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Biofilm and Urogenital Infections

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1. Introduction

Bacterial adherence and the growth of bacteria on solid surfaces as biofilm are both naturally occurring phenomena. Biofilms can be defined as an accumulation of microorganisms and their extracellular products forming structured communities attached to a surface. Biofilms are able to build up under natural circumstances, for instance on the urothelium or prostate stones and they can also colonize the surfaces of implanted medical devices. Biofilm infections have a major role on temporary and permanent implants or devices placed in the human body. In the process of endourological development a great variety of foreign bodies have been invented besides urethral catheters like ureter, prostatic stents, percutan nephrostomy, penile, testicular implants and artificial urinary sphincters. Many biofilms are quite harmful but others can have a positive impact, namely lining healthy intestine and female genito-urinary tract. Biofilms have significant implications for clinical pharmacology, particularly related to antibiotic resistance, drug adsorption onto and off of devices, and minimum inhibitory concentrations of drugs required for effective therapy.

2. Biofilm formation and growth

A biofilm is an aggregate of microorganisms in which cells adhere to each other and/or to a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS). Formation of a biofilm begins with the attachment of free-floating microorganisms to a surface. The first step of biofilm formation is always the deposition of a conditioning film produced by the host to the foreign body. It is followed by the attachment of microorganisms. The microbial adhesion and anchorage to the surface are made by exopolymer production. After this process their growth, multiplication and dissemination can be observed [1,2,3,4,5].

After insertion of the device into the body the material surface enters into contact with body fluids around the implant. In case of the urinary tract Tamm-Horsfall glycoprotein, various ions, polysaccharides and other components diffuse toward the implant surface from the urine within minutes [6]. Macromolecular components (serum albumin, fibrinogen, collagen, fibronectin) from these body fluids adsorb extremely fast onto the material surfaces to form a conditioning film, prior to the arrival of the first organisms [7]. The creation of a conditioning film alters the surface characteristics of implants. The role of the conditioning film is vital as many pathogens do not have mechanisms allowing them to adhere directly or strongly onto bare implant surfaces [8].

The next step in the development of a biofilm is the approach and attachment of microorganisms. The ability of microorganisms to adhere to surfaces is influenced by electrostatic and hydrophobic interactions, ionic strength, osmolality and urinary pH [9,10].

In order for bacteria to react to a surface or an interface like an air-water interface, these cells must be able to 'sense' their proximity to these surfaces. The planktonic 'free-floating' bacterial cells release both protons and signaling molecules as they move through the bulk fluid. These protons and signaling molecules must diffuse radially away from the floating cell, if not adjacent to any surface or interface. But a significantly higher concentration of either protons or signaling molecules can develop on the side of the bacterial cell close to any surface. This allows the cell to sense that it is near a surface because diffusion is limited on this side [4]. After the planktonic bacterial cell has sensed the surface, it may commit to the active process of adhesion and biofilm formation.

There is no single process or theory, which can completely describe microbial adhesion. The initial adhesion is reversible and involves hydrophobic and electrostatic forces. It is followed by irreversible attachment provided by bacterial polysaccharides which anchor the organisms to the surface. Subsequently, colonization takes by species factors, such as slow migration and spreading, rolling, packing and adhesion of the progress. A developed biofilm consists of groups of microorganisms, sometimes in mushroom-like forms, separated by interstitial spaces that are filled with the surrounding fluid [11]. The growth rates of organisms on a surface as well as the strategies used by microorganisms to spread over a surface are important for colonization. These strategies are species specific which can influence the distribution of a biofilm on a surface [12].

The final stage of microbial colonization of a surface is the formation of a biofilm structure. At this point, the microorganisms have created a microenvironment protective against many antimicrobial agents and host immune defense mechanisms. Biofilm has been described as having a heterogeneous structure with a rough surface [13]. The microcolony is actually the basic structural unit of the biofilm, similar to the tissue which is the basic unit of growth of more complex organisms. Depending on the species involved, the microcolony may be composed of 10-25% cells and 75-90% exopolysaccharide (EPS) matrix. The biofilm contains 'water channels' which allow transporting of essential nutrients and oxygen for the growth of the cells [14]. Microorganisms within the biofilm also secrete chemical signals that mediate population density-dependent gene expression, which has an important role in biofilm development [15]. In summary, the biofilm is usually built up of three layers [16]:

