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REVIEW

Ureteral stent technology: Drug-eluting stents and stent coatings



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Abstract Ureteral stents are commonly used following urological procedures to maintain ureteral patency. However, alongside the benefits of the device, indwelling stents frequently cause significant patient discomfort (pain, urgency, frequency) and can become encrusted and infected. The importance of these sequelae is that they are not only bothersome to the patient but can lead to significant morbidity, urinary retention, ureteral damage, recurrent infections, pyelonephritis and sepsis. When these problems occur, stent removal or replacement alongside antibiotic, analgesic and/or other symptom-modifying therapies are essential to successfully treat the patient. In an attempt to prevent such morbidity, numerous approaches have been investigated over the past several decades to modify the stent itself, thereby affecting changes locally within the urinary tract without significant systemic therapy. These strategies include changes to device design, polymeric composition, drug-elution and surface coatings. Of these, drug-elution and surface coatings are the most studied and display the most promise for advancing ureteral stent use and efficacy. This article reviews these two strategies in detail to determine their clinical potential and guide future research in the area.

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1. Introduction

Ureteral stents are widely used in urology to maintain urinary flow from the kidney to the bladder in the presence of kidney stones and other obstructing lesions including strictures and extrinsic causes. While the vast majority of these devices are placed for a relatively short amount of time (1–2 weeks), a portion of patients will require more chronic (weeks to years) of ureteral stenting. For those requiring short-term stenting, pain and discomfort caused by the device are the most common symptoms, especially during activity and urination. This is typically managed using oral nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic medications but can still result in patients presenting with moderate to severe urinary symptoms during the indwelling period. A small portion of patients may also develop stent-related infection and/or encrustation, but since the devices are only in for a short period of time, encrustation will typically be minor and infection can often be adequately dealt with using broad-spectrum antibiotics until device removal. Chronically-stented patients are more difficult to manage as they face all of the above sequelae on a continuous basis and often require new stents to be inserted immediately following the removal of any infected or encrusted device. This short turnaround time between stents enhances direct transfer of organisms from an infected device or urinary environment to the new one and once organisms securely adhere to the new device and form a biofilm, they are virtually impossible to eradicate. Even the use of high-dose antimicrobial agents alongside device replacement does not always prevent infection, as the same organism has often been cultured from the replacement stent even months later.

Question 1: Is there any other way to avoid urinary catheter-associated infection and other discomfort?

To date, no ureteral stent adequately addresses the issues of pain, discomfort, infection and encrustation associated with their use. However, numerous approaches have been employed in an attempt to do so, primarily the development of novel surface coatings and drug-elution strategies. This review focuses on these two areas of research to determine their potential in preventing stent-associated infections, encrustation and patient symptoms.

2. Stent coatings

Question 2: Surface coatings for ureteral stents typically target the prevention of infection and encrustation by inhibiting bacterial attachment and survival on the device, as well as resisting urinary crystal formation and adherence. Numerous strategies have been developed and tested, largely based upon the application of anti-adhesive (modifying surface charge, hydrophobicity and roughness) and antimicrobial (silver, antibiotics, detergents, others) compounds. What are their characteristics and what situations are they best suited for?

2.1. Heparin

Heparin is a highly-sulfated glycosaminoglycan widely used in medicine for a number of clinical indications, predominantly anticoagulation. Due to its relative safety, high negative charge and existing use as an anti-adhesive coating on blood-related tubing and devices, the molecule has been applied to urinary stents and tested for its ability to reduce biofilm formation and encrustation (Endo-Sof™, Radiance™, Cook Urological). In addition to the heparin coating, this stent possesses thermosensitive properties that allow more rigidity during placement followed by a softening once exposed to body temperature, promoting increased patient comfort. An initial study involving two patients with stents indwelling for 10 and 12 months showed no encrustation as well as no changes in the heparin layer, suggesting that it might be a useful tool for long-term urinary drainage [1]. However, a subsequent *in vitro* study by Lange et al. [2] failed to show any benefit for the heparin-coated device over controls in resisting bacterial adherence. Ultimately, further studies need to be conducted to determine whether stents with a heparin coating have true potential as long-term devices able to resist both encrustation and biofilm formation *in vivo*.

