Provisional chapter

Role of Bacterial Biofilms in Catheter-Associated Urinary Tract Infections (CAUTI) and Strategies for Their Control

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Additional information is available at the end of the chapter

1. Introduction

Urinary tract infections (UTI's) can be defined as bacteriuria (>10^5 CFU/mL in adults; >10^4 CFU/mL in children) of an uropathogen with associated clinical signs that include dysuria and urgency [18]. According to the United States Centers for Disease Control and Prevention (CDC), a symptomatic urinary tract infection must meet at least one of the following criteria:

- Patients had/did not have an indwelling catheter in place at the time of specimen collection or onset of signs or symptoms
- Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), urgency, frequency, dysuria, suprapubic tenderness or costovetebral angle pain or tenderness
- Patient has a positive urine culture of ≥10^5 with no more than 2 species of microorganisms [20].

UTI is considered to be the most common bacterial infection [107]. It is the second most common infection of any organ and is one of the most common infections in humans [157]. UTIs account for nearly 8 million physician visits and 1.5 million visits to emergency rooms annually in the United States [44, 87, 144]. Although every individual is susceptible to UTIs, certain specific subpopulations are more predisposed to the risk of UTIs. This includes infants, pregnant women, elderly, patients with spinal cord injuries and/or catheters, patients with diabetes, multiple sclerosis, or acquired immunodeficiency virus, and patients with underlying urologic abnormalities [13, 31, 43, 127, 130]. UTIs are usually localized to the bladder, kidneys or prostate. The etiology of UTIs has been regarded as well-established and consistent.

Escherichia coli is the predominant uropathogen responsible for almost 80% of all cases, followed by *Staphylococcus*, *Klebsiella*, *Enterobacter*, *Proteus* and *Enterococci* species [128]. The financial implications of UTIs are enormous due to high incidence. UTIs account for a total annual cost of more than $ 3.5 billion in the United States [87].

2. Catheter associated urinary tract infection

In addition to being the most common bacterial infection, UTIs are also the most common type of hospital acquired infections (HAI). HAIs can be defined as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or toxin, which occurs in a patient in a health care setting and was not present or incubating at the time of admission [64, 66]. UTIs account for 30% of all HAI [77]. Of these 30% infections, 80% of them are estimated to be catheter-associated [89]. According to the CDC, CAUTIs are defined as an UTI in a patient who had an indwelling urinary catheter in place at the time of or within 48 hours prior to infection onset. CAUTI can lead to complications such as cystitis, pyelonephritis, gram-negative bacteremia, prostatitis, epididymitis, endocarditis, vertebral osteomyelitis, septic arthritis, endophthalmitis and meningitis [20]. Additionally CAUTIs also result in prolonged hospital stay, increased cost and mortality [77]. An estimated 15-25% of hospitalized patients will have a urinary catheter at some point during their hospital stay [175]. Obstruction of indwelling catheters can lead to sepsis, even resulting in mortality [174]. Each year around 13,000 deaths are attributed to UTIs in the United States [77]. The cost associated with CAUTI episodes is about $750-$1000 per infection, and the estimated total cost in the United States ranges from $340-$450 million annually [132].

Millions of transurethral, suprapubic and nephrostomy catheters or urethral stents are used in patients every year. These devices overcome several host defenses and enable bacterial entry at a rate of 3 to 10% (cumulative rate) per day, which leads to bacteriuria in patients after a month [8]. In intubated patients, bacteria frequently ascend from the urethral meatus into the bladder between the mucosal and catheter surfaces. In certain cases, bacteria may ascend through the drainage system due to contamination of the drainage bag or disruption of the tubing junction. The presence of a device enables the persistence of the etiologic organism in the urinary tract. Several studies have demonstrated that bacteria exist as biofilms on these devices [53]. Formation of a biofilm and incrustation with calcium and magnesium struvites has a significant role in the pathogenesis and treatment of catheter-associated infections.

3. Biofilm

Biofilms have been around for billions of years. They have been identified in 3.2 – 3.4 billion year old South African Kornberg formation, and in deep-sea hydrothermal rocks [55]. Similar biofilms can be found in modern hot springs and deep-sea vents [124, 160]. The presence of biofilms in both ancient fossils and in similar modern environments indicates that biofilm

formation is an ancient and integral characteristic of prokaryotes. It is likely that biofilms provided homeostasis during the harsh and fluctuating conditions of the primitive earth such as extreme temperatures, pH and exposure to UV light, thus enabling complex interactions between individual cells. It is, however, generally accepted that planktonic cells existed before the development of biofilm communities. The concomitant development of both planktonic and sessile bacteria in biofilm communities could be attributed to the conditions offered by life on surfaces [151]. The ability of bacteria to adhere to surfaces and form biofilms in different environments is due to the selective advantage that surface association offers the bacteria.

