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Biomaterials in Urology - Beyond Drug Eluting and Degradable - A Rational Approach to Ureteral Stent Design

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1. Introduction

Ureteral stents are commonly used in urology to provide urinary drainage of the upper tracts, particularly following treatment of urolithiasis. Stents are commonly plagued with infections and encrustation, particularly in stone-forming patients (Denstedt and Cadieux 2009). This involves a multistep process outlined in Figure 1. The first step is formation of a conditioning film comprised of urinary proteins, ions, and crystals that are deposited at the stent surface (Tieszer, Reid et al. 1998). The conditioning film becomes an attractive surface for bacteria to adhere to and forms a biofilm which can lead to a urinary tract infection or encrustation (Wollin, Tieszer et al. 1998; Choong and Whitfield 2000; Choong, Wood et al. 2001; Shaw, Choong et al. 2005). Bacteria have been demonstrated to adhere to the stent surface in up to 90% of indwelling stents, which in 27% of cases leads to a positive urine culture (Reid, Denstedt et al. 1992).

Ideally, ureteral stent biomaterials would be able to limit or completely prevent the processes shown in Figure 1. Various attempts have been made to reduce the deposition of crystals, bacteria, and protein on stent surfaces including using low surface energy biomaterials (Tieszer, Reid et al. 1998), heparin coating (Cauda, Cauda et al. 2008), antimicrobial eluting biomaterials (Cadieux, Chew et al. 2006; Chew, Cadieux et al. 2006; Wignall, Goneau et al. 2008; Cadieux, Chew et al. 2009), diamond-like carbon coatings (Laube, Kleinen et al. 2007), polyethylene glycol and marine mussel adhesive proteins (Pechey, Elwood et al. 2009) to name just a few. Most have limited effectiveness and some have even shown increased bacterial adhesion compared to controls in the case of heparin coating (Lange, Elwood et al. 2009). While drug-eluting technology of biomaterials is both readily available and used clinically in other fields, its role in urology has been limited. Triclosan was used recently in ureteral stents. It held promise in *in vitro* (Chew, Cadieux et al. 2006) and animal infection models (Cadieux, Chew et al. 2006) but it fared poorly in those patients requiring chronic ureteral stents (Cadieux, Chew et al. 2009). The current methodology of technological implementation surrounding ureteral stent coating and design have come from trial and error or are borrowed technologies from coronary and vascular stenting. The time has come for the urological world to apply the same types of scientific discovery and development to problems specific to urinary devices rather than just applying the end product from other areas of medicine. What works in vascular stenting may not be directly applicable to the urinary environment.