2.2. Diamond-like carbon coatings

Although the development and use of diamond-like carbon coatings (DLCs) for reduced friction and wear have been studied for decades, the first description of their application on urological devices was in 2004 by Dr. Norbert Laube's research group [3] at the University of Bonn, Germany. They applied a plasma-deposited, diamond-like amorphous carbon material to segments of both urethral catheters and ureteral stents and demonstrated preliminary efficacy in reducing encrustation and ease of insertion. Based upon its overall nanocrystalline structure, outer monomolecular layer of non-polar hydrogen atoms and thin film application, the coating is chemically inert, biocompatible, superlubricious and extremely durable. That initial work was followed by both *in vitro* and *in vivo* studies published in 2007 that demonstrated great promise in reducing patient symptoms, infections and encrustation [4,5]. The latter study involved 10 chronically-stented patients suffering from numerous underlying disorders and requiring frequent stent changes due largely to heavy encrustation. Several different types of uncoated, polyurethane Double J stents were coated and 26 devices placed for a total of almost 2500 days across this population. Overall, the results showed reduced encrustation, biofilm formation, patient symptoms and complications, and also increased physician ease in device handling, placement and removal. Unfortunately, no further studies investigating this coating strategy on urological devices have been published since. Future studies should target short-term patients to investigate whether significant decreases in infection rates can be achieved in this population.

2.3. Teflon

Another coating displaying superlubricious properties is polytetrafluoroethylene (PTFE), also known as Teflon[®]. First discovered in 1938 by Dr. Roy Plunkett while trying to develop novel chlorofluorocarbon refrigerants, the strongly hydrophobic compound has since been used as a non-stick surface and lubricant in a plethora of applications, from non-stick frying pans to lubricants, seals and insulation in rocket tanks and telescopes used by NASA. Indeed, PTFE's coefficient of friction (0.05–0.1) is one of the lowest of any known substance, behind only aluminum-magnesium-boron polymers (0.02) and rivaling those of diamond-like carbon compounds (0.05–0.2) described above. Furthermore, its resistance to van der Waals forces, commonly used by bacteria for initial surface attachment, offer promise in resisting bacterial colonization and biofilm development. While numerous *in vitro* studies conducted over the past 2 decades have shown Teflon[®]-coated surfaces to reduce protein adherence and bacterial attachment versus controls, other studies have found that some proteins and bacteria, largely those with strong hydrophobic properties, are not affected [6,7]. Chung et al. [8] tested PTFE-covered metallic stents and found them to prevent hyperplasia in comparison to non-covered devices in a canine ureter model. The covered stents were also found to be patent during both short and intermediate time frames. Ultimately, further long-term studies are required to comment on long-term patency in patients and additional work is needed to specifically evaluate urinary pathogens for their ability to colonize and cause infection on these coatings.

2.4. Hydrophilic coatings

Hydrophilic coatings have been well explored as stent coating alternatives due of course to their hydrophilic properties, which act as a deterrent to hydrophobic bacterial surfaces and encrusting deposits within the urine. Polyethylene glycol (PEG) is a commonly used hydrophilic coating due to its success as an antifouling agent, a result of its high degree of mobility and steric hindrance in chemical structure [9]. The structure of this polyether allows it to couple numerous water molecules, reducing its coefficient of friction and driving its fluid-like behavior. Research into PEG as a coating has demonstrated resistance to bacterial, protein and mammalian cell attachment [10], suggesting that PEG may be capable of resisting conditioning film development. Concerns regarding the use of PEG arise in the inability to anchor enough molecules to generate a dense coating and the prevention of its thermal, oxidative, or hydrolytic degradation during the anchoring process. To overcome these drawbacks researchers have developed novel approaches for attaching PEG to surfaces including the use of 3,4-dihydroxyphenylalanine (DOPA), a peptide mimic based on the adhesive proteins used by mussels for attachment in marine environments [11]. Through *in vitro* and *in vivo* studies DOPA conjugated PEG has proven effective; demonstrating inhibition of both conditioning film and biofilm development [12], along with a significant reduction in uropathogenic *Escherichia coli* adherence in a rabbit model of cystitis [13]. More recently,

Liu and colleagues [14] demonstrated the suitability of PEG as a coating agent in paclitaxel-eluting stents.

