Journal of Urology & Nephrology Studies
DOI: 10.32474/JUNS.2023.04.000188
ISSN: 2641-1687

Review Article

Microbiology of Catheter-Associated Urinary Tract Infections

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Received: April 21, 2023 **Published:** May 01, 2023

Abstract

The most common complication that arises following the use of urinary catheters is a microbial infection. Typically, these infections are of endogenous origin by the fact that the faecal flora of the same patient represents a potential reservoir of infectious pathogens. In hospitalized patients, in whom the faecal flora is altered by the administration of antibiotics or other antimicrobial drugs, multi-resistant microorganisms are most frequently found as the causative agents of catheter-related infections. It is important to underline that the onset of infections is facilitated by the exposure of cell surfaces to microbial adhesion as consequence of the damage often caused by the catheter to the urinary epithelium and hydrophilic glycosaminoglycan layers which represent efficacious physiological barriers able to block the adhesion of proteins and oxalate crystals to the cell surface. The microorganisms responsible for catheter-associated urinary tract infections (CAUTIs) can be either Gram-negative and Gram-positive bacteria or fungi. Anyway, the most frequent causative agent is Escherichia coli with percentages ranging between 30 and 50% in both short- and long-term catheterization. All the bacterial and fungal species involved in CAUTIS have been reported to be able to grow in sessile mode so developing as microbial biofilm more resistant to antimicrobial drugs. However, in the past few decades, promising strategies for the set up of innovative catheters refractory to microbial adhesion and biofilm formation have been developed.

Keywords: CAUTI; Gram-negative bacteria; Gram-positive bacteria; fungi; biofilm; antibiotic-resistance

Introduction

The most common complication that arises following the use of urinary catheters is a microbial infection. Typically, these infections are of endogenous origin by the fact that the faecal flora of the same patient represents a potential reservoir of infectious pathogens. In hospitalized patients, in whom the faecal flora is altered by the administration of antibiotics or other antimicrobial drugs, multi-resistant microorganisms are most frequently found as the causative agents of catheter-related infections. It is important to underline that the onset of infections is facilitated by the exposure of cell surfaces to microbial adhesion as consequence of the damage often caused by the catheter to the urinary epithelium and hydrophilic glycosaminoglycan layers which represent efficacious physiological barriers able to block the adhesion of proteins and oxalate crystals to the cell surface. The main pathways that favor the pathogenesis of urinary tract infections associated with catheters have been identified [1-3] as follows :

a) Entry and transfer of microorganisms from the urethra to the bladder at the moment of the catheter implant. Generally, under normal conditions, microorganisms introduced in this way are eliminated or in any case, kept under control by the antibacterial defense mechanisms of the bladder mucosa, the most effective of which is represented by polymorphonuclear leukocytes.

b) Access of microorganisms to the bladder through the thin layer of fluid external to the catheter, at the urethral mucosa-catheter interface, the so-called extraluminal route; such access is obviously facilitated by catheter movements. The extraluminal microorganisms are mainly endogenous, coming from the gastrointestinal tract; they colonize the patient's perineum and ascend the urethra from the very first moments following catheter insertion. It has been reported that 66% of infections of catheter-associated urinary tract is acquired extraluminally and approximately 70% of episodes of bacteriuria in catheterized women occur due to the entry of microorganisms by this route.

c) Microbial migration inside the catheter cavity, intraluminal, after that the drainage system has been contaminated; this in fact can become accessible to the microorganisms present externally when the catheter is disconnected from the drainage tube for bladder irrigation, specimen collection, or accidental causes.

It has been shown that intraluminal access is responsible for 34% of catheter-associated urinary tract Infections. Microorganisms that usually take this route come from external sources and are often the result of care and assistance activities of patients carried out by healthcare professionals with contaminated hands; is the so-called cross-contamination which accounts for up to 15% of infections arising in patient groups [4]. The European Center for Disease Prevention and Control estimated for the years 2011-2012 a total annual number of 3.2 million patients with a Hospital Acquired Infection (HAI) in 779 monitored hospitals. The estimated percentage of Urinary Tract Infections (UTIs) was 19.0%, 59.5% of cases being Catheter-Associated Urinary Tract Infections (CAUTIs).

