when encrustation develops to the point where the lumen is occluded. This results in the complications associated with these implants. A study by Kohler-Ockmore and Feneley [1] showed that in patients with long-term indwelling urethral catheters 48% developed catheter blockage and 37% developed bypassing (where urine passes continually around the outside of the catheter) . These complications can be painful and result in incontinence of urine (this is distressing for the patient). It has been suggested that in many cases alternatives are possible, such as the use of supra-pubic catheters, which encrust less and therefore block less, condom sheaths or intermittent self catheterisation [2]. Whilst it is true that in certain circumstances these measures may be undertaken, often they are contra-indicated and the use of long-term indwelling urethral catheters remains commonplace [3]. Prevention of complications associated with urethral catheters is dependant on the use of strict asepsis during insertion and use of closed drainage systems. However complications still occur and these methods are only useful in the short-term [4]. One American study calculated that of patients with catheters in situ for 2–10 days, 25% will develop bacteruria, 24% of these will be symptomatic, and bacteraemia will develop in 3–6%. Each episode of symptomatic UTI was costed at $676, and bacteraemia at $2,836 [5].

When ureteric stents encrust and dysfunction this results in painful hydronephrosis which, if prolonged, can lead to irreversible renal damage. Development of sepsis upstream from the obstruction worsens this problem and renal impairment occurs much more rapidly. This situation is treated as an emergency by the insertion of a nephrostomy tube or changing the stent. If a stent becomes encrusted but does not obstruct, then removal becomes problematic and often requires the involvement of a specialist centre, sometimes requiring several complex operative procedures.

These problems are clearly common and costly to the health service.

## The mechanism of encrustation

Encrustation is a result of the ionic components in the urine crystallizing out onto the surface of the biomaterial and becoming incorporated into a bacterial biofilm layer. Ureteric stent encrustation is most commonly composed of calcium oxalate. Urethral catheter encrustations are usually composed of struvite (magnesium ammonium phosphate). There is a much stronger association between bacterial colonisation of urethral catheters with encrustation than ureteric stent

G. L. Shaw (✉) · S. K. Choong · C. Fry
The Institute of Urology and Nephrology,
University College London, London, UK
E-mail: gregshaw@doctors.org.uk

encrustation and bacterial colonisation [6]. There is clearly a difference in the mechanism involved with urethral catheter encrustation and ureteric stent encrustation. These two processes will be discussed separately.

Bacterial colonisation of urethral catheters is an invariable occurrence when a catheter has been in situ for more than 7 days. Colonisation often occurs even when standard microbiological analysis of urine which has passed through these catheters shows no infection [7, 8]. The bacteria commonly originate from the external urethral meatus or a contaminated spigot and spread occurs rapidly along the luminal aspect of the catheter [9]. *Pseudomonas aureginosa* is the organism detected most commonly when colonisation of urethral catheters is analysed, but the bacterium most commonly detected in association with encrustation is *Proteus mirabilis* [10, 11].

Analysis of urethral catheter encrustations predominately demonstrates biofilm containing struvite. *Proteus* produces an enzyme called urease, which cleaves urea to form ammonia and carbon dioxide. The carbon dioxide dissolves to form carbonic acid. However, as more ammonia is formed than carbonic acid this process results in a net decrease in $H^+$ ion concentration, rendering the urine more alkaline. This change in pH has a profound effect on the solubility of struvite and calcium phosphate. Calcium oxalate solubility is not effected by urinary pH to such a degree. Analysis of the type of encrustations formed at different pH values has shown that at a pH more acid than 6.8 the predominate composite is calcium oxalate, at a pH more alkaline than 6.8 the main composite is struvite. Struvite deposition occurs at a rate ten times greater at pH greater than 6.8 than oxalate at pH less than 6.8 [12].

Analysis of encrustations from catheter blockers almost invariably demonstrates the presence of *Proteus*, and when *Proteus* infection is eradicated the tendency to block catheters is abolished [13]. Thus, it is clear that *Proteus* colonisation is of utmost importance in catheter blockage. However, co-colonisation with other bacteria may be important and *Escherichia coli* has been shown to increase the rate of urease-induced encrustation in an in vitro model [14].

The process of encrustation is thought to involve eight steps (M from Sofer and JD Denstedt) [15].