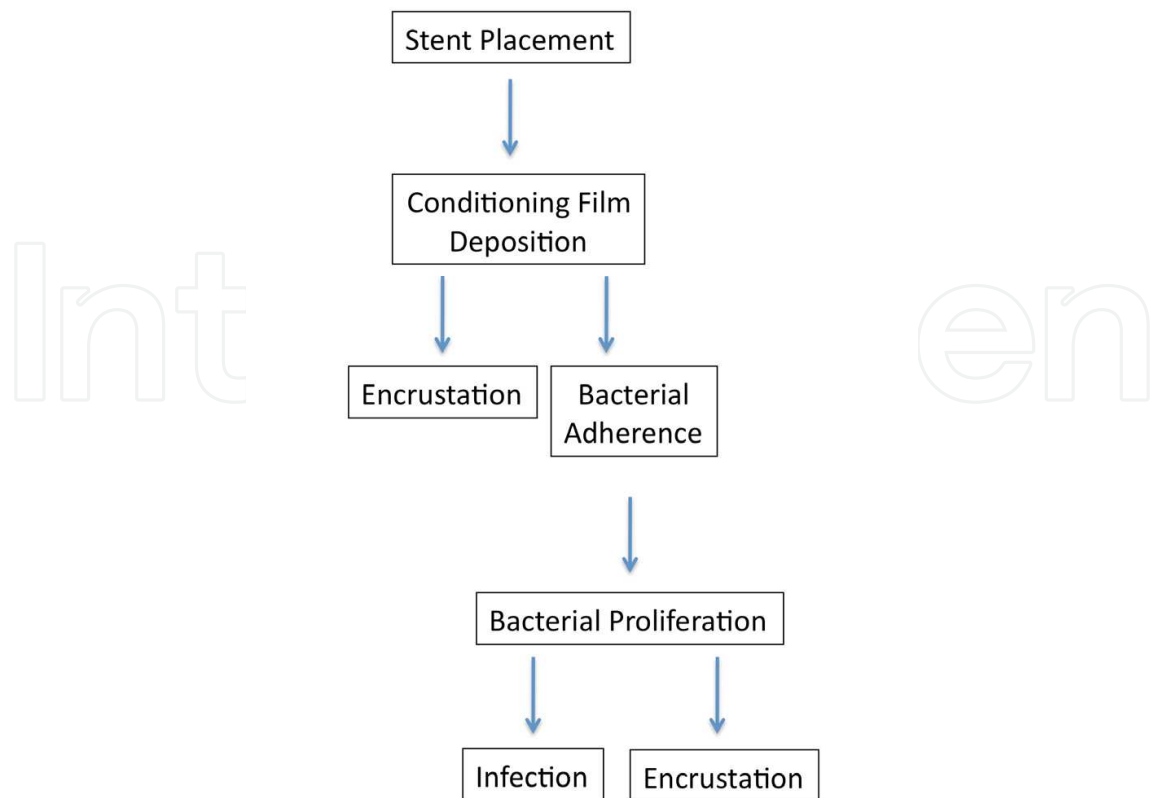


Fig. 1. The processes following stent insertion that lead to bacterial adhesion, infection, and encrustation. Following stent insertion, urinary components deposit on the surface, forming anchor points for both bacteria as well as ions/minerals. Subsequent bacterial colonization and proliferation leads to the formation of a resistant biofilm that leads to subsequent infection. In addition the interaction of ions/minerals with conditioning film components and bacterial induced crystallization will facilitate encrustation of the device. Inhibition of the common step of conditioning film deposition is a potential step in preventing patient symptoms associated with indwelling ureteral stents.

2. Problems arising from stents

Stents have been associated with increased morbidity causing infection,(Riedl, Plas et al. 1999) encrustation,(Paick, Park et al. 2003) hematuria,(Damiano, Oliva et al. 2002; Joshi, Newns et al. 2003; Joshi, Chitale et al. 2005) and discomfort (Joshi, Stainthorpe et al. 2001; Joshi, Okeke et al. 2002). The Ureteral Stent Symptom Questionnaire (USSQ) looks at different facets of life including sexual function which has been shown to be negatively affected by the presence of a stent (Sighinolfi, Micali et al. 2007). In fact, ureteroscopes, intracorporeal lithotriptors, and ureteroscopic techniques have improved to the point that the major morbidity of ureteroscopy has become the stent left *in situ* postoperatively. Studies evaluating differences in postoperative complications and stone-free rates in stented compared to non-stented patients have shown that stents are not a routine requirement following uncomplicated ureteroscopy (Hosking, McColm et al. 1999; Borboroglu, Amling et al. 2001; Denstedt, Wollin et al. 2001). The uncommon, but most severe problem arising from stents is the “forgotten stent” that is left in place for several months to years. These stents become encrusted and create difficulty for both patient and urologist, especially since their

removal involves multiple surgical procedures (Rana and Sabooh 2007) and may result in loss of the renal unit or potentially even death (Singh, Srinivastava et al. 2005).

3. Current stent biomaterials

The synthetic polymer, polyethylene, was previously used in stent construction, but was abandoned due to its stiffness, brittleness, and tendency to fragment. Blends of polyethylene and other polymers, such as polyurethane, have been shown to resist encrustation (Gorman, Tunney et al. 1998; Gomha, Sheir et al. 2004). Silicone is currently the most biocompatible stent material as it is the most resistant to biofilm formation, infection and encrustation (Watterson, Cadieux et al. 2003), and is one of the most lubricious materials available (Jones, Garvin et al. 2004); however, its softness and elasticity make it difficult to handle, particularly through tortuous or tight ureters. In addition, the low tensile strength of silicone makes it susceptible to extrinsic compression. The development of new stent materials aimed to meld the flexible and elastic properties of silicone with the rigidity of polyethylene which resulted in the development of polyurethane, the most common class of polymer currently used in stents. Polyurethane, however, is a stiff material that causes patient discomfort and significant ureteral ulceration and erosion have been reported in an animal model (Marx, Bettmann et al. 1988). New proprietary materials and combinations are softer, more comfortable, and easier to maneuver within the urinary tract. Examples of commonly used materials in stents include Percuflex® (Boston Scientific Corporation, Natick, MA), Silitek® (Surgitek, Medical Engineering Corporation, Racine, WI, USA), C-Flex® (Consolidated Polymer Technologies, Clearwater, FL, USA), Tecoflex® (Thermedics, Wilmington, MA, USA), and ethylene-vinyl-acetate (from the polyefin family of which polyethylene is a member). They have been designed to provide rigidity to facilitate handling by the surgeon and to provide adequate drainage while being soft enough to limit patient discomfort.

