International Journal of
Health Systems and Medical Science

ISSN: 2833-7433
Volume 1 | No 5 | Nov-2022

The Problem of Encrustation of Ureteral Stents and Ways to Solve It

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Abstract: Installation of a ureteral stent is an integral part of many urological operations. The advantages of stenting include low traumatic drainage, the absence of external drainage in the patient, reducing the risk of infectious complications and improving the patient's quality of life. However, the method is not without its drawbacks, in particular, stent encrustation and infection development is possible.

Keywords: ureteral stent, encrustation, biofilm, urolithiasis, bacteriuria.

Introduction: The use of catheters to provide drainage of hollow organs has long been widely used in various branches of medicine, including urology. The task of ensuring the passage of urine through the upper urinary tract is effectively solved by installing a stent (internal drainage) or a nephrostomy (external drainage).The reason for installing a ureteral stent is reconstructive plastic surgery on the ureter and ureteropelvic segment, endoscopic interventions in the treatment of urolithiasis. Up to 60% of interventions for the removal of stones in the ureter and up to 80% of interventions for the elimination of stones from the kidney end with the installation of a stent [1]. Stenting reduces the risk of ureteral obstruction in the postoperative period, ensures the passage of calculus fragments. In addition, stents contribute to the healing of mucosal damage caused by surgery [2]. Regardless of the timing of drainage, various complications may develop, from less significant ones (suprapubic pain, hematuria, dysuria, urgency) to more severe ones (vesicoureteral reflux, stent migration), but the most dangerous are stent encrustation and the formation of biofilms on its surface [3]. Ureteral stents, being foreign objects, become potential foci of infection. Infection can vary from subclinical carriage to septic complications followed by death. More than 65% of bacterial infections that caused long-term hospitalization of a patient in a hospital are caused by biofilms that have formed on medical instruments, catheters, and drains [4]. The main problem is the increased survival of bacteria in biofilms in the presence of aggressive substances, immune defense factors and antimicrobials. In particular, biofilms were able to withstand concentrations of antibiotics 100-1000 times higher than therapeutic dosages that suppress single bacterial cells. Increasing antibiotic resistance and the development of bacterial biofilms are major challenges in the treatment of urinary tract infections [5]. Infection can increase postoperative hospital stay, readmission rates, and the number of antimicrobials used. All this is sharply reflected in the increase in the number and cost of used medical resources [6].

Purpose of The Study: This review reflects the main aspects associated with the development of encrustation and the formation of biofilms on the surface of the ureteral stent, as well as some of the existing methods for the prevention and control of these complications.

Materials And Methods: When writing the review, the scientific and medical literature was studied in the databases Pubmed, Web of Sience, Science Direct, Scopus, Cyberleninka, elibrary, BRMMC and others for the period from 2015 to 2021 for the following keywords: ureteral stent, encrustation, biofilm, urolithiasis, bacteriuria. More than 100 scientific publications were found, an analysis of 24

scientific papers was made that most fully corresponds to the subject of the article. 16 works formed the basis of the first part of the review.

