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TOPIC PAPER

# Update on biofilm infections in the urinary tract

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**Abstract**
*Purpose* Biofilm infections have a major role in implants or devices placed in the human body. As part of the endourological development, a great variety of foreign bodies have been designed, and with the increasing number of biomaterial devices used in urology, biofilm formation and device infection is an issue of growing importance.
*Methods* A literature search was performed in the Medline database regarding biofilm formation and the role of biofilms in urogenital infections using the following items in different combinations: "biofilm," "urinary tract infection," "bacteriuria," "catheter," "stent," and "encrustation." The studies were graded using the Oxford Centre for Evidence-based Medicine classification.
*Results* The authors present an update on the mechanism of biofilm formation in the urinary tract with special emphasis on the role of biofilms in lower and upper urinary tract infections, as well as on biofilm formation on foreign bodies, such as catheters, ureteral stents, stones, implants, and artificial urinary sphincters. The authors also summarize the different methods developed to prevent biofilm formation on urinary foreign bodies.
*Conclusions* Several different approaches are being investigated for preventing biofilm formation, and some promising results have been obtained. However, an ideal method has not been developed. Future researches have to aim at identifying effective mechanisms for controlling biofilm formation and to develop antimicrobial agents effective against bacteria in biofilms.

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## Introduction

By definition, a biofilm is an accumulation of microorganisms and their extracellular products forming a structured community on a surface. Biofilm formation has a major impact on foreign bodies or devices placed in the human body. In the last decades, as part of the process of endourological development a great variety of foreign bodies have been invented, and with the steadily increasing number of biomaterial devices used in urology, biofilm formation and device infection is an issue of growing importance.

## Methods

We performed a literature search using Medline and the Cochrane Library from 1985 until February 2011, using the following items in different combinations: "biofilm," "urinary tract infection," "bacteriuria," "catheter," "stent," "encrustation." A total of 1,350 publications were identified. The identified articles were screened by title and abstract, and 95 were found to be relevant. A review of the bibliographies of the retrieved articles was performed to identify additional references. A total of 34 publications were selected in our update. The studies were rated according to the level of evidence based on the Oxford Centre for Evidence-based Medicine adaptation of the work of the Agency for Health Care Policy and Research. The manuscript was in part published originally in: Naber KG, Schaeffer AJ, Heyns CF, Matsumoto T, Shoskes DA, Bjerklund Johansen TE (eds): Urogenital Infections. European Association of Urology—International Consultation on Urological Diseases, 1st edition 2010, Arnhem, The Netherlands, ISBN:978-90-79754-41-0.

## Mechanism of biofilm formation

A biofilm is a structured community of microorganisms encapsulated within a self-developed polymeric matrix and adherent to a living or inert surface. The initial event in the formation of a biofilm is the deposition of urinary components on the biomaterial leading to the formation of a conditioning film. After insertion into the body Tamm-Horsfall glycoprotein, ions, polysaccharides, and other components diffuse toward the implant prior to the arrival of the first organisms. Many of the molecules are proteinaceous, and these proteins provide receptor sites for bacterial adhesins that facilitate adherence. Thus, the creation of a conditioning film alters the surface characteristics of implants. It is for this reason that implants with altered surface characteristics can be ineffective as mechanisms of preventing microbial attachment. The role of the conditioning film is vital as many pathogens do not have mechanisms to adhere directly onto bare implant surfaces.

The next step is the approach and attachment of microorganisms. In order for bacteria to react to a surface, they must be able to "sense" their proximity to these surfaces. Planktonic bacterial cells release protons and signaling molecules which diffuse radially away from the floating cell if not adjacent to any surface. But a higher concentration can develop close to any surface because diffusion is limited on this side. This allows the cell to sense that it is near a surface, following which it may commit to the active process of adhesion. The initial adhesion is reversible and involves hydrophobic and electrostatic forces, followed by irreversible attachment provided by bacterial polysaccharides.

The final stage is the formation of a biofilm structure. A developed biofilm consists of groups of microorganisms separated by interstitial spaces that are filled with surrounding fluid. The basic structural unit of the biofilm is the microcolony, which may be composed of 10–25% cells and 75–90% exopolysaccharide (EPS) matrix depending on the species involved. The biofilm also contains water channels which allow transporting of essential nutrients and oxygen for the growth of the cells [1]. A developed biofilm is built up of three layers:

1. linking film which attaches to the surface of tissue or biomaterials
2. base film of compact microorganisms
3. surface film as an outer layer, where planktonic organisms can be released free-floating and spreading over the surface.

