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Current Status of Ureteral Stent Technologies: Comfort and Antimicrobial Resistance

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Abstract The placement of a ureteral stent is one of the most commonly performed urologic procedures. Indwelling ureteral stents are often accompanied by significant patient morbidity, including lower urinary tract symptoms, flank pain, and urinary tract infections. This article reviews the current state of ureteral stent technology developed to address the problem of stent discomfort and infection.

Keywords Ureteral stent · Symptoms · Stent-associated infections

Introduction

Ureteral stent insertion is one of the most common urologic procedures; however, indwelling stents are often accompanied by significant morbidity, including lower urinary tract symptoms, flank pain, hematuria, and associated urinary tract infection (UTI). This review focuses on current strategies to decrease the two most common concurrent problems, namely urinary tract symptoms and stent-related UTIs.

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Incidence of Stent-Related Symptoms

Comfort Technologies

Bothersome urinary tract symptoms such as frequency, dysuria, urgency, hematuria, and flank pain are well-recognized causes of morbidity and are very common after ureteral stent insertion. In most patients, the severity of such symptoms has a considerable negative impact on their quality of life. In addition to the well-known urinary symptoms, stents are also associated with impairment in sexual function (64%), anxiety (24%), sleep disturbance (20%–45%), and loss of days at work (45%) [1, 2]. Multiple instruments have been used to measure the prevalence and impact of stent symptoms, with the most robust being the Ureteral Stent Symptom Questionnaire (USSQ), as it is a validated and comprehensive instrument with good internal consistency [1].

Stent Modifications to Improve Comfort

The etiology of stent-related symptoms is not completely understood, and multiple theories have been suggested, including vesicoureteral reflux of urine, physical irritation of the bladder mucosa, inflammation, and smooth muscle spasm, as such multiple stent designs and modifications have been tested based on these premises.

Stent Durometer and Design

Stent "hardness" or durometer is a physical property of the material that is related to the amount of cross-linking within the biomaterial molecules. Common stent durometer values are usually between 40 and 90 A, and the transition for soft and hard stents has been arbitrarily set at 65 A. Comparison

studies with different durometers designed to improve comfort have been the subject of multiple trials, but to date evidence remains conflicting. Lennon et al. [3] reported significantly less incidence of severe symptoms with a soft stent (55 A) versus a firm stent (80 A) in a randomized trial. A confounding factor was that the firm stent was composed of polyurethane, a material known to be less biocompatible. Joshi et al. [4] compared a dual durometer polymeric stent with a standard control stent and also showed no significant difference in USSQ scores at 1 week and 4 weeks poststenting. Pryor et al. [5] compared four different 7 Fr stents (Polyurethane 98 A [Cook Medical, Inc., Bloomington, IN]; Silitek 91 A [Gyrus ACMI, Southborough, MA]; C Flex 90 A [Cook Medical, Inc., Bloomington, IN]; soft 65 A [Van-Tec, Inc., Spencer, IN]) and found no difference in symptoms or pain. Lee et al. [6] compared a variety of 6 Fr commercially available stents: Inlay (Bard, Covington, GA); Endo-Sof (Cook Medical, Inc., Bloomington, IN); Microvasive Contour (Boston Scientific Corporation, Natick, MA); Vertex (Applied Medical, Rancho Santa Margarita, CA); Surgitek Classic Double-Pigtail (Gyrus ACMI, Southborough, MA). The authors found no difference in stent symptoms on day 1 and 5; only at day 3 did the Inlay stent show a significantly decreased symptom profile.

Another approach in the quest for a more comfortable stent has been modification of the distal segment of the stent. In the largest comparison study to date, four different dual durometer stents were compared: two standard distal coil stents (Polaris, Percuflex Plus [Boston Scientific Corporation, Natick, MA]) versus two loop stents (substituting the distal coil for two 3 Fr long loops, 5 cm long in the short loop stent and 8 cm in the long loop) [7]. Loop stents (Fig. 1) incorporate a novel feature such that the stent has 70% less stent mass in the bladder than a standard coil stent. This innovation failed to show a difference in USSQ scores, pain, and pain location among the varying stents. The analysis showed that patients with the short loop stent had less analgesic intake compared with patients with a long loop stent. Of the three patients requiring hospital admission due to flank pain, all were patients with a long loop stent. The Percuflex Plus Tail stent incorporates a 7 Fr diameter regular proximal coil that gradually tapes to a 3 Fr diameter solid string tail. Dunn et al. [8] in a randomized trial reported that the tail stent decreased urinary tract symptoms overall by 21%, most notably urinary frequency, and was associated with a significantly higher incidence of dysuria and bladder/pelvic pain at 2 weeks after stent removal. Flank pain was similar when compared with a standard stent. The tail stent, however, is no longer in the market. Lumiaho et al. [9] have reported their experience with a novel dissolvable nonrefluxing stent in the canine model. Poststenting, the animals were followed for a period of 8 weeks or stent dissolution (maximum 12 weeks) with serial urography, nuclear renograms, and voiding cystograms. The investigator showed a statistically significant decrease in vesicoureteral and renal reflux compared with standard stents. However, only human trials will demonstrate if a corresponding reduction of reflux will be accompanied by a decrease in stent symptoms.