Microorganisms involved

The microorganisms responsible for catheter-associated urinary tract infections can be either bacteria, Gram-negative and Gram-positive or fungi. However, the major culprits of nosocomial urinary tract infections are the Gram-negative bacteria and among the enteric, the most present is Escherichia coli, in association with both short- and long-term catheterizations, with percentages ranging between 30 and 50%. This finding confirms that the majority of infections are due to auto-infections and emphasizes that sources of external infections intervene only sporadically. Among the other Gram-negative bacteria, Pseudomonas aeruginosa is very frequent as well as some species capable of producing urease such as Proteus mirabilis, Morganella morganii, Klebsiella pneumoniae and Providencia stuartii. According to some authors, in urinary tract infections associated with catheters, is taking growing importance the group of "facultative Gram-negative pathogens", including genera considered in the past not very aggressive such as Providencia, Serratia, and Citrobacter [5-7]. In fact, they appear to have developed considerable antibiotic resistance over time, for which now tend to affect patients with reduced defensive capacities and favored in their diffusion from diagnostic-therapeutic instrumental manoeuvres, are particularly important in urological departments. Among the Gram-negative germs, Acinetobacter baumannii and Stenotrophomonas maltophilia are also quite often isolated. Gram-positive bacteria are certainly of minor importance as causative agents of catheter-related urinary infections, even if their isolation represents about 10% of cases. Among them the most common are Staphylococcus aureus and coagulase negative staphylococci (CNS), mainly Staphylococcus epidermidis.

Enterococcus faecalis, Bacillus subtilis and group B and D streptococci have also been sometime isolated. It is useful to add that the variety of isolated Gram-positive or Gram-negative bacteria, in most of the studies, has been closely correlated with the duration of catheterization and previous antibiotic therapy. With long-term catheterizations, polymicrobial infections caused by a wider variety of bacteria have been detected. It was observed, in these cases, that the infecting microorganisms change constantly: as new ones arrive, the previous infectious agents disappear spontaneously. In addition to the most common uropathogen, E. coli, which adheres to the urethral epithelium even in non-catheterized subjects, bacteria that tend to reside in the catheterized urinary tract for a long time are Pseudomonas spp. Proteus spp. and Providencia stuartii. In the list of microorganisms involved are also present Nocardia asteroides, Salmonella spp, Alcaligenes xylosoxidans and Mycoplasmas and Chlamidia which are increasingly emerging. In addition, Mycobacterium has sometimes been isolated in immunocompromised patients and in the same individuals it is frequent to isolate yeasts among which Candida albicans is the most common, followed by Candida glabrata and Candida tropicalis. These fungal species may be quite often isolated also from patients treated with repeated courses of antibiotics [8].

Acinetobacter spp

Acinetobacter is a non-fermentative, aerobic, ubiquitous Gram-negative bacterium found in the environment and on human skin. Of the 20 species identified over the last few years, Acinetobacter lwoffii, A. johnsonii and A. radioresistens are mainly found in humans. It is estimated that up to 25% of the population are carriers of Acinetobacter spp. at the level of the skin flora, especially in the armpits, in the groin region and in the spaces between the toes even if the percentage of carriers is higher in hospitalized patients. The most important species as an agent of hospital infection is A. baumannii (previously known as A. calcoaceticus var. anitratus). Due to severity of urinary tract infections caused by this species, it is imperative to accurately identify nosocomial isolates and test their susceptibility to antibiotics and ability to grow as biofilm [9,10].

Candida spp

Some species of the genus Candida are habitual commensals of the skin, mucous membranes and natural cavities of man. Candida is a dimorphic microorganism, i.e., endowed with a marked adaptability towards the environment in which it reproduces and is capable of differentiating itself into different forms. In conditions of moderate temperature, low pH and in the absence of inducers such as serum or N-acetylglucosamine the cells grow in the form of yeasts; the increase in temperature and pH and the addition of inducers instead stimulate filamentous growth, with the formation of pseudohyphae or real hyphae. The two forms are antigenically and chemically different and the filamentous one, endowed with invasive capacity, is the one held responsible for the pathogenic action. Several virulence mechanisms contribute to the pathogenicity of this species, including: the ability to selectively adhere to various mucous epithelia, thanks to the action of specific adhesins, the production of proteinases, the formation of hyphae and pseudohyphae and the production of phospholipases. C. albicans is the species that has the greatest ability to adhere to mucous epithelia which actively penetrates with the help of exoenzymes, causing lysis of host cells. Furthermore, C. albicans is also capable of releasing different types of toxins which can be released into the circulation reaching different organs and systems. C. albicans is the species most frequently isolated from clinical cases, followed by C. parapsilosis and other species (C. krusei, C. tropicalis, C. stellatoidea, C. pseudotropicalis) of recognized pathogenicity even if only sporadic. In the last decade, urinary catheter models of Candida albicans infection in experimental animals have been reported [11].