## The effect of antimicrobials on bacteria in biofilm

Antimicrobial agents effective against planktonic bacteria frequently fail to eradicate bacterial biofilms. The problem is that choosing of antibiotics is based on bacterial cultures derived from planktonic bacteria which differ in behavior and in phenotypic form from bacteria in biofilm. The failure of antimicrobial agents to treat biofilms has been associated with a variety of mechanisms [2]:

– Agents often fail to penetrate the full depth of the biofilm (*extrinsic resistance*).
– Organisms in the biofilm grow more slowly; therefore, they are more resistant to antimicrobial agents that require active growth.
– Antimicrobial binding proteins are poorly expressed in these bacteria.

– Bacteria within a biofilm activate many genes that alter the cell envelope, the molecular targets, and the susceptibility to antimicrobial agents (*intrinsic resistance*).
– Bacteria in a biofilm can survive in the presence of antimicrobial agents at a concentration 1,000–1,500 times higher than the concentration needed to kill planktonic cells of the same species.

Aminoglycosides and beta-lactam antibiotics were shown to be able to prevent the formation of "young" biofilms, while fluoroquinolones are effective in case of both "young" and "older" biofilms because of their good penetrative qualities. They are present in biofilms even one or two weeks after the end of the antibiotic treatment [3, 4].

Most researchers believe that antibiotics can only slow down the progress of biofilm formation by eliminating unprotected planktonic bacteria. However, during an acute febrile phase of a biofilm infection, antimicrobial therapy is sensible and essential because the planktonic and not the biofilm bacteria are responsible for febrile reactions.

## The role of biofilms in urinary tract infections

### Chronic bacterial prostatitis

Although the classification of chronic prostatitis has been standardized, the differentiation of chronic non-bacterial from bacterial inflammation is still challenging. The prostatic ducts and acini provide safe circumstances to planktonic bacteria to multiply and induce a host response. At this point, it is still relatively easy to eradicate them. However, if the bacteria persist they can form sporadic bacterial microcolonies adherent to the epithelium of the ductal system and provoke persistent immunological stimulation and subsequent chronic inflammation (LoE 2b) [5]. The diagnosis of chronic bacterial prostatitis can be difficult as colonized bacteria will not get into the prostatic secretion or urine sample. Antimicrobial therapy eradicates the planktonic bacteria but not the adherent bacterial biofilms deep within the prostate gland.

### Intracellular bacterial communities in recurrent cystitis

The exact mechanism of bacterial adherence and survival in the urinary tract is not well understood. Uropathogenic E. coli (UPEC) pathogenesis initiates bacterial binding to superficial bladder epithelial cells, which respond to invading bacteria in part by recognizing different bacterial adhesins and lipopolysaccharide via the Toll-like receptor pathway resulting in neutrophil recruitment and influx into the bladder lumen. Interactions mediated by type-1 fimbriae with the epithelium stimulate exfoliation of superficial epithelial cells, causing many of the pathogens to be shed into the urine. Despite the inflammatory response and epithelial exfoliation, UPEC are able to maintain high titers in the bladder for several days, and in chronic infections even persist for long period of times.

A bacterial mechanism of type-1 fimbria-mediated invasion into the superficial epithelial cells apparently allows evasion of these innate defenses.

Recent studies in experimental models [6] [7], partly supported by observations in human UTI [8], suggest that bacteria initially replicate intracellularly as disorganized clusters. Subsequently, bacteria in the clusters divide without much growth presumably due to changes in genetic programs. Furthermore, the clusters become compact and organized into biofilm-like structures, termed intracellular bacterial communities (IBCs) [6]. Bacteria in the IBCs are held together by exopolymeric matrices, reminiscent of biofilm structures. At some point during this developmental process of IBCs, bacteria on the edges of IBCs become motile again and start to move away from IBCs. Bacteria can leave infected bladder cells, probably due to compromised membrane integrity. UPEC undergo such IBC cascade to increase in numbers, resulting in high bacterial titers in the bladder. In addition, bacteria in these intracellular niches can create a chronic quiescent reservoir, which can persist undetected for several months without bacteria shedding in the urine [7].