Results: Mechanisms of drainage encrustation and biofilm formation on their surface. Drainage catheters have an excellent surface for the formation of crystalline deposits as well as the attachment of microorganisms [7]. According to a study of 300 removed stents, a correlation was established between the frequency of their obstruction and the duration of drainage. Lumen obstruction was detected in 155 (47%) stents, and its incidence was 26.8% when the stent was in the ureter for 6 weeks, 56.9% - from 6 to 12 weeks, and 75.9% - more than 12 weeks . Thus, the average period of stay of stents before the development of intraluminal obstruction was 72 days [8]. Often, due to the formation of calculi at the renal and vesical ends of the stent, multi-stage percutaneous and transurethral lithotripsy is performed [9]. Under conditions of direct urine flow, the initial stage is the formation of a conditioning film of salt crystals and organic components deposited on the stent surface, which provide the formation of receptor sites necessary for bacterial attachment. Two studies examined the conditioning film components found on the surface of inlaid and unencrusted stents [10, 11]. The researchers identified more than 300 unique proteins on the surface of these stents, such as Igκ, IgHG1, α1 antitrypsin, and histones H2b and H3a, which were most strongly associated with stent encrustation. The authors suggested that their net positive charge could attract negatively charged crystals and stimulate encrustation [10, 11]. The authors of another study proposed a different mechanism by observing that the films formed on the surface of the stent contained calcium-binding proteins, including uromodulin and S-100 proteins. These proteins allow calcium-containing crystals to attach directly to stent surfaces [12]. First, there is a reversible primary attachment of microorganisms to the surface (adhesion, sorption) from the environment. Non-specific adhesion of microorganisms occurs through hydrophobic and hydrophilic interactions and/or electrostatic forces. Nonspecific attachment of microorganisms to the uroepithelium is largely reversible. At the stage of final (irreversible) attachment, microbes secrete extracellular polymers that provide strong adhesion. Specific adhesion is realized through molecular interactions between microbial adhesins and receptors formed on the surface of the stent. Adhesins are specific macromolecular complexes of microbial cells that are part of bacterial pili or surface structures of the cell wall, with the help of which the pathogen is fixed on the catheter surface [13, 14]. The biofilm, as a community of microorganisms, forms a single genetic system in the form of plasmids — mobile circular low molecular weight DNA that carry the behavioral code for the members of the biofilm, which determine their trophic, energy and other relationships between themselves and the environment — in particular, an immunocompetent organism. The latter is defined as the social behavior of microorganisms - the so-called "quorumsensing" ("quorum sensing"). This mechanism allows bacteria to act collectively, much like cells in a multicellular organism. Quorum sensing allows bacteria to exchange information using specialized chemical molecules [15]. Bacteria as a result of their vital activity produce organic substances on the surface of the stent, form even more receptors for salt precipitation. In particular, they produce urease, which catalyzes the hydrolysis of urea to ammonia and carbon dioxide, which causes the urine pH to rise to 8-9. Alkalinization of the medium initiates the precipitation of poorly soluble salts of calcium, magnesium, and struvite, which in turn leads to encrustation of the stent. Thus, a vicious circle is closed, in which the factors leading to stent encrustation and the formation of a biofilm on its surface mutually determine and mutually burden each other [16].

The choice of material for the manufacture of a stent as a factor in the prevention of complications.

The choice of material for the manufacture of a stent as a factor in the prevention of complications. Depending on the material of manufacture, ureteral stents can be divided into two groups: metal and polymer. The advantages of the former include high torsional rigidity, which ensures the maintenance of the lumen of the stented organ under compression, corrosion resistance, which reduces the risk of metallosis as a result of metal resorption by surrounding tissues, thermal stability during implantation, and the ability to balloon dilatation with a diameter 2-3 times greater than similar indicators of polymer stents [17, 18]. Polymeric materials are more bioinert. The negative

aspects are a high risk of migration, a higher likelihood of developing irritative symptoms [19]. The complexity of the processes of encrustation and biofilm formation is also illustrated by the fact that, despite the use of various materials with different physical characteristics, none of them is resistant to the deposition of crystals and microorganisms [20]. The idea of achieving optimal bioinertness as a factor in preventing the development of infectious-inflammatory, adhesive, and, as a result, obstructive complications, is not new. Currently, the most common polymer compounds for the manufacture of catheters are: silicone, polyurethane and their modifications. Silicone has the best bioinertness, its disadvantages include thermal lability with loss of rigidity and a high coefficient of surface friction, which increases, on the one hand, the risk of migration and, on the other hand, causes difficulties in installation. Polyurethane is the cheapest material, but its biocompatibility leaves much to be desired, which leads to a significant increase in damage to the urothelium [21].

Application of coatings on the surface of the stent as a factor in the prevention of complications.