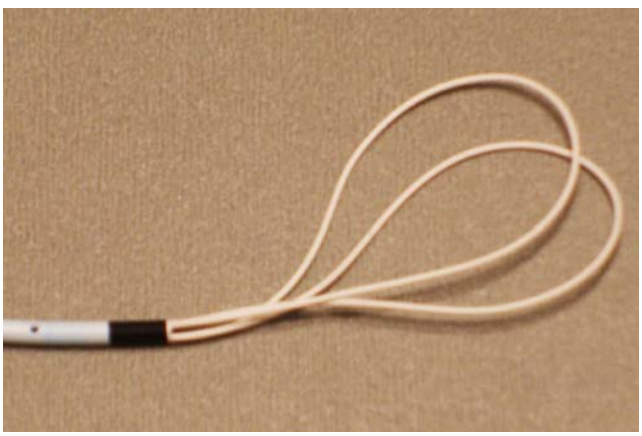

Fig. 1 A Polaris loop stent (Boston Scientific Corporation, Nantick, MA)

A further attempt at altering bothersome stent symptoms has been to modify stent diameter, in particular, decreasing overall diameter compared with the standard 6 or 7 Fr stent. Erturk et al. [10] and Chandhoke et al. [11] performed independent studies using a 4.7 Fr stent and did not show a decrease in stent-related symptoms compared with a group of patients with a 7 Fr stent. Damiano et al. [12] recently revisited the concept of decreased stent diameter, comparing a 4.8 versus 6 Fr stent; the trial again showed no difference in the quality of life or stent symptom scores.

Patient morphology as related to stent length has also been incorporated into stent length formulae in an effort to decrease stent-related symptoms. Al-Kandari et al. [13] randomly compared the impact of different stent lengths (oversized group had a proximal coil in the upper calyx and the distal coil across the midline of the bladder vs “normal” length with a coil just above the ureteropelvic junction, and distal to the ureterovesical junction). At 1 week, they found no difference in flank pain, but a highly significant difference in the severity of urgency, dysuria, and quality of life (P=0.001), favoring the normal length stent. Other reported risk factors for increased symptoms include an incomplete formation of the distal coil (frequency, hematuria, and pain), stent bladder coil crossing the midline, renal coil located in a calyx, and duration of indwelling time (relative risk increased by 1.2 for each week) [14, 15]. Design flaws of most of these risk factor reports were that symptoms were not quantified using a validated instrument [13–15].

Pharmacologic Interventions

As previously noted, despite the creativity of urologists and the medical device industry, numerous design modifications have failed to substantially address ureteral stent-related pain and urinary tract symptoms. Attention has recently turned to pharmacologic approaches to address this vexing problem. The use of pharmacologic agents to treat stent-related symptoms is a currently expanding field; two approaches have been used to date, namely, use of systemic medications and, more recently, the use of local agents delivered by way of drug-eluting biomaterials.

Oral Systemic Medications

Systemic drugs that provide general symptom relief but may not specifically target "end organ" (bladder, kidney) symptoms are currently the cornerstone of treatment for bothersome stent symptoms. A wide variety of drug families can affect the symptom pathway: analgesics, such as codeine and oxycodone, and anticholinergics, such as tolterodine and oxybutynin, have been used alone or as part of a multidrug approach. However, the cost of this type of therapy is the increase of untoward systemic side effects (ie, constipation, drowsiness, dry eyes, mouth).

Several trials have been conducted using systemic drugs to prevent or treat stent symptoms. Norris et al. [16] compared 10 mg of oxybutynin versus 200 mg of phenazopyridine versus placebo in a prospective, double-blinded, randomized trial. This investigation demonstrated that the use of either medication was not significantly better than placebo for the reduction of stent symptoms.