### Pyelonephritis and biofilm

Once bacteria reach the kidney, they are able to adhere to the urothelium and papillae. It was shown in animal models that bacteria could adhere in thin biofilms to the urothelium before invading the renal tissue (LeE 2b) [9]. Antimicrobial agents are more effective against these biofilms than against those on catheters [10], which may be due to the synergistic effect of antimicrobial agents and host defenses [11].

### Bacterial vaginosis

The vaginal flora of healthy women consists predominantly of Gram-positive lactobacilli. The vaginal microbiota of women with bacterial vaginosis (BV) showed a loss of *Lactobacillus* species and an increase in microbial diversity dominated by *Gardnerella vaginalis* [12].

The recurrence nature of this disease prompted the speculation that bacterial biofilms are involved in BV. Swidsinski and co-workers demonstrated the presence of bacterial biofilms on the vaginal epithelium of women with BV [13]. Furthermore, in a subsequent publication, Swidsinski and colleagues reported the resurgence of dense bacterial biofilms at 1-week post-cessation of metronidazole treatment [14]. These biofilms were comprised principally of *G. vaginalis* and

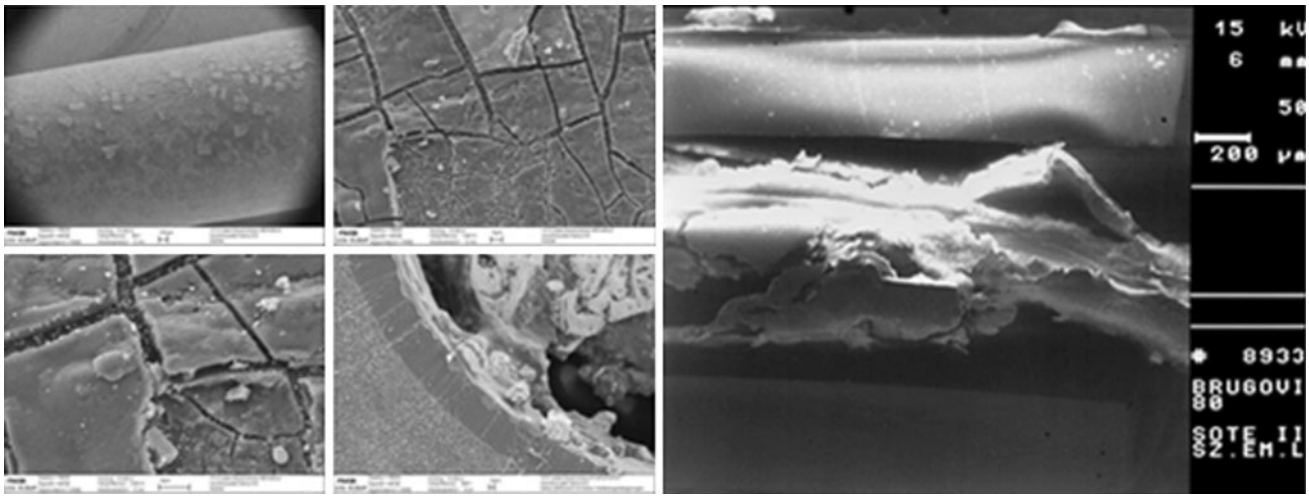


**Fig. 1** Scanning electron microscopic pictures of developed encrustations and biofilms on stents, different sections and enlargements

*Atopobium vaginae*. These data strongly support the involvement of bacterial biofilm in BV.

## Biofilm formation on foreign bodies in the urinary tract

### Indwelling urethral catheters

Urinary catheters are targets of biofilm development on their inner and outer surfaces once they are inserted (LoE 2b). By the *extraluminal route*, organisms ascend the catheter at the time of the catheter insertion. These organisms are primarily endogenous, originating from the gastrointestinal tract. They colonize the patient's perineum and ascend the urethra after catheter insertion.

Bacteria can ascend the catheter also by an *intraluminal route*, which occurs when organisms gain access to the internal lumen of the catheter. These organisms are usually introduced from exogenous sources, for instance with cross-transmission from the hands of health care personnel.