Citrobacter spp

Gram-negative, aerobic microorganisms belonging to the genus Citrobacter are commonly found in the environment and in the intestinal tract of both humans and some animals. The genus Citrobacter includes 11 different species of which C.freundii and C. diversus are the most significant nosocomial opportunists as etiologic agents of infections. These microorganisms are known to cause urinary tract infections, as well as intestinal and respiratory infections. The high incidence of mortality following infections by these microorganisms has been mainly associated with multi-antibiotic resistant strains.

Enterococcus spp

Enterococci are Gram-positive, facultative anaerobic, spore-forming cocci without motility organs. The genus includes at least 18 species, Enterococcus faecalis and E. faecium being the most frequently isolated in the hospital setting not only from urinary catheter-bearing patients but also in cases of bacteremia, endocarditis and meningitis, especially in immunocompromised patients. The broad spectrum of resistance against many antibacterial drugs poses serious problems in the therapy of infections supported by these microorganisms. In fact, Enterococci show a marked ability to acquire genetic material capable of conferring resistance to antibiotics, so much so that their supervening resistance to glycopeptides has led to the increasing prevalence of vancomycin-resistant enterococci. Despite their growing clinical importance, the pathogenetic mechanisms of enterococci have not yet been fully elucidated. Studies on E. faecium have shown that antibiotic resistance plays an important role in the pathogenesis of enterococcal infections. As for E. faecalis, the most important virulence factor identified appears to be cytolysin, active against a wide range of cells either prokaryotic or eukaryotic. Other contributing virulence factors so far investigated include gelatinase, protease and clumping substance [12].

Escherichia coli

Escherichia coli is the predominant, facultative gram-negative, microorganism of the bacterial flora resident in the human intestinal tract, although some strains may express factors of pathogenicity capable of causing, in some conditions, even serious pathological conditions. The virulent strains are able to colonize the epithelia of both the intestinal and urogenital tract with toxin production [13]. E. coli is the most frequent and important causative agent of urinary tract infections, being isolated in 50-85% of patients, in particular female. These infections seem to be supported by particular serotypes whose antigen configuration reflects the presence of specific adhesins, P fimbriae or pili (PAPpyelonephritis-associated-pili), which allow the adhesion of the bacterium to the surface of the mucous cells of the urinary tract, initiating the infectious process. A study in vitro has also demonstrated that its nonspecific adhesion on the epithelium of the bladder is mediated by sialic acid [14].

Klebsiella pneumoniae

Klebsielle are facultative anaerobes, provided with a capsule but without motility organs. The most important species is Klebsiella pneumoniae, a common commensal of the human upper respiratory tract. K. pneumoniae is also recognized as an important causative agent of urinary infections and septicemia in immunocompromised individuals. Most clinical isolates of K. pneumoniae exhibit a polysaccharide capsule which covers the entire surface of the bacterium, and which is generally considered an important virulence factor, since in vitro studies have shown that it plays an important role in the protection against phagocytosis. The Gram-negative opportunistic pathogen, Klebsiella pneumoniae, is responsible for causing a spectrum of community-acquired and nosocomial infections and typically infects patients with indwelling medical devices, especially urinary catheters, on which this microorganism is able to grow as a biofilm The increasingly frequent acquisition of antibiotic resistance by K. pneumoniae strains has given rise to a global spread of this multi-drug-resistant pathogen, mostly at the hospital level, and its resistance to antimicrobial agents has been reported to dramatically increases when K. pneumoniae strains grow as a biofilm [15].