3.1. Definition

The definition of biofilm has evolved over the years. Marshal in 1976 [94] observed the presence of fine extracellular polymer fibrils that anchored bacteria to the surface. Costerton and coworkers [1978; 28] defined biofilms as communities of attached bacteria that were found to be encased in a glycocalyx matrix of polysaccharide that mediates adhesion [28]. They also stated that biofilms consist of single cells and microcolonies which are embedded in the matrix [26]. This definition was later modified to include the ability of biofilms to adhere to surfaces and to each other forming microbial aggregates and floccules [29]. The adhesion to a surface also triggers the expression of genes controlling production of bacterial components required for biofilm formation, thus including the role of gene modulation in the definition [29]. Consequently, a definition of biofilm must include the ability of cells to attach to a surface, extrapolymeric encasing, presence of noncellular and abiotic components in the matrix, physiological attributes of these organisms and the differential gene expression in biofilm cells versus planktonic cells. Taking all this into account, biofilms can be defined as a microbially derived sessile community consisting of cells that are attached to an interface or to each other, are embedded in an extracellular polymeric matrix that they have produced and demonstrate altered phenotype associated with differential gene expression [38]. This definition also applies to biofilm cells that have broken off from a biofilm on a colonized medical device and circulate in the body fluids with the ability to establish itself in another niche.

3.2. Biofilm formation and structure

Biofilms can form on abiotic surfaces such as minerals, air-water interfaces, and biotic surfaces such as plants, other microbes and animals. In the human body, bacteria reside as biofilms on skin, oropharynx and nose, intestine and indwelling medical devices. To form a biofilm, bacteria are attracted to the surface by environmental signals. On reaching the surface, the bacteria attach to it as single cells or as clusters. When single cells attach to a surface they form a monolayer biofilm. A monolayer biofilm can be defined as one in which the bacteria attach only to the surface [75]. When bacteria attach to a surface as a cluster, they form a multilayer biofilm. Multilayer biofilms can be defined as a microbial community, where the bacteria are attached both to the surface and the neighboring bacterial cells [75]. The type of biofilm formed depends on the environmental conditions and surfaces that favor their development, the genes that are activated, the architecture of the biofilm and the matrix composition [75].

Monolayer biofilms are composed of a single layer of cells attached to a surface. These biofilms are favored when cell-surface interactions predominate. Since monolayer biofilms offer bacteria more proximity to surfaces, they commonly occur during the interaction of the bacterial pathogen with the host. In flagellate motile bacteria, monolayer formation occurs in two steps, where bacteria first become attached to a surface when they come in close proximity to it. After attachment, the bacteria break the forces tethering them to the surface, resulting in transient attachment. However, a few bacteria that have transitioned from transient to permanent attachment remain attached to the surface. Multilayer biofilms form when bacteria adhere to the surface as well as to each other. Several adhesion factors are known to mediate this transition, including preformed adhesins, conditionally synthesized adhesins and specific adhesins.

Preformed adhesins include flagellum and pili. Motility is believed to increase the initial interaction between bacteria and the surface. Several studies have also demonstrated that flagellar motility promoted surface adhesion in bacteria [76, 85, 167]. However, under certain conditions, flagellar mutants that are defective in the synthesis of flagellar components have shown an increased synthesis of adhesive matrix that promotes bacterial attachment and multilayer biofilm formation [83, 176]. These observations indicate that flagellar impedence may be important in priming the bacteria for the formation of a multilayer biofilm. Nevertheless, mutants lacking the flagellum or the flagellar motor are completely defective in monolayer and multilayer biofilm formation [83], implying that flagellar motor plays a vital role in biofilm formation independent of flagellar motility. Retractable pili are critical for gram-negative bacteria to attach to surfaces [75]. It is hypothesized that these structures pull bacteria along surfaces by attaching to the surface and retracting, thus helping the bacteria approach the surface more closely [75].

Bacteria can also conditionally synthesize adhesins to promote surface attachment. In *Pseudomonas fluorescens*, the transition from transient to permanent attachment is mediated by LapA (Large adhesion ProteinA) that associates with the bacterial surface [62]. In *E. coli*, a similar function has been attributed to the exopolysaccharide adhesin, PGA (poly-β-1,6-*N*-acetyl-d-glucosamine) which mediates the transition from temporary to permanent attachment [2]. Following the transient attachment which is accomplished through the array of adhesins such as flagella and pili, bacteria form stable and specific binding through interactions with eukaryotic cell receptors [59]. These interactions are mediated by specific adhesins which aid in internalization.