4. New materials

New materials include metal stents that are designed to keep the ureter open despite extrinsic ureteral compression secondary to lymphadenopathy due to malignancy. Ureteric obstruction may result in decreased renal function, pain, or infection requiring urinary diversion (Chitale, Scott-Barrett et al. 2002; Allen, Longhorn et al. 2010). As these stents must remain in place for long periods of time, they require frequent exchanges because they are susceptible to infection and encrustation with increased indwelling time. The goal in this patient population is to develop a stent that maintains ureteral patency during extrinsic compression, is soft to minimize discomfort, and is resistant to encrustation and infection.

5. Metal ureteral stents

Metal ureteral stents were introduced by Pauer in 1992 (Pauer and Lugmayr 1992) and have been utilized in the treatment of malignant ureteric obstruction (Kulkarni and Bellamy 2001; Liatsikos, Karnabatidis et al. 2009; Masood, Papatsoris et al. 2010; Papatsoris and Buchholz 2010; Sountoulides, Kaplan et al. 2010), ureteral strictures (Daskalopoulos, Hatzidakis et al. 2001; Papatsoris and Buchholz 2010), and ureteropelvic junction obstruction (Barbaliias, Liatsikos et al. 2002; Masood, Papatsoris et al. 2010; Benson, Taylor et al. 2011). Current

problems associated with metallic stents include biofilm formation, infection, migration, and tissue hyperplasia leading to luminal obstruction (Barbalias, Liatsikos et al. 2002; Wah, Irving et al. 2007; Liatsikos, Karnabatidis et al. 2009; Sountoulides, Kaplan et al. 2010).

Metal stents were originally used for the relief of end-stage malignant disease, where the ureteral stricture was either directly caused by the tumor or indirectly via pressure of a tumor on the ureter. Pauer and Lugmayr used metallic ureteral stents in 1996 (Pauer and Lugmayr 1996) to treat 54 malignant stenoses of the ureter in 40 patients via the implantation of a self-expandable permanent endoluminal stent (SPES), the Wallstent™. During a follow-up period of 10.5 months, 51 ureters maintained adequate patency. Of these, 51% needed no further intervention, while 49% needed intervention to re-establish patency. In comparison insufficiency was noted at a mean 4.3 weeks in control patients with an indwelling Double-J catheter. One of the drawbacks of metal stents is, however, that they induce local urothelial hyperplasia, with ingrowth of tissue through the struts that may result in recurrent obstruction during long term placement. Recently, a nickel-cobalt-chromium-molybdenum-alloy stent double pig-tailed stent (Resonance™ Stent, Cook Urological, Spencer, IN, USA) has been developed to provide long-term urinary drainage in patients with malignant ureteric strictures (Blaschko, Deane et al. 2007; Wah, Irving et al. 2007; Lopez-Huertas, Polcari et al. 2010; Wang, Lee et al. 2010). The tight winding of this metal stent helps to maintain stent flexibility and movement, while resisting in-growth of tissue. In addition to this, the movement of the stent causes opening of the coils, allowing the fluid to access the lumen. In a study of 15 patients, this metal stent provided adequate long-term (up to 12 months) urinary drainage in patients with malignant ureteric obstruction without significant bulky pelvic disease. These stents were also found to have minimal encrustation (Wah, Irving et al. 2007). An *in vitro* study has shown that this metal stent provides its best drainage when the ureter is tightly compressed onto its outer surface which is likely due to the result of increased flow between the coils of the metal stent. It was this feature that makes the Resonance™ stent useful in patients in which the ureter is obstructed due to malignancy (Blaschko, Deane et al. 2007; Liatsikos, Karnabatidis et al. 2009; Masood, Papatsoris et al. 2010; Sountoulides, Kaplan et al. 2010; Wang, Lee et al. 2010; Benson, Taylor et al. 2011).