Smooth muscle cells of lower urinary tract, including the ureter, are densely populated with α-adrenoreceptors, which mediate contraction and relaxation; thus, the use of α-adrenoreceptor–blocking agents is a logical target for research. In two trials using oral alfuzosin, there was a statistically significant positive impact on urinary symptoms, pain, physical activity, and sleep [17, 18]. In two additional studies reporting the use of the α-receptor blocker tamsulosin, Damiano et al. [19] and Wang et al. [20•] found significantly decreased pain and urinary symptoms while improving quality of life compared with placebo controls.

Drug-Eluting Biomaterials

Local therapy was first explored by Beiko et al. [21] in a placebo-controlled trial comparing intravesical instillation of oxybutynin versus ketorolac versus lidocaine. Forty-six patients were randomly assigned to receive one of the four agents at the time of stent insertion concurrent with shock wave lithotripsy for renal calculus. The authors' work demonstrated that ketorolac and oxybutynin resulted in a significant reduction of flank pain at 1 h after stent insertion. However, this effect was transient, and there was no difference in pain after 2 h, 27 h, or 7 days. A pilot study using submucosal ropivacaine injections has been completed; however, the findings were inconclusive in regard to decreasing stent symptoms [22]. Further trials will be needed to clarify the utility of this local anesthetic.

Local drug delivery by way of drug-coated or drug-eluting stents has generated recent interest in several medical fields, including urology. Chew et al. [23] evaluated drug tissue levels, drug release profiles, and histological changes of a novel drug-eluting stent (Lexington, Boston Scientific Corporation, Nantick, MA) loaded with ketorolac (mechanically mixed with the base polymer of the stent) at three different concentrations (17%, 13%, and 15%) versus a nondrug-eluting stent and an oral ketorolac group in the porcine model. The data demonstrated the following: most of the drug was released within 30 days of stent insertion; the drug-eluting stent achieved the highest concentration of ketorolac in ureteral and bladder tissues while the systemic drug levels were substantially lower compared with the oral control group, thus the potential benefit of a drug-eluting stent is concentrated release of drug to local target tissues, increasing effectiveness and decreasing systemic side effects.

Histologically, the ketorolac stent was biocompatible and produced only mild edema and inflammation comparable to the control stents. There was a slight increase in superficial mucosal erosion in the drug-eluting stent groups, but this did not result in wall thinning or perforation, and systemic side effects were not observed in any of the experimental stent animals.

Krambeck et al. [24], in a large, double-blinded, randomized clinical trial, compared a 13% Lexington stent versus a nondrug-eluting control stent after ureteroscopy. Although in the overall cohort of patients the Lexington stent did not significantly decrease pain or related interventions (early stent removal, unscheduled visit change in pain medication), in a subset of patients (<45 years of age; male), the Lexington stent was associated with a significantly less use or no use of pain medication.

Incidence of Stent-Related Infections

UTIs are common in the general population, and the urinary tract is the most common site of nosocomial infection [25]. Approximately 80% of nosocomial UTIs are preceded by some form of urologic instrumentation, most often indwelling bladder catheterization. As the use of indwelling ureteral stents has increased, so has the frequency of

stent- associated infections. In early stages, bacterial stent colonization plays an essential role in the pathogenesis of stent-associated infections [26, 27]. In a series by Riedl et al. [28], the incidence of stent colonization and bacteriuria in patients with long-term indwelling stents due to malignancy was 100%; in patients with short-term stents, colonization was found in 69% and associated bacteriuria in 45%. Akay et al. [29] reported a lower incidence of UTIs (24%) and colonization of the proximal (31%) and distal (34%) stent segments. In females, the colonization rates were two times higher than in males (42% vs 28% distal segment and 40% vs 24% proximal segment) and a 26% versus 23% rate of UTIs. In patients with diabetes or chronic renal failure, the incidence of bacteriuria has been documented to be increased 10-fold [29]. Patients with chronic indwelling stents, diabetes, bladder outlet obstruction, or other significant comorbidities, as well as patients who are immunosuppressed (eg, the transplant population), should be monitored closely in order to minimize infectious complications [29]. The incidence of UTIs has been documented to increase with the duration of stenting: from 20 days to 30 days, the urine was found to be infected in 7.1% of patients; from 30 days to 90 days in 23.6%; and more than 90 days, urinary infection was present in 47.1% [30]. No bacterial colonization was observed in patients with stents indwelling for less than 2 weeks [29]. In an in vivo study, the bacteriuria rate was 29.9%, whereas the stent colonization rate was more than twofold higher (67.9%), theoretically because urine flow is continuous from the kidney into the bladder [30]. The most frequent pathogens cultured from the urine were *Escherichia coli* and *Staphylococcus*, and stent cultures yielded *Enterococcus sp* as the most frequent bacteria, followed by *E. coli* [30]. Lojanapiwat [31] reported a rate of stent bacterial colonization in 33%, 50%, and 54% when indwelling time was less than 4 weeks, 4–6 weeks, and more than 6 weeks, respectively. Positive urine cultures were noted in 75%, 61%, and 82% in the same time periods. *E. coli* and *Enterobacter* were the most common organisms; less frequent organisms included *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Proteus*, *Klebsiella*, *Candida*, *Diphtheroid*, and *Acinetobacter*.