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

3. Antimicrobial susceptibility of bacteria in biofilm

Infections caused as a result of biofilm formation are characterized by particularly strong antibiotic and immune resistance patterns. Bacteria within the biofilms differ in behaviour and in phenotypic form from the planktonic bacteria. Antimicrobial agents are effective against planktonic bacteria and appear to clear mucosal surfaces of adherent bacterial microcolonies but frequently fail to eradicate bacterial biofilms on urological devices. The use of antibiotics is currently one of the possibilities of the prevention of biofilm formation. However, even in the presence of antibiotics bacteria can adhere, colonize and survive on implanted medical devices as has been shown for urinary catheters and ureteral stent surfaces in vitro and in vivo [17,18,19]. The problem in conventional clinical microbiology is how to treat patients in the best way when choosing antibiotics is based on bacterial cultures derived from planktonic bacterial cells which differ very much from bacteria in the biofilm mode. This can stand behind the clinical failure rate of treating chronic bacterial infection.

The failure of antimicrobial agents to treat biofilms has been associated with a variety of mechanisms (4) [18,19,20,21,22,23,24]. One mechanism of biofilm resistance to antimicrobial agents is the failure of an agent to penetrate the full depth of the biofilm (extrinsic resistance). The extracellular matrix for instance may block the penetration at the very beginning.

- One mechanism is the failure of an agent to penetrate the full depth of the biofilm (*extrinsic resistance*). The extracellular matrix may block the penetration at the very beginning.
- The organisms growing at a slower rate within the biofilm are more resistant to the effects of antimicrobial agents, which require active growth.
- Bacteria within biofilm are phenotypically so different from their planktonic counterparts that antimicrobial agents developed against the latter often fail to eradicate organisms in the biofilm. Bacteria within a biofilm activate many genes which alter the cell envelope, the molecular targets and the susceptibility to antimicrobial agents (intrinsic resistance). Current opinion is that phenotypic changes caused by a genetic switch, when approximately 65-80 proteins change, play a more important role in the protection from antimicrobial agents than the external resistance provided by the exopolysaccharide matrix.
- Bacteria within a biofilm can sense the external environment, communicate with each other and transfer genetic information and plasmids within biofilm.
- Bacteria in a biofilm can usually survive the presence of antimicrobial agents at a concentration 1000-1500 times higher than the concentration that kills planktonic cells of the same species.

According to in vitro and in vivo studies aminoglycosides and beta-lactam antibiotics can 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 [25-28].

Most researchers believe that antibiotics can only slow down the progress of biofilm formation by eliminating unprotected planktonic bacteria and reducing the metabolic activity of bacteria on the biofilm surface [23, 29-30]. However, during an acute febrile phase of a biofilm infection.

4. Indwelling urethral catheters

Due to the urinary catheter the development of bacteriuria and biofilm formation is inevitable. Urinary catheters are readily targets of biofilm development on their inner and outer surfaces once they are inserted. The long-term use of them leads to infection in most of the cases. The surface of a catheter (depending on its material) provides sufficient circumstances for bacteria to adhere and spread along in two ways. One route is when organisms ascend the catheter extraluminally by direct inoculation at the time of the catheter insertion or migrate in the mucous sheath that surrounds the external aspect of the catheter. Extraluminal organisms are primarily endogenous, originating from the gastrointestinal tract. These organisms colonize the patient's perineum and ascend the urethra after catheter insertion [13,31,32,33,34] Approximately 70% of bacteriuria in catheterized women is believed to occur through the extraluminal entry.
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 [13,32,33,35]. Adhesion of microorganisms to catheter materials depends on the hydrophobicity of the organism and catheter surface.

5. The biofilms and the encrustation and blockage of catheters

An additional problem in use of medical biomaterials in the urinary tract environment is the development of encrustation and consecutive obstruction. When the drained urinary tract becomes infected by urease producing bacteria such as *Proteus mirabilis*, the bacterial urease generates ammonia from urea and elevates the pH of the urine. Under these alkaline conditions, crystals of calcium phosphate (hydroxyapatite) and magnesium ammonium phosphate (struvite) are formed and trapped in the organic matrix surrounding the cells [20, 21, 36,37]. Progression of these encrustations eventually blocks the catheter lumen.

6. Ureteral stents

In vitro and in vivo studies confirmed the difficulty in detecting biofilm formation by using conventional laboratory procedures [38, 39]. Reid at al found that 90% of indwelling silicone double J stents were colonized by adherent bacteria, however the incidence of urinary infection detected clinically was only 27% [38]. The difficulty in detecting biofilm formation by using conventional laboratory procedures was confirmed in a large study where 237 ureteral stents were tested. It was shown that 68% of stents were actually colonized but only 30% of patients were found to have bacteriuria [39]. Therefore, a negative urine culture does not rule out the possibility of stent colonization. The study testified correlation between the length of the indwelling time and the development of infection.