3.3. Biofilm matrix

Bacterial cells in the biofilm are surrounded by a variety of molecules that make up the matrix of the biofilm. The matrix is highly hydrated and can contain up to 97% water [154]. In addition, the matrix is composed of polysaccharides, proteins, DNA, surfactants, lipids, glycolipids, membrane vesicles and ions like calcium. This composition varies with different conditions or stages during biofilm maturation. The biofilm matrix is dynamic and interactive, and is essential to the integrity and function of the biofilm.

3.3.1. Matrix components

Exopolysaccharides are a major component of the biofilm matrix. The absence of polysaccharide synthesis and export leads to an inability to form multilayer biofilms in most bacteria. Bacteria capable of forming biofilms possess distinct genetic loci that encode for the synthesis of polysaccharides. One of the most common exopolysaccharides in the biofilm matrix is a polymer of β-1, 6-N-acteyl-D-glucosamine called PGA or PNAG. Several bacterial species, including *E. coli*, *S. aureus*, *Actinobacillus* spp., and *Bordetella* spp. make use of PGA to construct their matrix [30, 70, 71, 114, 173]. The synthesis and export of PGA is carried out by the *icaADBC* locus in Staphylococcal species and the *pgaABCS* locus in *E. coli*. PGA is required for bacterial attachment and biofilm formation in *E. coli*. Mutations in this locus prevent attachment even after prolonged incubation [173]. In *S. aureus*, the *icaADBC* locus is important for attachment and biofilm formation on indwelling medical devices [42]. In *S. epidermidis*, this locus is also shown to be required for virulence and immune evasion, thus emphasizing the role of biofilms in disease [172]. Another commonly found polysaccharide in the biofilm matrix is cellulose which has been identified as a major component of the matrix in *E. coli*, *Salmonella*, *Citrobacter*, *Enterobacter* and *Pseudomonas* [140, 142, 181, 182]. In *E. coli* and *Salmonella* Typhimurium, cellulose synthesis is made possible by the *bcsABZC-bcsEFG* locus [140, 182]. In addition to PGA and cellulose, some *E. coli* strains also make colanic acid, which is a branched chain polymer synthesized by the *wca* locus [146]. Mutants that are defective in colonic acid formation can attach to surfaces, but are incapable of forming multilayer biofilms [32].

The biofilm matrix is also composed of proteins exported to the matrix by cells within the biofilm. Proteinaceous appendages such as fimbriae and pili confer adhesive properties in bacteria. In *E. coli* and *Salmonella*, curli fimbriae produced by the *csgBAC* and *csgDEFG* operons are part of the biofilm matrix [57]. Transcriptional profiling studies have demonstrated that fimbria and pili gene expression is upregulated in biofilms compared to planktonic cells [12]. Another group of proteins associated with the matrix are the *Bap* or Biofilm-associated proteins. These proteins hold bacterial cells together in the biofilm by interacting with similar proteins on the surface of neighboring cells. Bap proteins have been shown to be critical for biofilm production in *S. aureus* [82]. Besides proteins that bind other proteins on neighboring cells, the biofilm matrix also contains lectins and sugar binding proteins. These proteins recognize sugar moieties on the surface of eukaryotic cells and bind to them, thereby facilitating cell-cell interactions [163]. Besides the above mentioned proteins, autotransporter proteins have been identified to be part of the biofilm matrix. The proteins can transport themselves to the cell surface without the need for other transport systems [48]. In *E. coli* autotransporters proteins such as *ag43*, AIDA and TibA have been shown to promote biofilm formation [135]. These proteins serve to maintain close-range interactions between cells in the biofilm.

Another major component of the biofilm matrix is eDNA (extracellular DNA). In *P. aeruginosa*, the biofilm matrix has significant amounts of DNA that is essential for biofilm integrity [95]. Addition of DNase to the culture media resulted in an inhibition of biofilm formation and dissolution of preformed biofilms [177]. It is hypothesized that DNA could serve as a grid that enables bacteria to move using type IV pili. The ability of type IV pili to bind DNA has been

demonstrated in *P. aeruginosa* [171]. The eDNA is similar in composition to the genomic DNA, and is hypothesized to be released from whole cell lysis or secretion from outer membrane vesicles containing DNA [6].