Proteus mirabilis

Bacteria of the genus Proteus are Gram-negative microorganisms, facultative anaerobes, present in soil and as components of the human intestinal flora. Proteus mirabilis is responsible for most human infections and represents, after Escherichia coli, the most frequent etiologic agent of urinary infections, especially in catheterized patients. Despite the mechanisms of pathogenesis have not been fully elucidated, several virulence factors have been described which include urease, invasiveness, proteolytic enzyme production responsible for the cleavage of immunoglobulins IgG and IgA and proteins of outer membrane (OMPs). The production of urease and the consequent alkalization of urine due to ammonia production contribute to the severity of the infection damaging the renal epithelium and giving rise to the possible formation of stones due to precipitation of calcium and magnesium salts. The fact that the main inorganic constituent of stones is struvite is consistent with the pathogenesis of chronic infection due to urease-positive organisms: bacteriological analyses confirm, in fact, Proteus mirabilis as the most frequently implicated biofilm-forming microorganism in catheter encrustations [16-18]. This phenomenon is also favored by the presence of surface defects which are frequently observed in catheters.

Providencia spp

To the genus Providencia belong Gram-negative pathogens which include 5 species: Providencia alcalifaciens, P. heimbachae,

P. rettgeri, P. rustigianii, and P. stuartii. The bacteria of these species are known all as responsible for superinfections in skin burns but also as causative agents of urinary tract infections, often difficult to treat due to their insensitivity to a large number of antibacterial drugs.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a Gram-negative, non-spore forming, aerobic, non-fermenting and oxidizing bacillus belonging to the genus Pseudomonas, which includes several species commonly found in water and wet environments, some of them being involved in human pathology. P. aeruginosa is usually motile,due to the presence of a polar flagellum, although strains with multiple flagella and flagella-free strains have been also identified. The opportunism of P. aeruginosa is related to the decrease of the humoral and cellular defenses of debilitated or immunocompromised hosts, and is responsible for the onset of urinary infections, infections in burns, otitis, endocarditis, pneumonia, etc. A variety of mechanisms contribute to the virulence of P. aeruginosa : expression of adhesins, secretion of hydrolytic enzymes, release of toxins and production of biofilms [19]. P.aeruginosa infections are often difficult to treat as the bacterium exhibits a high resistance to many of the most commonly used antibiotics, but it is usually sensitive to some synthetic penicillin's (carbenicillin and ticarcillin), to the new cephalosporins (cefotaxime, ceftriaxone, etc.) and many aminoglycosides (gentamicin, tobramycin etc.)and polymyxin B.

Serratia spp

Bacteria of the genus Serratia are found more frequently in soil than in clinical samples. The genus Serratia includes six species, three of which can be isolated from man: S.marcescens, S. liquefaciens and S. rubidae. Serratia marcescens is a typical opportunistic pathogen, which can be isolated from numerous extra-intestinal infections and which, in the hospital environment, can also give rise to epidemic outbreaks involving numerous patients. Due to the low sensitivity of the bacterium to numerous antibiotics, S. marcescens infections are often very severe and usually involve patients debilitated.

Staphylococcus spp

Staphylococci are round-shaped, Gram-positive bacteria (cocci) with a diameter of about 1 μm which, when duplicating, assume the characteristic cluster arrangement due to the mode of cell division that occurs in three perpendicular planes. Non-spore-forming aerobes, devoid of motility, ferment carbohydrates and produce yellow pigments. The genus Staphylococcus includes about 30 species. Staphylococcus aureus is distinguished from other species for coagulase production, mannitol fermentation and production, in solid medium, of a yellow-gold pigment, from which it takes its name. Among the coagulase-negative staphylococci, S. epidermidis is one of the microorganisms predominant in the bacterial flora of the skin, often growing as biofilm after contamination of the inner and outer surfaces of implantable medical devices including urinary catheters [20-23]. The virulence of staphylococci, especially S. aureus and S. epidermidis, is multifactorial and it is mediated by the pathogenic action of exotoxins, exoenzymes, structural and metabolic bacterial components. Staphylococcal infections are the basis of different pathological pictures, which differ considerably depending on the site of the infectious process and its routes of diffusion (e.g contiguity, hematogenous metastatic spread, etc.).