6. Biodegradable stents

Despite the fact that the biocompatible materials and stent designs have improved over the years, they have one key disadvantage, which is the fact that they have to be removed via a separate procedure unless the retention suture is left on the stent. Avoiding a secondary procedure for ureteral stent removal would decrease patient morbidity and make this technology attractive. More recent research has focused on the design of stents that do not need to be removed and are biodegradable. The design of a biodegradable stent must take into consideration the biocompatibility properties of the material, as well as the degree of expansion and degradation rates, and most importantly it must be able to fulfill the basic requirement of a stent in that it must be able to guarantee urinary flow from the renal pelvis through the ureter and into the bladder for the desired period of time. Degradable materials also must retain their properties after sterilization and be able to withstand a long shelf-life before use. One of the challenges involved in designing a biodegradable stent is the control of the rate and direction of degradation. Schlick and Planz (Schlick and Planz 1997; Schlick and Planz 1998) designed a stent composed of plastic, the degradation of which was

dependent upon the urine pH. *In vitro* experiments with artificial urine showed that the stents were stable at urine pH less than 7.0 for at least 30 days, while they dissolved completely within 48 hours at pH greater or equal to 7.0. The principle behind this stent is that it would remain stable at physiological urine pH of 5-6, but can be triggered to dissolve by medically altering urinary pH. Although very promising, this technology remains at an experimental stage and awaits animal trials. An additional factor that may need to be taken into consideration is the influence of encrustation protein deposition as it can form a platform for bacterial adherence and infection. The influence of encrustation and protein deposition must also be considered as it can form a platform for bacterial adherence, all of which may influence urine pH. Uropathogens in general are known to increase urine pH, and may have an effect *in vivo*. In addition to this, medically increasing the urinary pH may introduce an additional risk for infection as more alkaline pH favours bacterial survival and some increased stone formation (calcium phosphate and struvite stones). In addition, encrustation of the stent may also prevent its exposure to the altered pH environment, thus limiting its rate of decomposition.

A spiral stent (Spirastent®, Urosurge Medical, Coralville, IA) is a polyurethane stent with metal helical ridges designed to prevent kinking and compression in chronically obstructed patients. In *in vitro* studies, this stent increased flow and theoretically increased the space between stent and ureter to facilitate passage of stone fragments. (Stoller, Schwartz et al. 2000) The spiral design has been incorporated into biodegradable materials for urethral stents. (Isotalo, Talja et al. 2002; Laaksovirta, Isotalo et al. 2002) Laaksovirta et al used a self-reinforced poly-L-lactic and poly-L-glycolic acid (SR-PLGA) copolymer spiral urethral stent (SpiroFlow stent, Bionx Implants Ltd, Tampere, Finland) following prostatic laser coagulation. (Laaksovirta, Isotalo et al. 2002) This stent degraded in 6-8 weeks and resisted encrustation at 4 weeks in artificial urine. After 8 weeks, the SpiroFlow® stent was significantly less encrusted than the metal urethral stents Prostakath® (Engineers and Doctors A/S, Copenhagen, Denmark) and Memokath® 028 (Engineers and Doctors A/S). SR-PLGA is the most commonly utilized material for prostatic stents, but it has also been developed as a ureteral stent and may be incorporated into new degradable, encrustation-resistant ureteral stents in the future. (Olweny, Landman et al. 2002)

An alginate based ureteral stent was designed to stay in place for at least 48 hours after uncomplicated ureteroscopy. (Lingeman, Preminger et al. 2003; Lingeman, Schulsinger et al. 2003) Of 87 patients, 80.5% of patients retained their stents greater than 48 hours. Seventeen patients had early stent passage (earlier than 48 hours), but did not require any supplemental procedures to insert another stent. Although these results were promising, several patients (14) still had stent fragments remaining at 30 days, while 3 patients had stent fragments remaining after 90 days. All three of these patients underwent shockwave lithotripsy and two went on to have endoscopic ureteroscopy to remove the fragments from the kidney. Because of the lack of all stents to degrade by 3 months, this stent is no longer commercially available. (Lingeman, Preminger et al. 2003)

The authors are currently involved in developing a new biodegradable stent (Poly-Med Inc., Anderson, SC) that dissolves within 1 to 4 weeks in a porcine model. The animals stented with degradable stents displayed less histologic inflammation than animals stented with control polyurethane biostable Double J stents (Chew, Lange et al. 2010). Weekly intravenous pyelograms displayed less hydronephrosis in the degradable stent group. All stents degraded by 4 weeks and degradation began after 1 week in a very controlled fashion

and no animal had a distal obstructed ureter Due to retained stent pieces. Properties such as stent softness from these biodegradable stents may improve patient comfort. Clinical studies will be necessary to determine if biodegradable stents are more comfortable.