7. Penile prostheses

The prosthesis-associated chronic pain due to subclinical infection is more common than clinically apparent infection (3). Staphylococcus species, especially Staphylococcus epidermidis are the most common pathogens found in penile prostheses infection (35-56%) [40], while Gram-negative enteric bacteria are liable for 20 % of infections [41,42]. S.

epidermidis was cultured in 40% of penile prosthesis removed for malfunction with no clinical evidence of infection [43]. Staphylococcal species were also found to enhance biofilm formation. These cases can be 'silent' for many years before becoming clinically evident [44] in contrast to Gram-negative bacterial infection (*Pseudomonas aeruginosa, E.coli, Serratia marcescens, and Proteus mirabilis*) being responsible for 20% of infections, which usually become manifest in a month after implantation [43].

To reduce the risk of device associated infections many modifications have been developed such as antibiotic and hydrophilic coated devices.Hydrophilic penile prosthesis coating was has been shown to decrease bacterial adherence in vitro and in animal models [45]. Antibiotic prophylaxis is desirable for the above-mentioned facts. Since the most common pathogen is the Staphylococcus epidermidis, first-generation cephalosporins, broad-spectrum penicillin should be used [46]. In cases of chronic pain, long-term administration of quinolones eased 60% of symptoms. Lack of success involves the necessity of implant removal.

8. Artificial urinary sphincters (AUS)

Around 3% of the AUS become infected and symptoms are mainly associated with the control pump device. Avoiding the risk factors as infected urine, prolonged urinary retention and large bladder residual can reduce this high occurrence [43,46]. Since the parts of the sphincter 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. This is not always achievable as many of these patients are paraplegic or have a neurogenic bladder with recurrent UTIs [43,46].

9. Infected urinary calculi

In case of urease-producing bacteriuria the infection can be conjoined with the formation of struvite and calcium phosphate calculi as described above. The infected calculi grow rapidly and provide safe environment for the bacteria adhered to the biofilm [47]. The complete removal of all stone fragments during stone operation (PCNL, URS, ±combined with ESWL), prolonged administration of antibiotics (8-10 weeks for destroying urease-producing bacteria) and metaphylaxis are the features of the most effective treatment strategy.

10. Chronic bacterial prostatitis

Although the diagnosis and classification of chronic prostatitis have been standardized, the differentiation of chronic non-bacterial from bacterial inflammation is still challenging. Being out of the sweeping effect of streaming urine the prostatic ducts and acini provides safe circumstances to planktonic bacteria to multiply rapidly and induce a host response with infiltration of acute inflammatory cells into the ducts. The ducts become engorged with infiltrate composed of dead and living bacteria as well as living and dying acute inflammatory cells, desquamated epithelial cells and cellular debris. At this point it is relatively easy to eradicate all the offending organisms which are in a 'planktonic state' with appropriate antibiotic therapy. If the bacteria persist from either clinically acute or more likely, subacute inflammation, they can form sporadic bacterial microcolonies or biofilms

adherent to the epithelium of the ductal system (2b) [48,49]. These bacteria also produce an exopolysaccharide slime or glycocalyx that envelops these adherent microcolonies. The bacteria persisting in the prostate gland within these focal biofilms can provoke persistent immunological stimulation and subsequent chronic inflammation [48]. 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. Another cause of unsuccessful treatment may be the fact that the bacteria within biofilms differ significantly from their planktonic counterparts in metabolic rate, molecular targets and expression of antimicrobial binding proteins [3,19]. There is a need in development of diagnostic tools which would be able to recognize small adherent bacterial biofilms which exist deep within the prostate gland in chronic bacterial prostatitis. New treatment regimens should be carried out in order to be able to deliver much higher antibiotic concentrations to the biofilm within the prostatic duct.