Application of coatings on the surface of the stent as a factor in the prevention of complications. Currently, there is a considerable amount of work on the development of stent materials and coatings that reduce the risk of bacterial adhesion and encrustation. General requirements include high biocompatibility, low friction, high resistance to biofilm formation and long service life. With respect to heparin coatings, encouraging results have been obtained. In the work of F. Cauda et al. 5 patients with bilateral ureteral obstruction underwent bilateral stenting using a heparin-coated stent and a standard polyurethane stent for 1 month. After removal, the stents were studied using scanning electron microscopy, energy dispersive spectroscopy, and microinfrared spectrophotometry. The same methods were used to examine the stents prior to placement. The thickness, extent, and composition of salt deposits on the surface of coated and uncoated stents were compared. In addition, two heparin-coated stents were examined using the same methods after 10 and 12 months of use. The results of the study showed no encrustation of stents within 10-12 months of use compared with 76% encrustation of conventional polymer stents [22]. However, later DirkLange et al. refuted these data in the experiment. Triumph stents coated with triclosan and Radiance stents coated with heparin were studied. The Polaris and Endo-Sof walls served as controls, as they formed the basis for the Triumph and Radiance stents, respectively. Each stent was divided into fragments 1 cm in size, which were subsequently incubated for a week in separate tubes containing strains of bacterial cultures: E. coli, Kl. pneumoniae, Enterococcus faecalis, St. Aureus and Ps. aeruginosa.

After 7 days of incubation, biofilms were visualized using fluorescence microscopy. As a result, only Ps. aeruginosa; while each of the cultures was found on the surface of all other stents; and there was no significant difference between the number of bacterial strains found on the surface of the Radiance and Endo-Sof stents. Heparin was previously thought to reduce stent encrustation in vivo. However, in these studies, patients were given prophylactic doses of antibiotics to sanitize urine. Thus, heparin can reduce encrustation in a sterile environment, but studies have shown that it is not effective in inhibiting bacterial adhesion and biofilm formation [23]. Triclosan-coated stents (Triumph) were developed with a similar goal of reducing the risk of urinary tract infection. Triclosan is effective against Gram-positive and Gram-negative bacteria. An animal study demonstrated a significant decrease in the production of pro-inflammatory cytokines by the urothelium, as well as a decrease in the concentration of the P. mirabilis strain [24]. In vitro studies have also demonstrated reduced adhesion of E. coli, Kl. pneumoniae and S. aureus [25]. However, two small clinical trials in patients receiving triclosan-eluting stents found no difference in biofilm formation, encrustation, or infection, but a significant reduction in irritative symptoms [26, 27]. The study of a hydrogel coating capable of absorbing water, forming a thin layer of liquid on the surface of the stent in order to prevent bacterial adhesion, was also unsuccessful. The hydrogel coating did not significantly reduce bacterial adhesion. However, it significantly increased the duration of antibacterial activity of ciprofloxacin and gentamicin, also applied to the stent surface. The peculiarity of these stents makes it possible to combine a hydrophilic matrix with a hydrophobic drug, which increases their antibacterial activity and duration of release [28]. Methoxypolyethylene glycol (mPEG) conjugated to 3,4-dihydroxyphenylalanine (DOPA), enriched with compounds