1. Protein absorption onto the biomaterial, this is dependant upon the surface energy of the biomaterial, the temperature and composition of the urine.
2. Formation of a conditioning film. Here organic molecules from bacteria are deposited on the protein substrate.
3. Initial bacterial approach and attachment, beyond this point the process is irreversible.
4. Bacterial growth, colonisation and biofilm formation. The bacteria become immobilised in an exopolysaccharide matrix. They then produce urease.
5. Urinary and biofilm pH increase due to the production of ammonium ions.
6. $Ca^{2+}$ and $Mg^{2+}$ ions are attracted to the matrix, this and the decreased solubility of calcium phosphate and struvite result in the next step.
7. Precipitation of crystals
8. Self propagation of crystal formation.

Bacteria contained within the encrustation layer show different characteristics from those in the urine. Those in the urine are known as planktobacteria, they are motile and metabolically active and are relatively sensitive to antimicrobial agents. Within the biofilm layer the bacteria are phenotypically distinct in that they are non-motile, they are less metabolically active and the transfer of plasmids, including those conferring antimicrobial resistance, is facilitated. Once a mature biofilm is established, eradication of the bacteria within it becomes much more difficult.

Ureteric stent encrustation is less commonly associated with infection. When stents become colonised this tends to be with organisms other than *Proteus* [13], such as *Escherichia coli*. Bacterial biofilm is almost always detectable on stents which have been in situ for prolonged periods. Bacterial biofilm is known to promote encrustation since the biofilm layer draws crystals onto its surface and these become incorporated within it. Patient and biomaterial factors are of more importance than is the case with urethral catheters where *Proteus* infection and its effects on urine pH overshadow the effects of the other variables. In the absence of infection those risk factors associated with urinary calculus formation (hyperoxaluria, hypercalciuria and hypocitraturia etc.) are important [16].

## Management of complications associated with encrustation

Blockage of urethral catheters results in painful urinary retention and unpleasant urinary bypassing (where urine passes alongside the catheter). Patients with these problems are generally managed by district nurses, Accident and Emergency Departments and Urology emergency clinics. Often an attempt is made to clear the obstruction by washing out the catheter with solutions designed to displace and dissolve the obstructing encrustations. Saline is most commonly used. It has been a long-held view that bladder washout is the best and simplest way to maintain patency of prostheses, the effect being more significant than the administration of antibiotics [17]. However, it is likely that bladder washout disrupts the closed drainage system and may allow bacterial contamination to occur.

Other washout solutions have been developed, such as Suby G. This solution contains citrate and is acidic. The rationale behind this solution is that the citrate will

complex with $Ca^{2+}$ ions, thereby preventing their involvement in the formation of encrustation, and the low pH of the solution will also solubilise the components of the encrustation layer. Some workers have shown this to be effective in dissolving encrustations [18, 19, 20]. It has been postulated that although the instillation of acidic solution into the bladder will result in a short-term decrease of pH, this effect is transitory as it is rapidly negated by a reactive increase in the activity of bacterial urease, bringing about a prolonged increase in pH with a resultant increase in encrustation; furthermore, bladder washout with acidic solutions is associated with chemical cystitis [21].

Bacteriocidal washouts have also been developed and an array of solutions has been tested by one group [22, 23, 24, 25]. Of the various antibacterial washout solutions tested, all except 7% mandelic acid were only effective with low concentrations of bacteria in the urine ($< 10^4$CFU/ml). By contrast, 7% mandelic acid was effective with bacterial concentrations similar to those found in the infected urinary tract ($10^7$–$10^8$ CFU/ml). This in vitro study demonstrated that various washout solutions were bacteriocidal to organisms in urine, however the biofilm formed a physical barrier to the solution reaching the viable bacteria, rendering the solutions ineffective in treating bacterial colonisation once the biofilm was established.

## Prevention of encrustation

Much work has concentrated on the types of biomaterial used in prostheses. Attempts have been made to produce biomaterials which resist encrustation, yet at the same time are biocompatible and have physical properties rendering them suitable to their function.

Traditionally latex was used to manufacture these implants. More recently silicone has been employed as it is relatively inert at the biomaterial/tissue interface and has superior biomechanical properties. Silicon prostheses have been shown to be more resistant to encrustation than other biomaterials [26]

Biomaterial substances have also been coated in attempts to minimise their frictional coefficient, and make prostheses easy to insert and comfortable to the patient. These coatings include hydrogels, which are compounds that absorb water but do not dissolve. Teflon is another material with which prostheses may be coated to reduce their frictional coefficient. However, there is now a body of evidence which suggests that conventional hydrogel and Teflon coatings facilitate the swarming of *Proteus* over the surface [27, 28, 29, 30], and this results in an increased tendency for the materials to encrust. This has led to the development of several hydrophilic coatings which resist encrustation yet at the same time make the prostheses more slippery. These coatings include phosphorylcholine [31, 32] and poly vinyl pyrollidone [33].