In 2007, John and colleagues [15] demonstrated that hydrophilic gel (hydrogel) coated stent segments did not reduce bacterial adhesion compared to controls. However, when stent segments were pre-dipped in antibiotic solutions prior to incubation with *E. coli* or *Enterococcus faecalis* on agar plates, there was significantly more growth inhibition in the hydrogel-coated groups depending on the organism and antibiotic used. For instance, the cefazolin/hydrogel coated stents produced the largest zones of bacterial growth inhibition but only displayed a short duration of activity; hydrogel/ciprofloxacin and hydrogel/gentamicin combinations showed standard inhibition zones but were found to possess longer durations of activity. Thus the coupling of hydrogel coated and drug-eluting stents may prove advantageous.

2.5. Silver

Silver has been widely used as an antimicrobial agent for centuries, from preventing food spoilage by ancient civilizations to preventing and treating wound infections, to its current use in the eyes of newborn babies immediately following delivery. One advantage of the compound is that while it exhibits broad-spectrum antimicrobial activity like several other heavy metals, it lacks the concomitant host toxicity. While precise mechanisms for all of its antimicrobial activities are still lacking, silver is known to cause bacterial membrane destabilization and to strongly bind numerous bacterial enzymes, abolishing their activity [16]. Silver-coated urethral catheters have been in use for over 20 years but their true efficacy is still a matter of much debate. Several meta-analyses comparing over 20 different studies have made a case that silver alloy (but not silver oxide) coated devices are effective in reducing overall catheter-associated UTI rates by up to 45% [16,17]. However, a recent systematic review conducted by Beattie and Taylor [18] indicated that although the collective evidence favors the use of silver-alloy urinary catheters in reducing catheter-associated UTI, it cannot make a definitive conclusion owing to the poor quality of some studies as well as their significant heterogeneity. Furthermore, Liu et al. [14] indicated that silver alloy-coated catheters might increase the risk of developing urethral strictures following robotic-assisted laparoscopic radical prostatectomy compared to uncoated controls. Collectively, the overall lack of a definitive stance on the efficacy of silver in the urinary tract, coupled with the slightly higher cost of Ag-coated catheters, has resulted largely in indifferent and inconsistent use of the devices as well as a lack of the ion's incorporation into current stent coating technologies. Future work involving silver as a constituent of stent coatings is definitely warranted, perhaps in combination with other antifouling and/or antimicrobial strategies as an additional line of defense.

2.6. Antimicrobial peptides

Antimicrobial peptides are small molecular weight proteins with broad-spectrum antimicrobial activity against bacteria, viruses and fungi. They are considered one of the most

ancient forms of the host defense system, and are noted in a wide variety of life forms ranging from insects to humans. Antimicrobial peptides are very diverse in both their structure and mechanism of action. RNAlII-inhibiting peptide (RIP) is a heptapeptide that is highly effective in the treatment of polymicrobial, as well as drug-resistant infections. In *Staphylococcus aureus*, RIP has been demonstrated to downregulate expression of genes involved in biofilm formation and toxin production; while upregulating genes involved in stress responses and inhibiting cell-to-cell communication [19–21]. RIP-coated ureteral stent segments implanted in rat bladders have been shown to reduce both adherence to the stent and survival of planktonic cells by 99% compared to uncoated controls [20]. Moreover, when the coated stent was combined with systemic administration of teicoplanin, both adherent and planktonic bacterial levels were reduced by almost 1 million fold. The theory behind this synergistic effect lies in the reduction of adhesion and biofilm formation by RIP, allowing teicoplanin to exert bactericidal effects on any cells present in the urinary tract. Additionally, a non-peptide based analog with similar effects has been discovered by researchers at Tufts University [22].

Tachyplesin III is another antimicrobial peptide that has been thoroughly studied. Originally isolated from hemolymph of Southeast Asian horseshoe crabs, Tachyplesin III has 17 amino acids with two disulfide bridges and a cyclic β -sheet structure [23]. The antimicrobial peptide exhibits broad-spectrum activity against Gram-negative and positive bacteria, as well as fungi. In 2007, Cirioni et al. [20] demonstrated Tachyplesin III's powerful bactericidal role against multi-drug resistant isolates of *Pseudomonas aeruginosa*. In the same year, Minardi et al. [24] showed that Tachyplesin III coated ureteral stents inhibited bacterial growth by almost 1000 fold compared to uncoated stents *in vivo*, highlighting the potential of this antimicrobial as a stent coating.