E. coli is the most common bacteria associated with urinary infection, and it makes use of several virulence factors to aid in this process. Type I pili are found on most *E. coli* strains and are most prevalent on uropathogenic *E. coli*, where they contribute significantly to bladder infection [32]. The fimbrial protein fimH, which is found on various uropathogens, binds to mannose-containing molecules such as Tamm-Horsfall protein (THP), which is the most abundant protein in urine and has been found to adhere to ureteral stents [33]. Similarly, *Proteus mirabilis* and *Pseudomonas aeruginosa* have also been found to bind THP.

Biofilm Formation

The initial step in device-associated infection is the uropathogen adherence to a conditioning biofilm on a prosthetic device [34]. A conditioning film is produced by the nonspecific deposition of host urinary components on the stent surface, which occurs within minutes of device placement [35]. This film is composed of proteins, electrolytes, and other organic molecules. These substances adhere to the device, altering the surface of the biomaterial and providing receptor sites for bacterial adhesion, depending on the molecular compounds involved [36]. A number of factors are involved in the microorganism's ability to adhere to surfaces, such as electrostatic and hydrophobic interactions, ionic strength, osmolality, and urinary pH, plus its surface properties and these of the biomaterial [37]. The initial adhesion involves hydrophobic and electrostatic forces. This is followed by irreversible attachment provided by bacterial polysaccharides, which anchor the organisms to the surface. Subsequently, colonization takes place by a series of species-specific factors, such as slow migration and spreading, packing, rolling, and adhesion of pathogens. An established biofilm consists of groups of microorganisms separated by interstitial spaces that are filled with the surrounding fluid. The bacterial cells are immobilized at the solid surface and embedded in a highly hydrated, predominantly anionic, mixture of bacterial exopolysaccharides and host extracellular macromolecules [38]. Biofilms are comprised generally of three layers: a linking film that attaches to the surface of a tissue or a biomaterial; a base film of compact microorganisms; and a surface film on the outer side of which planktonic organisms can arise and spread [39]. The cells in these biofilm communities are protected from adverse environmental exposition; this isolation allows microorganisms that are apparently fully sensitive to antibiotics and antiseptics in conventional laboratory testing methods to become fully resistant in the biofilm mode in vivo [40•]. Thus, in order to achieve clinical cure, the stent should be removed once a device-related infection is established.

Salo et al. [41] found that a significant proportion of uropathogenic *E. coli* strains is capable of forming biofilms in vitro, this being most common among strains isolated from patients with pyelonephritis. Almost all the biofilm-forming strains were susceptible to antibiotics. The ability of bacteria to persist and grow in a biofilm seems to be one of the significant factors in the pathogenesis of UTIs.

Candida infections are commonly associated with biofilm formation that can occur both on mucosal surfaces and on plastic surfaces of indwelling devices. These biofilms consist of matrix-enclosed microcolonies of yeast, hyphae, and pseudohyphae arranged in a complex structure, and are resistant to antifungal agents. Biofilm represents a pheno-

typic characteristic of a *Candida* strain that is inherited and thus stable during chronic infection; data from murine infection models support the notion that enhanced in vitro biofilm is associated with prolonged disease and a worse outcome [42].

Stent Coatings to Decrease Urinary Tract Infections

Various surface modifications to stents have been developed to prevent bacterial adhesion, including silver-coated surfaces, controlled release antibiotics, and surface modifications to change hydrophobicity or functional groups having antimicrobial activity [43]. New biomaterials and coatings have been created to inhibit bacterial biofilm formation and stent encrustation.

Triclosan is a broad spectrum antimicrobial that has been in use for more than 40 years and is currently found in numerous medical products; it acts by inhibiting the activity of bacterial enoyl-acyl carrier protein reductase [44], a critical enzyme in bacterial fatty acid biosynthesis, and also by membrane destabilization. A triclosan-eluting stent was shown to decrease the number of UTIs and the device-associated bacterial load in a rabbit model of cystitis caused by *P. mirabilis* [45] and was effective against other common urological pathogens [46]; this novel stent also demonstrated a reduction in the expression of tumor necrosis factor (TNF)-α, thus reducing local inflammation [47].