11. Intracellular bacterial biofilm-like pods in the recurrent cystitis

Entry of E. coli into the urinary tract is not well understood, although sexual intercourse is the most clearly defined predisposing factor. Presumably, a small number of E. coli from the vaginal or enteric flora are introduced into the bladder during an average incident, and it seems plausible that in most cases the innate defenses in the bladder would be able to prevent infection. However, sometimes Uropathogenic E.Coli (UPEC) clearly possess mechanisms to overcome these defenses and establish a foothold in the bladder. UPEC pathogenesis initiates with bacterial binding of superficial bladder epithelial cells. Initial colonization events activate inflammatory and apoptotic cascades in the epithelium, which is normally inert and only turns over every 6 to 12 months. Bladder epithelial cells respond to invading bacteria in part by recognizing bacterial lipopolysaccharide (LPS) via the Toll-like receptor pathway, which results in strong neutrophil influx into the bladder. In addition, interactions mediated by adhesin FimH at the tips of type 1 pili with the bladder epithelium stimulate exfoliation of superficial epithelial cells, causing many of the pathogens to be shed into the urine. Genetic programs are activated that lead to differentiation and proliferation of the underlying transitional cells in an effort to renew the exfoliated superficial epithelium. Despite the robust inflammatory response and epithelial exfoliation, UPEC are able to maintain high titers in the bladder for several days.

A bacterial mechanism of FimH-mediated invasion into the superficial cells apparently allows evasion of these innate defenses. Initially, bacteria replicate rapidly inside superficial cells as disorganized clusters. Subsequently, bacteria in the clusters divide without much growth in cell size, resulting in coccoid-shaped bacteria, presumably due to changes in genetic programs. Furthermore, the bacterial clusters became highly compact and organized into biofilm-like structures, termed intracellular bacterial communities (IBCs), inside bladder superficial cells [50]. The IBCs push the bladder superficial cell membranes outward to give a “pod” like appearance by scanning electron microscopy. Bacteria in the IBCs are held together by exopolymeric matrices, reminiscent of biofilm structures [51]. At some point during this IBC developmental process, bacteria on the edges of IBCs become elongated again, become motile and start to move away from IBCs. Bacteria can exit out of 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 in the bladder, which can persist undetected for several months without bacteria shedding in the urine [52,53,54]. Bacteria in IBCs are completely resistant to 3- and 10-day courses of antibiotics [55].

12. Biofilm and pyelonephritis

Once bacteria reach the kidney either by ascending infection or vesicoureteral reflux they are able to adhere to the urothelium and papillae. Nickel et al showed that bacteria could adhere in thin biofilms to the urothelium before invading the renal tissue with resultant pyelonephritis [47]. These bacterial biofilms are more easily eradicated by antimicrobial agents, in contrast to the biofilms on catheter surfaces [51], which may be ascribed to the effective synergistic actions of antimicrobial agents and host defenses against the biofilms on urothelium [56].

13. Biofilm in bacterial vaginosis

Bacterial vaginosis (BV) is the most common vaginal disorder in adult women [57]. Although it is a non-fatal disease, BV presents an increased risk for other more severe clinical outcomes, such as preterm birth and HIV infections [58,59]. As defined by Amsel clinical criteria, BV exhibits at least 3 of the following 4 clinical symptoms: 1) elevation of vaginal fluid pH to above 4.5; 2) detectable "fishy odor" of vaginal fluid upon addition of 10% potassium hydroxide; 3) presence of clue cells, vaginal epithelial cells covered with bacteria, in vaginal fluid; and 4) milky vaginal discharge. The vaginal flora of healthy women consists predominantly of Gram-positive lactobacilli, especially *Lactobacillus cripatus* and *Lactobacillus jensenii* [60-62]. Productions of antimicrobial proteins as well as the maintenance of acidic pH and hydrogen peroxide (H_2O_2) in the vaginal fluid by these bacteria contribute critically to the establishment of a healthy ecosystem in the vagina [61-63]. On the other hand, the vaginal microbiota of women with BV showed a loss of *Lactobacillus* species and an increase in microbial diversity dominated by *Gardnerella vaginalis* and to a lesser extend, many other bacterial organisms, including *Porphyromonas, Mobiluncus*, and *Prevotella* species [64-66].

The attempts to demonstrate *G. vaginalis* as the causative pathogen of BV have failed [67], many studies have demonstrated unequivocally that *G. vaginalis* is present in the majority of BV vaginal cultures in high numbers [64, 68, 69]. One additional complication with BV is the high recurrent rate of infection, despite of efficient resolution of infection by antibiotic treatments [70]. The recurrence nature of this disease prompted the speculation that bacterial biofilms are involved in BV. *G. vaginalis* poses the intrinsic ability to form biofilm *in vitro* [71-73]. Similar to other bacterial biofilm phenotypes, *G. vaginalis* biofilm is more resistant to antibiotic treatments compared to it planktonic counterparts [73].