Another alternative that has yet to be studied for urological applications is melamine, a synthetically derived antimicrobial peptide, that incorporates the active regions of protamine (from salmon sperm) and melittin (from bee venom) [25]. Melamine is effective against both Gram-positive and negative bacteria and has been documented to retain activity when covalently attached to contact lenses *in vitro*. Further, the peptide is not cytotoxic at active concentrations and bacteria do not appear to readily gain resistance. When tested in both guinea pig and rabbit models, melamine contact lenses were found to prevent bacterial growth [26]. As such, the use of melamine covalently linked to ureteral stents may represent an antimicrobial peptide of interest to researchers active in stent development.

3. Drug-eluting stents

As discussed earlier, the patient discomfort surrounding stent placement is a significant factor in quality of life considerations by urologists. A commonly used management strategy for stent discomfort is through oral agents; however this treatment method is associated with possible

side effects and minimal efficacy [27,28]. As such, researchers have explored the use of local drug delivery as an alternative. Research into local drug delivery methods has assessed both drug-coated and drug-eluting devices. Drug-eluting stents (DES) have been used widely in the treatment of cardiovascular disease and significant progress has been made in the past few years to evaluate the use of DES in the urinary tract.

Question 3: Regarding the prevention of device-associated urinary tract infections and reduction of patient discomfort, what viable drug-eluting stent options are available and how efficacious are they?

3.1. Triclosan

Triclosan is a broad-spectrum antimicrobial with a long (over 40 years) history of use in numerous medical and hygienic products [29]. Dependent upon the concentration used and organism targeted, triclosan can act either bacteriostatically or bactericidally. Its primary known mechanism of action is the binding and subsequent inhibition of the enoyl-acyl carrier protein reductase (Fab I), an enzyme critical for bacterial fatty acid biosynthesis. At higher (bactericidal) concentrations it is believed to also act through additional targets including membrane destabilization [30,31]. A plethora of work done in the oral cavity and on the skin over the past several decades have demonstrated a combination of strong antimicrobial and anti-inflammatory effects at both body sites, suggesting that it may exhibit similar properties in the urinary tract and potentially help reduce bacterial UTIs and their associated symptoms. Based upon this hypothesis, a ureteral stent impregnated with triclosan was developed by Boston Scientific Corporation (BSCI) and assessed both *in vitro* and *in vivo* for its ability to inhibit bacterial survival, biofilm formation and infection development associated with the device. Firstly, Chew et al. [32] demonstrated significant antimicrobial effects *in vitro* for both the device and its eluate against numerous uropathogens including *Klebsiella pneumoniae*, *E. coli*, *Proteus mirabilis* and *S. aureus*. *E. faecalis* and *P. aeruginosa* were already known to display partial and complete resistance to triclosan, respectively, and the same result was found in the study. This work was followed by an *in vivo* rabbit study where triclosan-eluting stent curls were able to clear instilled *P. mirabilis* infections in over half of the animals tested within 7 days compared to none of the controls [33]. Following these initial successes, additional *in vitro* studies showed that triclosan could reduce pro-inflammatory cytokine expression triggered by bacterial challenge or mechanical disruption using bladder and kidney cell models, and showed that triclosan worked synergistically with numerous clinically-relevant antibiotics [34–36]. However, two clinical trials that were conducted involving both acute and chronically-stented patients were unable to demonstrate significant clinical benefits to the device over controls [37,38]. In the chronic study, subjects harbored a control stent for 3 months followed by the triclosan-eluting device. The triclosan group showed no improvement in device colonization or urine culturing despite a significant

reduction in antibiotic usage compared to controls. The acute study was a prospective randomized trial investigating the capacity of triclosan stents to reduce stent-associated infections and biofilm formation in patients stented for 1–2 weeks. Although no significant differences in bacteriological parameters were observed between the groups, the triclosan group showed significant reductions in several common ureteral-stent-related symptoms. Overall, it presently remains unclear as to whether triclosan has any role in urology in preventing biofilm formation and stent-related infections. However, the anti-inflammatory effects observed both *in vitro* and *in vivo* alongside its demonstrated synergism with other antimicrobials suggest that it could be combined with other coating strategies to create a stent that would potentially reduce infection and ease patient discomfort caused by the device.