secreted by marine mussels, has demonstrated in vitro and in vivo resistance to bacterial attachment resulting in improved infection clearance compared to uncoated stents. However, this did not lead to a decrease in incrustation on the surface of the stents [29]. In 1984 J.A. Hayward et al. suggested that biomaterials coated with lipids similar to those located on the outer surface of erythrocytes would be biocompatible and therefore suitable for use in the manufacture of medical devices [30]. It has been proposed that phosphorylcholine (PC) (the main group of polar heads on the outer surface of erythrocytes) be incorporated into synthetic polymers to mimic the naturally occurring membrane lipid, dipalmitoylphosphatidylcholine (DPPC). Compounds were synthesized based on the monomer 2-methacryloyloxyethylphosphorylcholine (MPC) copolymerized with long-chain alkyl methacrylates, which had the structural and ionic properties of natural DPPC. Due to their poor mechanical properties, these polymers were not suitable as a base material for the manufacture of medical devices, but they were used as surface coatings [31]. These coatings were applied to catheters where they formed polar hydrophilic surfaces. In experiments on a laboratory catheterized bladder model, PC coatings did not reduce P. mirabilis crystalline biofilm colonization of latex or silicone catheters. In addition, no significant difference was found between the amount of calcium and magnesium salts on the surfaces of coated and uncoated catheters. In a parallel clinical study, the effectiveness of PC coatings applied to the surface of ureteral stents was evaluated using scanning electron microscopy and bacteriological analysis. Forty-four PC-coated stents, as well as 28 control stents, were placed in patients for a 12-week period. As a result, it was noted that PC-coated stents are also vulnerable to encrustation and colonization by bacterial biofilm, but to a lesser extent than conventional stents.

L. Lin et al. reported for the first time positively charged polyethyleneimine (PEI) chains applied to the surface of stents to prevent bacterial adhesion [32]. PEI is a polycationic polymer with primary, secondary and tertiary amino groups, widely used in biomedical applications due to its biocompatibility and cationic nature. It has been suggested that PEI brushes prevent bacterial adhesion due to their dynamic movement in a liquid medium. In addition, the cationic structure of PEI destroys the membrane and thus kills bacteria during contact. As a result, the double anti-adhesive and contact-killing effect showed the high efficiency of PEI-brushes deposited on polyurethane stents, both in vitro and in vivo. Cytotoxicity analysis showed that the modified stent is biocompatible [33]. However, to date, this technology is reflected in a few publications of the results of studies conducted on laboratory animals. Further research is needed. Silver coatings are another potentially effective strategy for preventing biofilm formation, given the wide spectrum of antimicrobial activity of silver, without the risk of developing resistance in microorganisms. Ionized silver released from the metal after physical contact with liquids is able to inhibit the replication of the bacterial genome. However, there are ambiguous conclusions among published studies about the antimicrobial activity of silver particles, possibly due to different methods of their purification and manufacture. Further in vitro and in vivo studies are needed. Diamond-like carbon coatings (DLC) have excellent biocompatibility. In a clinical study of 10 patients prone to stent encrustation, DLC coatings showed significantly less encrustation [34]. In 2017 M.I. Kogan et al. An experiment was carried out to compare a nanostructured coating based on amorphous carbon and atomic silver (CAg) with a coating with an alloy of titanium with a shape memory effect based on Ti-Ni-(X) and a β-titanium alloy when implanted in the bladder of white laboratory Wistar rats . Each group included 20 animals. In the groups of titanium alloys, pronounced processes of lithogenesis were noted; by the 30th day of the experiment, a calculus was found in the lumen of the bladder of animals of these groups, occupying the entire lumen of the bladder. The thickness of salt deposits was 3-5 times higher than the thickness of the implant, and their weight was 284.4±41.5% of the initial weight of the implant. No intensive stone formation was registered in the CAg group. More than 60% of the surface of stents with a nanostructured coating was free from salt deposits, the thickness of which did not exceed 100 μm, and the weight of the implant increased by 15.2±4.9% [35]. According to D.K. Riley et al., who conducted the largest randomized clinical trial in 1309 patients with silver-impregnated urinary catheters, found that silver coating was ineffective in preventing bacteriuria, and, conversely, an increased incidence of staphylococcal superinfection occurred with silver coating [36].

Conclusions: Despite the great progress in the development of new materials and coatings, the problem of encrustation and biofilm formation on the surface of catheters and internal drains is far from a final solution. However, studies aimed at finding substances with maximum bioinert properties are a promising direction for understanding and solving the problem of complications of urinary tract stenting.

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