The most frequently isolated strains from catheterized patients are *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Escherichia coli*, while the strongest biofilm producers are *Proteus mirabilis*, *E. faecalis*, *Candida tropicalis*, and *Staphylococcus aureus*. Strains with strong biofilm forming ability appear to be responsible for biofilm formation in mixed-species biofilms [15].

### Ureteral stents

Bacterial biofilm can also develop on ureteral stents that are lying completely within the urinary tract (LoE 2a). It has been shown that while 68–90% of ureteral stents become colonized, the rate of bacteriuria in the same patients is only 27–30% [16, 17]. These studies confirmed the difficulty in detecting biofilm formation by using conventional laboratory procedures. Therefore, a negative urine culture does not rule out the possibility of stent colonization.

### The role of biofilms in the encrustation of catheters

A frequent clinical problem with the use of medical biomaterials in the urinary tract is the development of encrustation. When the drained urinary tract becomes infected by urease-producing bacteria such as *Proteus mirabilis*, the biofilms that form on the devices are especially problematic. The urease derived from *Proteus mirabilis* hydrolyzes urea six to ten times faster than the urease of other species. The ammonia generated by the urease elevates the pH of the urine. Under these alkaline conditions, hydroxyapatite and struvite crystals are formed and trapped in the organic matrix surrounding the cells. In the meantime, bacteria continue to form biofilm on the surfaces. Progression of these encrustations eventually blocks the catheter lumen [18] (Fig. 1).

Biofilm formation and incrustation also contribute to the limited efficacy of different antimicrobial catheter coatings, because the deposition of crystalline layer to the catheter allows bacteria to attach and multiply without having contact with the underlying protective coating [19].

### Infected urinary calculi

In case of urease-producing bacteriuria, the infection can be conjoined with the formation of struvite and calcium phosphate calculi. The infected calculi grow rapidly and provide safe environment for the bacteria adhered to the biofilm (LoE, 3) [9]. The complete removal of all stone fragments, prolonged administration of antibiotics, and metaphylaxis are the features of the most effective treatment strategy.

Artificial urinary sphincters (AUS)

Around 3% of the AUSs become infected. Avoiding the risk factors as infected urine, prolonged urinary retention, and large bladder residual can reduce this occurrence [20]. Since the parts of the device form one continuous surface, the AUS is suggested to be removed entirely as the first step to eliminate the infection. The reimplantation must be preceded by the complete treatment of the infected area [20].

Penile prostheses

Staphylococcus species, especially *Staphylococcus epidermidis*, are the most common pathogens found in penile prostheses infection. The majority of prosthesis infections occur secondary to bacterial seeding at the time of surgery. Culture positive bacteria were found in 70% of patients with clinically uninfected penile prostheses during revision surgery for mechanical malfunction, with 90% growing Staphylococcus species [21], which have an enhanced ability to produce glycocalyx biofilm. Because in most cases bacterial contamination occurs at the time of surgery, most common pathogenic organisms most likely to produce infections must be targeted when choosing prophylactic antibiotics.

To reduce the risk of device-associated infections, many modifications have been developed. Hydrophilic penile prosthesis coating has been shown to decrease bacterial adherence in vitro and in animal models [22]. Further, this coating absorbs intraoperative antibiotics that can elute into surrounding tissues to further decrease infection (LoE 2b). However, clinical data on the hydrophilic-coated penile prosthesis are limited.

The use of penile prosthesis coated with a combination of rifampin and minocycline was approved in 2001. The use of these antibiotic-coated prostheses reduced the infection rate with 58% compared to similar implants without the coating [23].

## Methods of prevention for biofilm formation in the urinary tract

Modification of the biomaterial surface

Since biofilm formation has been realized as the main problem of all implants and devices, modification of the biomaterial surface was regarded the most promising prevention strategy for bacterial biofilms.

*Antibiotic-impregnated catheters*

In a recent Cochrane Review, the authors found that antibiotic-impregnated catheters significantly lowered the rate of asymptomatic bacteriuria (ABU) compared with uncoated catheters at less than one week of catheterization in case of minocycline, rifampicin, and nitrofurazone (LoE 1a) [24]. The difference was not statistically significant at greater than one week, and the authors concluded that the data were too few to draw conclusions about long-term catheterization.

*Silver alloy coating*

According to the same Cochrane Review, silver alloy catheters significantly reduced the incidence of ABU at less than one week of catheterization (LoE Ia) [24]. Beyond one week, the estimated effect was smaller but the risk of ABU was still less in the silver alloy group. There are no available clinical trials with appropriate setting in case of long-term catheterization.