3.2. Alternative antimicrobials

Researchers at the M.D. Anderson Cancer Center developed a technique of loading a urinary catheter with Gendine, a novel antiseptic dye consisting of Gentian violet and chlorhexidine [39]. Gendine-coated silicone urinary catheters were then found to have significantly less adhesion and colonization by various Gram-positive and negative bacteria compared to the uncoated catheter *in vitro*. Further, *in vivo* studies demonstrated the Gendine-coated catheters were more effective at preventing device-associated infection. More recently, Cirioni et al. [40] explored the interaction of systemic amikacin with a clarithromycin-eluting stent. Results indicated that this combination worked synergistically *in vivo* to prevent device-associated biofilm formation by *P. aeruginosa*. A further line of research involves the combination of protamine sulphate (PS), an antimicrobial peptide, and chlorhexidine (CHX) in a catheter coating [41]. Early work by researchers demonstrated synergy between PS and CHX, particularly against *E. coli*. Moreover, CHX and PS coated devices provided decreased colonization *in vitro* and increased durability against both Gram-negative and positive pathogens. *In vivo*, the coated devices were found to have reduced *E. coli* colonization and device-associated infection. Given the success of these coatings on catheters (Gendine and CHX and PS) and combination therapies further *in vivo* studies are required to validate their efficacy and safety.

3.3. Ketorolac

Ketorolac is a NSAID that is widely used for postoperative pain in many surgical areas. Beiko et al. [42] first explored the use of ketorolac as a local therapy agent within the urinary tract in 2004. This double-blind randomized trial assessed the safety and efficacy of intravesical instillation of numerous agents in reducing ureteral stent-associated discomfort in patients requiring a stent following extracorporeal shockwave lithotripsy. Of the three agents assessed (ketorolac, oxybutynin, and alkalinized lidocaine) ketorolac was found to be the most effective agent in reducing stent-associated discomfort. However, the reduction in patient discomfort was only notable within the

first hour, and there was no significant difference in pain between the ketorolac treatment and control group at further time points. In 2010, Chew et al. [43] evaluated the safety of ketorolac-eluting stents in a porcine model. In this study control, 15%, 13%, or 7% ketorolac-loaded stents were placed transurethrally and ketorolac levels were measured in various tissues. Results indicated the ketorolac-eluting stent was safe as no adverse events, gastric ulcerations or internal organ abnormalities were noted in any of the ketorolac-stent groups. Additionally the majority of ketorolac was released within the first 30 days. The efficacy of the ketorolac-eluting stent was then assessed in a prospective, multicenter, randomized, double-blind clinical trial. At completion the study enrolled 276 participants across 14 centers throughout the United States [44]. The study was able to corroborate the safety results of the aforementioned study, while noting a 49% increase in patients lowering or eliminating their pain medication in the ketorolac-eluting stent cohort. Conversely, the ketorolac-eluting stent did not demonstrate a clear advantage in reduction of the number of unscheduled physician contacts, early stent removal, pain medication change or patient assessed pain; however, trends were notable in subset analyses. Most notably, men and patients under the age of 45 required less pain medication in the treatment group. Given that other research teams have documented age as a factor in ureteral stent pain [45], mainly that younger patients experience more pain, a decrease in pain within this age group may be critical. While the study incorporated the use of a validated visual analog pain scoring system it did not include the use of the ureteric stent symptom questionnaire (USSQ), the only validated condition specific questionnaire [46]. The authors accounted for this lack as the USSQ is designed to assess patient outcome at 1 month; patients within this trial were stented for 4–10 days, making the USSQ not practical. However, as pain is a subjective quality, no conclusions can be accurately drawn from this study without further assessment on the ketorolac-eluting stents effect on quality of life.