7. Stent coatings

One of the most common stent coatings is hydrogel, which consists of hydrophilic polymers that absorb water and increase lubricity and elasticity.(Marmieri, Pettenati et al. 1996; John, Rajpurkar et al. 2007) These properties facilitate stent placement, making the device rigid and easily maneuverable in its dry state, but once exposed to urine, the hydrogel begins to absorb and trap water in its polyanionic structure, causing it to soften and theoretically increase patient comfort. Data on encrustation and infection are less convincing, as hydrogel has been shown to both reduce (Gorman, Tunney et al. 1998) and increase encrustation and biofilm formation (Desgrandchamps, Moulinier et al. 1997). Hydrogels have been used in an attempt to soak and retain antibiotics but an *in vitro* study did not show increased efficacy of bacterial killing compared to non-antibiotic soaked hydrogel coated stents (John, Rajpurkar et al. 2007).

Glycosaminoglycan (GAG), a normal constituent of urine, is a natural inhibitor of crystallization. Other novel stent coatings include pentosan polysulfate (Zupkas, Parsons et al. 2000) (a member of the Glycosaminoglycan family a normal constituent of urine and a natural inhibitor of crystallization), phosphorylcholine (Stickler, Evans et al. 2002) (a constituent of human erythrocytes that mimics a natural lipid membrane), and polyvinyl pyrrolidone (Tunney and Gorman 2002) (a hydrophilic coating, similar to hydrogel, that absorbs water).

Attempts to reduce encrustation have included other stent coatings, such as the bacterial enzyme, oxalate decarboxylase, which has been shown to decrease encrustation in silicone discs placed in rabbit bladders.(Watterson, Cadieux et al. 2003) A novel coating of mPEG-DOPA₃, a natural constituent produced by mussels that produces strong adhesive properties, also has the ability to avoid biofouling in the environment. The polyethylene (PEG) component provides the antifouling property while the DOPA₃ provides the adherence that PEG lacks on its own. Adherence of these combined compounds on silicone disks has resulted in a strong ability to resist bacterial adherence and growth *in vitro*.(Ko 2007) Further development of this type of coating was studied *in vivo* using a rabbit *E. coli* cystitis model (Pechey, Elwood et al. 2009). This study showed that the anti-adhesive coating was successful at inhibiting bacterial adhesion and decreased the incidence of infection, however it was unable to prevent non-bacterial mediated encrustation.

Plasma deposited diamond like carbon coatings have been used to coat stents in an attempt to prevent encrustation (Laube, Kleinen et al. 2007). *In vitro* experiments have shown a 30% decrease in encrustation of these stents in artificial urine compared to the non-coated controls. Ongoing clinical trials appear to indicate a further enhancement of these results *in vivo*, however a mechanism for this needs to be elucidated. Encrustation of ureteral stents remains one of the most common problems associated with ureteral stenting and more research will need to be done for an optimal stent design which resists the deposition of bacteria, minerals and proteins.

In vascular medicine, the anticoagulant heparin has been shown to inhibit bacterial attachment to venous catheters (Ruggieri, Hanno et al. 1987; Appelgren, Ransjo et al. 1996), which has been attributed to its highly negative charge. Similarly, effects of heparin have

also been observed for ureteral stents. Riedl *et al.* (Riedl, Witkowski *et al.* 2002) used heparin-coated and uncoated polyurethane ureteral stents and inserted them into obstructed ureters with indwelling times between 2 and 6 weeks. Electron microscopy showed that the uncoated control stents were covered with amorphous anorganic deposits and bacterial biofilms as early as 2 weeks following stent insertion, while the heparin-coated stents remained unaffected by encrustation following 6 weeks of indwelling time. Cauda *et al.* (Cauda, Cauda *et al.* 2008) performed a long term study involving patients with bilateral ureteral obstructions treated via the insertion of a heparin-coated stent into one ureter, and an uncoated control stent into the other ureter. Overall, the uncoated control stents were found to be encrusted with amorphous, crystalline inorganic deposits and bacterial biofilm as early as 1 month post-insertion, while the heparin-coated stents remained visibly free of encrustation as long as 10 months post-insertion. Biofilm encrustation was evident only on the external surface of the coated stent after 1 year of being in place. Heparin coated ureteral stents (Radiance Stent, Cook Urological) were tested in an *in vitro* model of infected urine and did not display any reduction in bacterial adherence compared to control stents (Lange, Elwood *et al.* 2009). These preliminary results are somewhat promising, but clinical trials involving a larger number of patients are needed to ensure that heparin coating of stents is effective across a broader patient range.