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia is a Gram-negative, aerobic, non-spore forming microorganism, from 0.5 to 1.5 μm in size, endowed with motility due to the presence of polar flagella. S. maltophilia is generally considered an opportunistic bacterium which is ubiquitous in the environment and present in the human commensal flora but can also be isolated in ice making machines, humidifiers, liquids for hemodialysis, parenteral solutions and even antiseptic solutions, such as chlorhexidine or quaternary ammonium. The nosocomial transmission of this microorganism to patients can occur both directly from the sources described above, or through the contaminated hands of the healthcare workers, resulting in colonization of the epidermis (skin ulcers) or mucous membranes (tracheobronchial infections) or, sometimes, spread through the blood (bacteremia). The factors and mechanisms of virulence of S. maltophilia have not yet been well defined. Up to now, however, the presence of extracellular enzymes has been highlighted, such as DNase, RNase, fibrinolysin, lipase, hyaluronidase, protease and elastase, which perform presumably a role in the pathogenicity of S. maltophilia. On the other hand, its adhesion ability to polymers could in part explain why S. maltophilia has been frequently isolated in patients with implantable medical devices [24]. Concerning the well-known multi-drug resistance of this microorganism has to be reminded that the external membrane of S. maltophilia is very poorly permeable to antibiotics.

Microbial biofilm and other factors favoring CAUTI's

Once the organisms have gained access to the bladder, different factors can contribute to or facilitate the onset of microbial infection. Some microorganisms can find a favorable environment for their development in the small amount of urine till present in the bladder because it cannot flow out of the openings at the tip of the catheter while other microorganisms can find comfortable niches in correspondence of the inevitable lesions of the urethral wall. In the last few decades an increasing attention was also focused on the micro-fractures and defects of the materials used for the construction of catheters, mainly observed by scanning electron microscopy on the internal and external surfaces of the catheters. In fact, it has already been demonstrated that these defects can represent critical zones for the initiation of adhesion phenomena and microbial colonization in vascular catheters. As for the phenomena of occlusion of the catheters, attention more recently has been focused on the development of microbial biofilms and their role in promoting the increase of antibiotic-resistant microorganisms involved in infection. In fact, it appears increasingly evident that the production of microbial biofilm has important implications for diagnosis, prevention and treatment of catheter-related urinary tract infections [25,26].

Scanning electron microscopy investigations show that the internal surfaces of the catheters, of tubes and drainage bags are commonly covered by microorganisms immersed in a polysaccharide matrix: that is, bacteria readily produce biofilms on internal surfaces and external parts of the catheters shortly after implantation, thus causing bladder infection The first step in biofilm formation occurs immediately after insertion of the catheter, the surfaces of which become rapidly covered by substances present in the body fluids of the host, first of all proteins. Some studies have highlighted the presence of nitrogen, carbon, sodium, calcium and phosphorus as constituent elements of a protein film that forms in the absence of microorganisms. Then, once microorganisms have access to the urinary tract they can adhere to the surfaces of the catheter, this phenomenon depending on the hydrophobicity of both the microorganism and the surfaces themselves. Catheters with both hydrophilic and hydrophobic surfaces allow colonization of a wider variety of microorganisms [27,28]. Once adhered to the surface of the catheters, the microorganisms pass from a reversible to an irreversible adherent state, thanks to the interaction between the bacterial polysaccharides and different substances produced by the host organism: among the latter, fibrin, fibronectin and cellular components of the urethral epithelium.

In this way a thick biofilm develops and strongly attaches. Scanning electron microscope analyses showed microbial biofilms with thicknesses from 3 μm up to a maximum of 490 μm; such biofilms usually are consisting of microorganisms of a single species but can also be polymicrobial. The growth process of microbial biofilms is influenced by factors such as the transfer efficiency of nutrients, the frictional resistance to fluid flow, the adhesion of other microorganisms and the crystal formation in cases of alkaline urine. Microorganisms behave in biofilm very differently from planktonic bacteria and are well protected by mechanical urine flow, host defenses and even antibiotics. The sessile bacteria grow more slowly than planktonic ones, presumably due to limited amount of oxygen and available nutrients. They also produce chemical signals that mediate expression of genes favoring the growth in sessile form and show high efficiency in transferring genetic information, as some recent studies on the transfer of plasmids have reported. Once formed, the biofilm expands rapidly as bacteria move up the pathway intraluminal, extraluminal and internal surfaces of the drainage system. The intraluminal route is the fastest, probably due to the turbulent movement of the microorganisms in the urine stream; antibiotics can slow this rise but are not able to prevent it. Thus, as a rule, asymptomatic bacteriuria develops, due to colonization of the catheter surface.