Swidsinski and co-workers demonstrated the presence of bacterial biofilms on the vaginal epithelium of biopsies from women with BV [68]. These biofilm showed characteristics of dense surface bacterial biofilm and were comprised predominantly of *G. vaginalis*. Although *G. vaginalis* was also detected in biopsies from healthy women, they were present in very small numbers and infrequent. The sensitivity and specificity of FISH technique also allowed the researchers to identify the presence of Gram-positive (*Streptococcus* spp.,

Enterococcus spp. and *Staphylococcus* spp.) and Gram-negative (*Escherichia coli* and *Proteus* spp.) bacteria embedded within the *G. vaginalis* biofilms. Furthermore, in a subsequent publication, Swidsinski and colleagues reported the resurgence of dense bacterial biofilms at 1-week post-cessation of metronidazole treatment [74]. These biofilms were comprised principally of *G. vaginalis* and *Atopobium vaginae*. These clinical data strongly support the presence and involvement of bacterial biofilm in BV. It is interesting to note, however, that Saunders et al. [72] demonstrated that incubation of preformed *G. vaginalis* biofilm with certain strains of *L. reuteri* or *L. iners* resulted in the disruption of biofilm and decreased viability of *G. vaginalis*.

14. Prevention of biofilm formation in the urinary tract

The harsh and potentially fatal consequences of microbial biofilm infections generated efforts to prevent their formation, particularly on indwelling medical devices using chemical and mechanical approaches. Catheters coated with hydrogel, silver salts, and antimicrobials have been evaluated; however, they provide minimal reduction in infection incidence (75).
Antibiotic (minocycline, rifampicin, nitrofurantoin) impregnated catheters lowered the rate of asymptomatic bacteriuria compared to catheters without impregnation at less than one week but 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. [76]
Silver alloy catheters significantly reduced the incidence of asymptomatic bacteriuria at less than one week of catheterization [76]. Beyond one week the estimated effect was smaller but the risk of asymptomatic bacteriuria was still less in the silver alloy group. There are no available clinical trials with appropriate setting about the effect of silver alloy coated catheters on bacteriuria or biofilm formation in case of long-term catheterisation.
De Ridder et al found that fewer patients using hydrophilic-coated catheter (64%) for CIC experienced UTIs compared to the uncoated catheter group (82%)[77]. However, in a randomised controlled study the authors did not find significant difference between hydrophilic-coated and uncoated indwelling urethral catheters in place for 6 weeks with respect to symptomatic urinary tract infection and microbiological analysis of urine culture [78].
Heparin coated ureteral stents did not show any organic (biofilms) or anorganic (crystals) deposits after being in situ for up to 6 weeks whereas significant biofilms were demonstrated in 33% of uncoated stents [79].

15. Use of low-energy surface acoustic waves (SAW)

Biofilm formation can be prevented- or delayed- by applying low intensity nanowaves along the surfaces of an indwelling catheter. This approach opens new options for pharmacological prevention of urinary tract infections (80,81).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. demonstrated the the effectiveness of Low-Energy Surface Acoustic Waves in the prevention of biofilm formation in an animal model in vivo. They found that SAW treatment reduced biofilm formation in vitro, leaving catheters virtually clean of adherent microorganisms, irrespective of the types

of bacteria that were examined. In the animal model SAW treated catheters showed strong inhibition of bacterial biofilm compared to controls [82].
In a double blind sham controlled randomized study related to short term catheterization, applying SAW releasing device to catheters prevented biofilm formation in all of the catheters whereas biofilm was present in 63% of the control group [83].
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 catheterisation (8 weeks). SAW treatment lowered the rate of significant bacteriuria (33% vs. 81%) and the rate of biofilm formation was also significantly lower in the SAW group compared to the controls[84].

16. Conclusion

The number of biomaterial devices used in urology has been increasing permanently. Biofilm infections have a major impact on implants or devices placed in the human body. The mechanism and the different bacterial and host factors taking part in the formation of biofilms have been extensively researched in the last decades, such ideal method has not been developed yet. Antimicrobial agents are effective against planktonic bacteria and appear to clear mucosal surfaces of adherent bacterial microcolonies but frequently fail to eradicate bacterial biofilms on urological devices. Several different approaches to disease prevention are being investigated and some promising results have been obtained.

17. References

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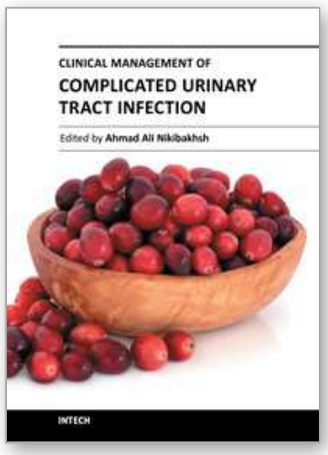

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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