The use of antibiotics has been employed for many years in an attempt to inhibit bacterial colonisation and encrustation. Cormio et al. demonstrated, using a static model with human urine, that adding ceftriaxone or ciprofloxacin was effective in inhibiting the adherence of bacteria to biomaterials [34, 35]. As outlined above, systemic antibiotic and topical bacteriocidal agents are not effective in eradicating infection once biofilm is established. An alternative strategy is to impregnate biomaterials with antibiotic agents. Novel biomimetic and bioactive silicones are under development. These materials are designed to allow the incorporation of antibiotics [36]. DiTizio et al. have described a liposomal hydrogel coated biomaterial, the liposomes of which contain ciprofloxacin, and this has been shown in-vitro to resist encrustation [37]. One group has produced a gentamicin-releasing urethral catheter which has been shown in a rabbit model to inhibit encrustation, in the short-term [38].

Reid et al. demonstrated in a clinical trial that oral ofloxacillin eradicated bacterial biofilm in patients with spinal injuries, whereas trimethoprim and sulphamethexazole did not [39]. The same workers also demonstrated that ciprofloxacin and ofloxacin taken orally resulted in the antibiotic being adsorbed onto the prostheses [40]. This effect has also been demonstrated by another group [41], and this suggests that these antibiotics are able to penetrate the biofilm layer and eradicate the bacteria within it.

The use of silver as a means of preventing bacterial colonisation and encrustation has been the subject of much work. Silver alloys can be coated onto the surface of biomaterials. One group observed the effect of a silver releasing device in prostheses within a dynamic model, using human urine. They found that the spread of microbes along the surface of the biomaterial was prevented, in the short-term, from passing beyond the device [42, 43]. This has been confirmed by other studies [44]. To the contrary, Sabbuba et al. have suggested that swarming of *Proteus* over Foley catheters was not inhibited by silver [28]. In addition, Cormio et al., using an in vitro static human urine model, showed that coatings containing silver did not impair bacterial adhesion to biomaterial [45]. This controversy prompted one meta-analysis of the effectiveness of silver bearing catheters. Saint et al. demonstrated clearly that silver alloy coated urethral catheters are effective in decreasing the rate of urinary tract infection in patients with long-term catheters, with a consequent decrease in the occurrence of complications [46]. However, this has to be weighed against a slightly higher cost of these prostheses.

One elegant in vitro study published in the Lancet described the inflation of catheter balloons with triclosan (10 g/l) rather than water. This resulted in impregnation throughout the catheter with the agent and subsequent inhibition of bacterial colonisation and encrustation [47].

The patient with a spinal cord injury, or any other patient who is immobile, has a greatly increased rate of encrustation. These patients are likely to have long-term urethral catheters. The increased encrustation rate results from a greater prevalence of bacterial colonisation, urinary stasis and hypercalciuria. Several studies have looked at dietary measures which might inhibit encrustation. A small clinical trial showed a tendency to decreased biofilm load on catheters removed from patients who had been consuming large amounts of cranberry juice and suggested that larger scale studies were warranted [48]. Habash et al. showed that supplementing the diet with cranberry juice resulted in decreased bacterial adhesion to biomaterial but did not inhibit encrustation significantly [49]. Other workers have suggested that in these patients the most important factors are adequate hydration and urine output [50] and limited calcium, magnesium and alkali ingestion [51].

A recent development which may have an impact on ureteric stent encrustation is the development of bioabsorbable materials and stents [52]. These materials will be absorbed before they have the opportunity to encrust. They will not be suitable for use in patients for whom long-term stenting is desirable. However, they will be useful in situations such as after ureteroscopy where the stent is only required for 2 weeks or so. In this situation stent removal via the cystoscope will not be necessary.

## Evaluation of rates of encrustation

Evaluation of different biomaterials and prostheses can be undertaken in a number of ways. Clinical trials have been carried out [51, 53] but are costly and time consuming. Novel means of preventing encrustation would require in vitro evidence of efficacy before clinical trials could be justified.

Animal models have been developed and include the use of rabbit, mini-pig and pig [45, 54, 54, 55]. In these, the biomaterials and prostheses have been inserted surgically in the animals bladder for removal after a set period. There is some evidence that these models are limited as the animals tend to develop infection with different microbes to humans [45] and analysis of the biochemical makeup of the deposits demonstrates that they are different to those that occur in humans [55].

Other workers have used inanimate laboratory models. There are two main types:

1. Static models where samples are immersed in a reservoir of substrate. This is limited since the constituents of the substrate change as encrustation develops.
2. Dynamic models, where urine flows over or through the biomaterial. These are superior as the biomaterials are constantly exposed to fresh substrate, as would be the case in the urinary tract.