Glycosaminoglycans are natural inhibitors of crystallization, as they bind to urinary components in a way that blocks crystal growth sites [48]. Heparin is a glycosaminoglycan with the highest negative charge density of any known biological molecule and is considered the strongest inhibitor of crystallization demonstrating prevention of bacterial adhesion in vascular materials and urology both in vitro and in vivo [49]. In a series comparing heparin-coated stents versus triclosan-eluting stents in an in vitro model, no decrease in bacterial adhesion was noted, showing that antibiotic- eluting stents resisted most bacteria, but not the formation of biofilms [50]. There is evidence that heparin-coated stents have less encrustation in terms of thickness and extension both on their internal and external surfaces, and less compact and uniform presence of calcium oxalate than noncoated stents, even after 10 months and 12 months indwelling [51].

Antimicrobial peptides are among the most ancient form of defense systems. Such agents can be found in a wide variety of species ranging from bacteria to insects to humans [52], and exhibit a broad spectrum of activity against a wide range of microorganisms. Tachyplesins are a group of antimicrobial peptides and tachyplesin III is a representative antimicrobial peptide, isolated from Southeast Asian horseshoe crabs. In a rat study, a coating of ureteral stents with this peptide inhibited bacterial growth up to 1,000 times compared with untreated animals [53], suggesting that peptides may become promising candidates for prevention of infections of medical devices.

Other antimicrobial substances, such as RNAIII-inhibiting peptide (RIP), have been shown to inhibit staphylococcal biofilm formation and toxin production [54] by limiting cell-to-cell communication, leading to the prevention of cell adhesion and virulence, rather than directly killing the bacteria. In a rat model with RIP-coated stents, a significant reduction in bacterial load was noted, and when teicoplanin and RIP were combined, no evidence of bacteria was detected on the stent or in the urine, showing that RIP by itself reduced bacterial load and also enhanced the effect of teicoplanin [55].

Diamond-like coating is a thermodynamically metastable state of carbon, in which diamond-like and graphite-like bonding coexist with a large fraction of sp^3 bonds. In general, they are characterized by high mechanical hardness and chemical inertness, and the properties of these films can be adapted for several applications. In an in vivo model, no crystalline biofilm formation was observed; in all cases, the coated surface remained free of encrustation [56]. Due to low friction, the coated stents could be placed and removed much more easily than the stents that patients had previously experienced, and the frequency and severity of acute symptomatic UTIs were distinctly decreased [56].

During the past several years, biofilm has been the subject of numerous studies focusing on understanding its formation and adhesion to biomaterials, its relation with device-related infections, and the development of new materials and coatings that aid in its prevention. Although some advances have been achieved both in vitro and in vivo, significant clinical advances remain elusive. Success in creating a biofilm-resistant stent may not come in the form of one specific strategy but in a combination of multiple approaches that can simultaneously target several aspects of bacterial attachment, growth, and biofilm formation [57].

Key Points

- Up to 80% of stented patients have some degree of stent-related urinary tract symptoms (dysuria, frequency, urgency, hematuria, or flank pain).
- Etiology of stent-related symptoms is not completely understood (vesicoureteral reflux of urine, physical irritation of the urothelium, inflammation, and smooth muscle spasm are some of the suggested origins).
- The use of stent durometer, diameter, or loop design modifications has failed to provide objective evidence of symptom decrease.

- Data suggest that indwelling time and stent length (crossing the bladder midline or positioning in a calyx) are risk factors for stent symptoms, whereas oral α-receptor blockers may improve symptoms.
- Stent indwelling time is the most important risk factor for stent-associated UTI (>2 weeks).
- Biofilm formation on ureteral stents follows a progressive course, from conditioning film deposition, followed by reversible and irreversible bacterial adherence, leading to stent colonization and associated UTI.
- Despite significant advances in basic science research involving biocompatibility issues and biofilm formation, infection and encrustation remain associated with the use of biomaterials in the urinary tract and therefore limit their long-term use.
- Future advances in urinary tract biomaterials and stents include biodegradables, novel coatings, drug elution, and tissue engineering.

Conclusions

Although the perfect ureteral stent does not yet exist, technological innovations in this field have led to multiple new designs and materials to further decrease the incidence of stent-related complications. Advances in the field, especially in drug-eluting stents, hold considerable promise. In the future this technology has the potential for expansion into other urological disorders.

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