However, if a particularly virulent bacterium reaches the bladder, it may rapidly adhere to the mucous membrane and induce a symptomatic bacteriuria. The precipitation phenomena, e.g., in the case of a Proteus mirabilis infection, can occur at the same time or after the formation of microbial biofilm on catheter surfaces; it can therefore be hypothesized that the precipitated salts form a single and substantially continuous structure with the biofilm itself. Morris and Stikler, on the basis of a series of literature data, have schematized the main stages of the encrustation process as follows:

a) Urinary tract infection from a urease-positive species.

b) Formation of a film of organic material on the catheter surface.

c) Adhesion of urease-positive bacteria to the catheter.

d) Development of a microbial biofilm consisting of a community of bacteria in a matrix of exopolysaccharides produced by themselves.

e) Elevation of urine and blood matrix pH as a consequence of urease activity on urea.

f) Attraction of calcium ions and magnesium within the matrix.

g) Crystallization, induced by the alkaline environment, of ammonium phosphates of calcium and magnesium.

The same authors also suggest that through the fouling process, the crystals formed in the alkaline urine of the bladder can adhere to the surface of the biofilm and that of the catheter. Regarding the activity of antibiotics against the microorganisms growing in sessile form, as in the case of the formation of microbial biofilm on the surface of bladder catheters, it is known that bacteria within the biofilm can survive concentrations of antimicrobials 1000 times higher than those usually lethal for planktonic bacteria of the same species. Several mechanisms have been hypothesized:

a) The biofilm itself could act as a “mechanical barrier”, protecting the bacteria from the natural defense mechanisms of the host and preventing and/or slowing down the entry of antibiotic molecules inside.

b) The extensive anionic matrix surrounding the bacterial cells in the biofilm, consisting of proteins, glycoproteins, electrolytes, carbohydrates and microbial catabolites in general, it seems be able to constitute a further “chemical barrier” as establishing links with the antibiotic molecules, prevents the latter from reaching their cellular targets.

c) Since the activity of several antibiotics is related to the metabolic activity of the target organisms, such antibiotics are less active towards the bacteria constituting the biofilm as they are considered metabolically less active than their planktonic equivalents. In addition, many of the proteins that bind antibiotics are poorly expressed in sessile-growing bacteria, and this would prevent effective binding of the antibiotic to the microbial cells themselves.

d) The microbial biofilm also constitutes an ideal niche for the exchange of plasmids, favoring the transfer of genetic material, and therefore of antibiotic resistance, between microbial strains, also belonging to different species, present inside it.

Conclusion

In conclusion, biofilms play a pivotal role in healthcare-associated infections, especially those related to the implant of medical devices, such as urinary catheters. In fact, patients with a urinary catheter in place for over 30 days are considered to have a long-term, or chronic, catheter and, of course, the longer urinary catheters remain in place, the greater is the tendency of bacteria to colonize their surfaces and to grow as biofilm. In the past few decades promising strategies for the development of novel medical devices refractory to microbial adhesion, colonization and biofilm formation have been developed. In particular, tremendous efforts have been devoted to the setup of antimicrobial coatings for urinary catheters as one of the most direct and efficient strategies to reduce infections. In particular, polymer-based coatings have been the subject of extensive research and a large variety of antimicrobial agent-releasing polymers has been developed by either adsorption or impregnation with antibiotics alone or in combination with biofilm-dispersing agents. Innovative experimental approaches have been focused also on development of polymer coatings able to prevent microbial adhesion by their functionalization with groups exhibiting either killing or repelling activity [29-36]. The design of antifouling and/or antimicrobial coatings is one of the most promising strategies to face the critical issue of catheter-associated urinary tract infections.

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DOI: 10.32474/JUNS.2023.04.000188