8. Drug eluting stents

The most serious complications of long term stenting involve infection triggered by bacterial adherence and biofilm formation on the surfaces of stents as well as patient discomfort due to stent placement. Much research has gone into the prevention of infection, and the most promising results have come from drug eluting stents. Triclosan is an antimicrobial used in many products including soap, surgical scrub, toothpaste, and mouthwash. It inhibits the highly conserved bacterial enoyl-ACP reductase, which is responsible for fatty acid synthesis and cell growth. Cadieux *et al.* reported that, compared to control stents, triclosan-loaded stents implanted in rabbit bladders infected with *Proteus mirabilis* were associated with significantly fewer urinary tract infections. (Cadieux, Chew *et al.* 2006) Chew *et al.* have shown that bacterial adherence to triclosan eluting stents is markedly reduced compared to regular stents. (Chew, Cadieux *et al.* 2006) These studies indicate that human clinical trials involving these stents are warranted.

Ureteral stents may also be loaded with pharmaceuticals to aid patient comfort, and to prevent encrustation. Irritative and painful stent symptoms have traditionally been managed with oral medications such as anticholinergics and analgesics, or even by stent removal. Drug-eluting stents release a medication that acts locally on the bladder to decrease irritation and pain. In an attempt to determine which medication might improve stent-related symptoms, Beiko *et al.* intravesically instilled 3 different medications into the bladder of 40 patients who received a ureteral stent at the time of shockwave lithotripsy. (Beiko, Watterson *et al.* 2004) Intravesical ketorolac significantly reduced flank pain scores following stent insertion compared to lidocaine or oxybutynin following SWL. A ketorolac-eluting ureteral stent was designed and shown to produce the highest levels of ketorolac in the ureteral tissues in a porcine model (Chew, Davoudi *et al.* 2010). The levels of ketorolac in the ureter were 11 fold of that found in the serum thereby reducing potential systemic side effects while delivering medication directly to the target area. The stent was biocompatible and systemic levels of ketorolac were negligible. A double-blinded prospective randomized controlled trial comparing ketorolac-eluting ureteral stents to

controls showed no difference in pain scores except in young males who had less symptoms with the ketorolac eluting stent (Krambeck, Walsh et al. 2010).

Liatsikos *et al* have tested paclitaxel eluting metal stents in the pig ureter to examine the tissue effects and stricture formation. (Liatsikos, Karnabatidis et al. 2007) Paclitaxel eluting stents produced less ureteral inflammation and hyperplasia of the surrounding tissue compared to the bare metal stents. Ureteral patency was lost in the control stents and maintained by the Paclitaxel eluting stents. These studies were carried out over a 21 day period and require further validation via long term animal trials.

Stent encrustation worsens with increased indwelling time and concurrent infection with urease-producing organisms. Oxalate is normally broken down in the gastrointestinal tract by the enzyme oxalate decarboxylase, which is found in a commensal organism *Oxalobacter formigenes*. Oxalate that escapes degradation and fecal excretion is absorbed into the bloodstream and filtered in the kidneys where, under certain conditions, it can combine with calcium to form calcium oxalate stones. Watterson *et al.* coated silicone disks with oxalate decarboxylase and implanted these into rabbit bladders. (Watterson, Cadieux et al. 2003) After 30 days, the oxalate decarboxylase-coated disks were significantly less encrusted than control disks. Coating ureteral stents with such an enzyme could theoretically prevent encrustation as the stent would elute an enzyme to degrade urinary oxalate.