3.4. Paclitaxel

Bare metal stents and metal drug-eluting stents have been used extensively in the treatment of cardiovascular disease with much success; recently they have also been applied to many urological conditions. An example of this is the work by Liatsikos and colleagues [47] that assessed the use of paclitaxel-eluting metal mesh stents within the pig ureter. Paclitaxel is an anticancer agent that promotes polymerization of tubulin while inhibiting the disassembly of microtubules; therefore disrupting the normal microtubule dynamics and causing cell death. Paclitaxel research also indicates the agent induces the expression of tumor necrosis factor- α (TNF- α) and has an anti-proliferative effect on bladder urothelium [48,49]. Earlier work also explored the use of a paclitaxel-eluting polyurethane covered stent in a canine urethral model; wherein the treatment stent was found to reduce stent related tissue hyperplasia [50]. This early data made paclitaxel an excellent candidate for incorporation into the drug-eluting ureteral stent explored by Liatsikos et al. [47]. The purpose of this study was to

identify if a paclitaxel-eluting stent would reduce stent-associated luminal occlusion within the ureter. Researchers found the paclitaxel-eluting stent caused minimal urothelial hyperplasia and limited intraluminal tissue growth; furthermore there was less inflammation of surrounding tissues. Given the extensive use of paclitaxel-eluting stents in the treatment of cardiovascular disease and the early results indicated here it is recommended that further trials be conducted to better assess the efficacy of paclitaxel-eluting ureteral stents.

3.5. Zotarolimus and indomethacin

One of the most common adverse effects of a ureteral metal stent is hyperplastic reaction, thus Kallidonis and colleagues [51] sought to decrease these effects through the use of a zotarolimus-eluting stent. Zotarolimus is an anti-proliferative agent used extensively in cardiological stents. Researchers evaluated the effect of the zotarolimus-eluting ureteral stent using both porcine and rabbit animal models. In the porcine control group 7/10 ureters were completely obstructed, while no obstruction (0/10) was noted in the porcine treatment group. Furthermore, 2/6 rabbit control group ureters were occluded, while none of the treatment group ureters (0/6) were. Overall, while there was documented hyperplasia in all groups, lower amounts were associated with the zotarolimus-eluting stent.

Finally, indomethacin represents another potential candidate for use in drug-eluting ureteral stents. Early research into indomethacin, an NSAID, has demonstrated that it is possible to sustain its elution and that it exhibits strong biocompatibility [52]. Further, indomethacin-eluting stent material has been shown to reduce both monocyte chemoattractant protein-1 (MCP-1) and RANTES (regulated upon activation, normal T-cell expressed, and secreted), chemokines that regulate the recruitment of inflammatory cells to tissues during the inflammatory process [53]. Recent research from Kotsar and colleagues [54] assessed the effects of an indomethacin-eluting urethral stent in rabbits. Results from the study indicated that indomethacin is highly biocompatible in an animal model; however this represents some of the first work assessing indomethacin as a stent-eluting agent and further work is required to fine-tune its elution profile and agent dosage. Regardless, indomethacin and zotarolimus are both promising agents for potential use in ureteral drug-eluting stents; further research is required for both to ensure efficacy and safety.

4. Anti-encrustation coating

While this urinary device review has focused mostly on infection, inflammation and pain prevention, encrustation remains a major limiting factor of device usage and efficacy. Recently, Ron and colleagues [55] assessed the influence of rhenium-doped fullerene-like molybdenum disulfide (Re:IF-MoS₂) nanoparticles as a coating on the growth and attachment of *in vitro* encrustation stones on silicone catheters. Interestingly, the Re:IF-MoS₂-coating displayed a unique tendency to self-assemble into mosaic-

like arrangements, modifying the surface in such a way as to be encrustation-repellent. While the application of nanoparticle-based coatings in biology is still relatively in its infancy, they clearly represent a valid method for achieving desired structures homogeneously over a surface. This is critically important as surface imperfections are major sites where bacteria, biological molecules and crystals can attach.

5. Conclusion

Although the perfect ureteral stent does not exist, the devices continue to improve. Currently, technological innovations are focusing on the enhancement and evolution of stent design, material composition, elutable substances and surface coatings. Since the two largest hurdles to overcoming stent related infection and encrustation are the continuous deposition of host conditioning film material on the device and the potential for consistent transient entry of microorganisms into the tract, it is paramount that novel strategies work in a multi-faceted manner; that is, targeting both anti-fouling and antimicrobial properties simultaneously. Indeed, many strategies described herein were expected to yield more efficacious results based upon their success in other areas and fields, yet failed when challenged in an infectious urinary setting. Ultimately, success may lie in the development of multiple devices, each with its own clinical target, or in one device that is able to simultaneously incorporate multiple strategies that can work in synergy.

Conflicts of interest

The authors declare no conflict of interest.

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