Artificial urine has been used to generate encrustation [29, 56, 57]. Although it is perhaps more sanitary or practical to use artificial urine, it is well known that it contains only a few of the many constituents of human urine. In addition, several constituents of human urine, not present in artificial urine, influence the rate of encrustation [58, 59]. Tamm-Horsfell protein is one agent in human urine which is not present in artificial urine. This protein is known to have an effect on crystallisation of urine components. .Hedelin et al. showed that the effect of adding citrate to human and artificial urine altered the encrustation properties in different ways [59, 60], and further work by this group attempted to identify the constituents responsible for this altered behaviour. They showed, by adding glycosaminoglycan/heparin and pyrophosphate to artificial urine, that these were not responsible for the different encrustation properties of artificial urine as compared to human urine.

Sterile models have been used to analyse encrustation properties of biomaterials [61]. This type of model approximates to the situation in the ureter, however it is unlikely that this type of model will be suitable for the analysis of biomaterials for use in the lower urinary tract where bacterial colonisation predominates [62].

Attempts have been made to produce infected models of the lower urinary tract. This is difficult because of the problems associated with using live organisms. The behaviour of the organisms is difficult to control and the infection level must be kept at a fairly constant level. Contamination with other organisms must be evaluated and controlled to provide useful results. These difficulties have led to the use of Jack bean derived urease, as an alternative. This is much simpler to use and provides an approximation to genuine infection. However differences between encrustation occurring in urease models and infected models have been demonstrated [55, 63].

Quantification of encrustation deposits can be performed in several ways. The simplest is dry weighing. Electron microscopy allows one to inspect the surface of a biomaterial and evaluate the degree of encrustation. The site of encrustation can be evaluated in this way, rather than just the amount [64]. It is also possible to dissolve encrustation deposits and then analyse the solute for calcium or magnesium content giving an evaluation of the amount of encrustation having been deposited. This can be done reliably by absorption spectrometry [62]. Ion specific electrodes may prove to be valuable in this capacity. They can be used to measure the concentration of $Ca^{2+}$, $Mg^{2+}$ and $NH^{4+}$ ions. Dissolution of encrustation deposits and measurement of the concentration of these ions in solution reflects the amount of encrustation which has been deposited and its composition [65].

## Areas of interest for future development

Aspects of design of catheters and stents are recognised as being possible targets for improvement, to reduce the tendency to block. The lumen should be as large as

possible and should be shaped so that there are no acute angles. Compliant prostheses permit pulsatile flow through them and this limits encrustation. The surface should be as smooth as possible, particularly around the eye-holes as encrustation develops first at the site of imperfections in the surface.

Metal strips when attached to urethral catheters alter the micro-electric environment and have been shown in vitro to limit biofilm formation [66]; more work is required to ascertain if this is clinically applicable.

Recently axially propagated ultrasound has been shown to remove *Proteus* biofilm from glass [67]. This is potentially applicable as a method of preventing encrustation by clearing biofilm from indwelling catheters periodically.

Glycosaminoglycans and heparin coatings for prostheses may prove to be clinically useful and have been shown in vitro and in a rabbit model to inhibit encrustation and improve biocompatibility [68, 69, 70]

Citrate has been shown to inhibit urease induced crystallisation when taken orally or added to urine in vitro [59, 71]. Oral citrate is unpleasant to take. However, a novel wax-coated preparation makes taking it more palatable and may allow its use to become more widespread

Acetohydroxamic acid is a potent irreversible inhibitor of urease [72, 73], This and other urease inhibitors have been shown to be effective in dissolving struvite/infection stones. The effect of this agent on catheter encrustation has been promising in vitro [74], but has not been clinically evaluated. Clinical systemic use of this agent to treat infection stones resulted in intolerable side effects.

Oxalate degrading enzymes can be incorporated into biomaterial coatings. This has been shown in a rabbit model to decrease the amount of encrustation. The inhibition of calcium oxalate deposition is most applicable to ureteric stent encrustation [54].

The ability of lactobacilli to inhibit the colonisation of biomaterials in vitro has been demonstrated and is thought to be due to the production of biosurfactant which inhibits adhesion of the pathogenic organisms to the biomaterial [75, 76].

These findings all represent exciting new developments which may prove to be clinically applicable in preventing this costly and resource consuming complication. Further in vitro studies are required to evaluate their usefulness. Development of the widespread use of use of in vitro models which accurately simulate the conditions in the human urinary tract will allow appropriate preliminary studies. Perhaps then clinical evaluation will be warranted.

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