9. Identifying potential targets in stent design

When considering the design of new indwelling ureteral devices such as stents or catheters, the sequential steps triggering a given side effect should be taken into consideration, however this has been complicated by the complexity of mechanisms involved. Rational drug design hypothesizes that the alteration of a biological target has therapeutic value and forms the basis for the invention of new medications predicated on the identification and knowledge of a specific biological target. The first step involves turning to basic science and considering the molecular and biochemical pathways involved in the condition to identify specific targets for drug design. Once a target has been identified, its molecular structure is determined and a suitable drug that will alter it in a favorable manner is designed. Usually the target is a key molecule in a metabolic or signaling pathway specific to a disease condition or pathology (Mandal, Moudgil et al. 2009).

We believe that the same principals can also be applied to the design of ureteral stents, as the current stent designs have failed to live up to their expectations in the complex environment of the urinary tract. Given the fact that the mechanisms causing stent symptoms are unknown makes it difficult to identify a key target in the context of rational drug design to relieve patient symptoms. The identification of such a target in the urinary tract would be beneficial, as it will allow for the reduction or elimination of stent symptoms by targeting a single mechanism. However, in order for that to become a possibility, key steps in the mechanisms surrounding stent-related symptoms need to be identified to allow for their inhibition.

Although identifying a single receptor or enzyme target in the development of stent encrustation and infection is unlikely, a more solid understanding of the mechanism involved in this process is required. Several processes occur following stent insertion and the cumulative effect can result in stent associated symptoms suffered by the patient. It has been well documented that a urinary conditioning film deposits on the stent surface shortly following device insertion that consists of urinary components (Tieszer, Reid et al. 1998).

These components are believed to facilitate bacterial adhesion leading to bacterial colonization, proliferation, and biofilm formation with subsequent infection. Once a biofilm has formed, this environment facilitates recurrent infection and eradication of bacteria is difficult. Bacteria embedded within the biofilm change to a low metabolic state and undergo a low replication rate, thus rendering antibiotics (which are most effective against bacteria in high metabolic states and undergoing replication) ineffective. In many cases, embedded bacteria are also protected since antibiotics cannot penetrate the biofilm and the protecting exopolysaccharide layer excreted by the bacteria onto its surface. Thirdly, bacteria can upregulate resistance genes once inside the biofilm (Lewis 2005).

Aside from biofilm formation and infection, another symptom associated with patient morbidity caused by indwelling ureteral stents is device encrustation. Stent encrustation can be idiopathic and caused by calcium oxalate crystals. In other instances, stent encrustation can be attributed to the presence of urease producing bacteria, which break down urinary ammonia into ammonium (thus effectively taking a hydrogen ion), which results in a rise in urinary pH and crystallization of magnesium, ammonium and phosphate ions. These crystals then adhere to the surface of the stent via the interaction with components of the conditioning film. The conditioning film on the stent surface is considered to be a great contributor to bacterial associated encrustation because it facilitates bacterial adhesion and crystal adhesion to the stent surface. In addition to this, the conditioning film has also been implicated in idiopathic encrustation (in the absence of bacteria) of the stent with calcium oxalate crystals. As such, certain conditioning film components have been proposed to be able to bind minerals from the urine, forming a nidus for crystal growth and device encrustation. To date, we have identified 3 potential targets to interrupt the sequence of events involved in the evolution of stent encrustation and infection: 1) preventing conditioning film formation, 2) preventing initial adherence and encrustation and 3) inhibition of further bacterial proliferation.

10. Current stent biomaterial design

Over the years, attempts have been made at preventing stent associated symptoms by targeting either bacterial adhesion and encrustation or inhibition of bacterial proliferation. Drug eluting technology to prevent bacterial adhesion has previously been used in a triclosan-eluting ureteral stent. Triclosan is an antimicrobial found in over 800 commercially available products such as soaps, hand scrubs, and toothpaste. This stent proved to be successful at eliminating bacterial loads *in vitro* (Chew, Cadieux et al. 2006) as well as a *Proteus mirabilis* urinary tract infection in a rabbit model (Cadieux, Chew et al. 2006), but did not show any significant differences in long term clinical trials (Cadieux, Chew et al. 2009). Similarly a heparin-coated stent was designed to prevent bacterial adhesion given the material's highly negative charge. This stent was shown to decrease encrustation in patients (Hildebrandt, Sayyad et al. 2001; Riedl, Witkowski et al. 2002; Cauda, Cauda et al. 2008), however was unable to prevent bacterial adhesion (Lange, Elwood et al. 2009). The use of diamond-like amorphous carbon as a coating on stents is a new technology that has shown some promise in terms of inhibiting encrustation (Laube, Bradenahl et al. 2006; Laube, Kleinen et al. 2007), however experiments aimed at determining its ability to inhibit bacterial adhesion is lacking. One of the drawbacks of these new technologies is the fact that they are susceptible to blockage by the deposition of the urinary conditioning film, which covers any coating and blocks elution of drugs from the stent, rendering it ineffective and promoting bacterial adhesion and encrustation via mechanisms discussed above.