*Hydrophilic coating*

Hydrophilic-coated catheters are widely used in clean intermittent catheterization (CIC). In a prospective, comparative multi-center study, the authors found that fewer patients using hydrophilic-coated catheter (64%) for CIC experienced UTIs compared to the uncoated catheter group (82%)[25].

However, in a recent randomized controlled study, the authors did not find significant difference between hydrophilic-coated and uncoated urethral catheters in place for 6 weeks with respect to symptomatic UTIs and microbiological analysis of urine culture [26].

*Heparin*

Heparin with its strong electronegativity that repels cellular organisms is an excellent candidate for an anti-adhesive stent coating. In 1987, Ruggieri et al. showed a 90% reduction of bacterial adhesion on catheters by heparin coating [27]. Heparin-coated ureteral stents did not show any organic or anorganic deposits after being in situ for up to 6 weeks whereas significant biofilms were demonstrated in 33% of uncoated stents [28].

On the other hand, Lange and co-workers tested heparin-coated, triclosan eluting and non-eluting control ureteral stents for adherence of common uropathogens for 7 days. Heparin coating did not decrease bacterial adherence compared with uncoated controls in this in vitro setting [29].

*Gendine*

Gendine is a novel antiseptic, containing Gentian Violet and chlorhexidine. Hachen and colleagues compared the in vitro anti-adherence activities of Gendine-coated urinary catheters and uncoated controls against several

multidrug-resistant bacteria. Gendine-coated catheters reduced the biofilm adherence of all organisms compared with uncoated catheters. Scanning electron microscopy analysis showed that a biofilm layer overlaid the controls but not the Gendine-coated catheters. The authors confirmed their results in an in vivo rabbit model [30]. Although preliminary data using this coating are promising, studies in the clinical setting are not available so far to validate its efficacy.

*Triclosan*

Triclosan is an antibacterial compound that has been used in consumer products for about 40 years. Triclosan eluting stent decreased the rate of UTIs and the bacterial load in a rabbit model of cystitis caused by Proteus mirabilis [31]. In the study by Lange and co-workers cited above [29], triclosan eluting stent resisted all bacteria except *Pseudomonas* and *Enterococcus*. Mature biofilms were observed on all stents with lower viability on the triclosan eluting stent.

Use of low-energy surface acoustic waves (SAW)

The concept of using low-energy SAW is based on the hypothesis that these acoustic waves are able to disrupt the formation of biofilms if transmitted directly to indwelling medical devices by inhibiting the adhesion of planktonic bacteria to their surface. Hazan et al. devised an approach in which the acoustic waves spread from a portable actuator generating piezoelectric vibrations at frequencies ranging from 100 to 300 kHz to the catheter surface [32].

They exposed SAW-treated and control catheters to streaming fluid containing different uropathogens for 3 days. SAW treatment reduced biofilm formation, leaving catheters virtually clean of adherent microorganisms. They confirmed their result in an in vivo animal model where rabbits where catheterized with SAW-treated and control catheters for 1 week. SAW-treated catheters showed strong inhibition of bacterial biofilm compared with the controls.

In a double-blind, sham-controlled randomized study related to short-term catheterization, applying SAW releasing device to catheters prevented biofilm formation in all the catheters whereas biofilm was present in 63% of the control group [33].

A workgroup of the authors of the present article performed a prospective parallel group comparative study on the efficacy of the SAW treatment in case of long-term catheterization (8 weeks). SAW treatment lowered the rate of significant bacteriuria (33% vs. 81%), and the rate of biofilm formation was also lower in the SAW group compared with the controls [34].

## Conclusion

With the increasing number of biomaterial devices used in urology, having an effective method for preventing biofilm formation is of utmost importance. Although the mechanism of biofilm formation has been extensively researched, such ideal method has not been developed yet. Several different approaches are being investigated, and some promising results have been obtained. The future goal is to identify effective mechanisms for the prevention and control of biofilm formation and to develop antimicrobial agents effective against bacteria in biofilms. Easier methods for diagnosing biofilm infections have to be defined.

**Conflict of interest** All co-authors have seen and agree with the contents of the manuscript, and there is no financial interest to report.

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