11. Seeking novel targets in the pursuit of rational stent design.

Given the fact that the urinary conditioning film has been directly implicated in causing both bacterial adhesion and associated/non-associated encrustation, it becomes important to switch our focus from designing a biomaterial that inhibits direct bacterial and ion/mineral deposition to one that inhibits conditioning film components. It is important to focus on understanding this biological target further and the first step is to identify components of the conditioning film. Santin et al have previously identified human serum albumin as well as Tamm-Horsfall Protein (THP) as major conditioning film components found on four stents removed from patients (Santin, Motta et al. 1999). More recently, Canales et al have studied the conditioning films of stents removed from 27 patients, identifying hemoglobin alpha and beta chain, albumin, calgranulin B, fibrinogen beta chain, vitronectin, annexin A1, calgranulin A, fibrinogen gamma chain, and THP as the ten most common adherent components (Canales, Higgins et al. 2009). In addition, this group also hypothesized that the presence of histones likely contribute to stent encrustation given their unique net positive charge. Despite the fact that these papers have contributed to a large extent to the identification of conditioning film components, it still needs to be determined whether urinary conditioning films differ between stent types or patients, as the molecules targeted in stent design should be “universal” and need to be common between patients and stent types.

Our group has recently compared the composition of conditioning films found on certain stents from Boston Scientific (Polaris) to those on Bard stents (Inlay) after they have been removed from patients (Lange et al, unpublished data). Both of these stents differ in their biomaterials, as the Polaris stent is made of an olefinic copolymer, while the InLay stent is made of polyurethane. To date, there does not appear to be a significant difference in the conditioning film composition from patients with the same stent type or between the two different stent types, indicating that conditioning film deposition is not affected by different stent biomaterials or patients. Similar results have also been obtained by Tieszer et al, who showed via X-ray photoelectron spectroscopy that the elemental composition of conditioning film components was unaffected by stent biomaterial or patient characteristics (Tieszer, Reid et al. 1998). Our study found that the fifteen most common proteins include cytokeratins, serum albumin, hemoglobin subunits alpha and beta, THP, fibrinogen gamma chain, protein S100A9, vitronectin and apolipoprotein. Interestingly, the majority of the fifteen most commonly found proteins are binding sites for bacteria and thus facilitate bacterial adhesion and biofilm formation. In addition to this, the presence of calcium binding proteins such as the S100 proteins or THP may act as a nidus for encrustation. We found that significantly less Polaris stents contained THP and fibrinogen gamma chain compared to the InLay stent, eliminating these two proteins as potential targets. Overall these results validate specific conditioning film components as targets for future stent biomaterial design as they appear to play a role in stent associated infection and encrustation. Further analysis will have to be performed to determine whether commonalities exist between the physical characteristics of these components and whether they can be targeted to inhibit their deposition.

Our current experiments are aimed at studying the temporal deposition of urinary components onto the surface of stent pieces, as some proteins such as serum albumin are known to bind to other proteins rather than the surfaces themselves. In the context of urinary component deposition, it is possible that certain proteins with a higher affinity to

the stent surface form a base layer to which other proteins such as serum albumin attach. Such a mechanism of deposition would be favorable for the purpose of rational stent design, as the proteins forming the base layer would make excellent targets for adhesion prevention. If temporal aspects can be determined in addition to the various layers of proteins, potential targets could be identified to prevent the initiating events of encrustation and infection.

12. Conclusions

We propose that the principles used by our colleagues in pharmaceutical research in the pursuit of rational drug design can be transferred to the design of novel ureteral stent biomaterials: 1) To understand the potential targets in ureteral stent encrustation and infection and 2) Develop biomaterials to limit these processes. Current research to date has focused on the prevention of bacterial adherence and encrustation; however, we propose that research interests should shift to the initial primary steps in conditioning film formation, thus perhaps preventing the whole cascade of events from occurring. Once these processes have been more clearly defined, the pursuit of highly specific engineered biomaterials can be started. Identification of specific targets would help direct the development of new materials and hopefully succeed where previous work has failed.

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