An important characteristic of bacterial cells within the biofilm is the chemical mediated cell-cell crosstalk known as quorum sensing. Quorum sensing allows bacteria to coordinate their gene expression in a density-dependent manner [75]. These circuits involve chemical mediators or autoinducers that are secreted by the bacteria and accrue in the extracellular environment. When the autoinducer concentration exceeds a certain threshold, quorum sensing is activated. In most gram negative bacteria, the prototype quorum sensing system is the LuxI/LuxR system [61]. LuxI proteins synthesize the autoinducer such as acylated homoserine lactone (AHL), which modulates the activity of LuxR to activate gene expression upon binding. In case of gram positive bacteria, oligopeptides serve as autoinducers which then activate gene expression in a two component system [61]. Activation of quorum sensing has been shown to stimulate biofilm formation in *P. aeruginosa*. Quorum sensing mutants of *Pseudomonas* make biofilms that are sensitive to detergents such as sodium dodecyl sulfate indicating that the matrix synthesis is defective [34]. In light of the role that quorum sensing plays in the formation and regulation of biofilms, it is proposed that use of quorum-sensing inhibitors may be a potential approach for the treatment of biofilm associated infections.

Existence as a biofilm is advantageous to the bacterium since it enables its survival under a variety of conditions. However when the environmental conditions change or their microenvironment becomes unfavorable, bacteria can return to their planktonic state. This is referred to as dispersion of biofilms. Dispersion of biofilms can be brought about by degradation of the biofilm matrix, which will lead to disruption in cell to cell adhesion and escape from the biofilm. Several bacteria have been shown to produce enzymes that can degrade matrix components and result in biofilm dispersion [15, 69]. Another mechanism of dispersion is through the induction of motility. Onset of dispersal has been shown to coincide with a return in motility of the biofilm associated cells [72]. Certain bacterial biofilms also produce surfactants such as rhamnolipids. Biofilms formed by strains of *P. aeruginosa* with increased rhamnolipid production dispersed after 2 days, whereas wild type biofilms under the same conditions did not disperse until day 10 [14]. Biofilm dispersal is of medical significance as the bacterial cells released from the biofilm can enter the body fluids and can establish themselves in another niche, thereby resulting in secondary infections.

3.4. Medical device associated biofilms

The biofilms on medical devices can be composed of gram-positive and gram-negative bacteria, or yeast. Commonly isolated bacteria include gram-positive organisms such as *E. fecalis*, *S. aureus*, *S. epidermidis*, *Streptococcus viridians* and gram- negative organisms like *E. coli*, *Klebsiella pneumonia*, *P. mirabilis* and *P. aeruginosa*. These organisms can reside on the skin of healthy patients or health-care workers, in the water to which entry ports are exposed or in the environment, from where they eventually contaminate the medical device. Indwelling devices can be colonized by single or multispecies biofilms. In the case of urinary catheters, initially the biofilms are composed of a single species and continued further exposures lead to

multispecies biofilms [148]. There are several factors that influence the rate and extant of biofilm formation on devices. First the bacteria must attach to the surface of the device long enough to result in permanent attachment. This initial rate of attachment depends on the number and type of bacterial cells in the fluid in which the device is exposed to, the flow rate through the device and the physicochemical characteristics of the exposed surface [37]. On indwelling devices, the components in the fluid milieu to which the device is exposed to can change the surface properties and influence bacterial attachment. Following permanent attachment to the surface, the bacteria produce exopolysaccharides to form the biofilm. The rate of growth and establishment of a biofilm depends on flow rate, nutrient availability, antimicrobial concentration and temperature.

4. Urinary catheter biofilms

CAUTIs account for around 80% of all nosocomial UTIs [89]. The risk of developing an UTI significantly increases with the use of indwelling devices. It has been reported that the risk of developing CAUTI increases 5% with each day of catheterization, and virtually all patients are colonized by day 30 [91]. Several studies also support the role of biofilm in the establishment of CAUTIs [161, 167]. The predominant pathogens associated with UTIs include *E. coli* (25%), *Enterococci* (16%), *P. aeruginosa* (11%), *Klebsiella pneumonia* (8%), *Candida albicans* (8%), *Enterobacter* (5%), *P. mirabilis* (5%) and coagulase-negative *Staphylococci* (4%) [40]. These pathogens are normally found in the lower intestinal tract of humans, and can be introduced into the urinary tract via indwelling devices.

4.1. Biofilm formation on indwelling urinary tract devices

Prior to the initial attachment of bacteria to the device surface, it is critical that the surfaces are conditioned, where the attachment of proteins and polysaccharides from the fluid environment form a film on the exposed surface of the device [161, 167]. This conditioning film facilitates the initial bacterial attachment, which normally adhere poorly on uncoated surfaces [58]. Indwelling devices used in the urological settings include open and closed catheters, urethral stents and sphincters and penile prostheses. Biofilm formation has been documented from infection sites associated with all of these device types [24, 161]. Among all these devices, urinary catheters serve as the common substrate for the development of UTIs [166]. Numerous studies have demonstrated the presence of adherent biofilms on catheters removed from patients [104]. Additionally, scanning electron microscopy studies have documented extensive biofilm formation on urinary catheters [111]. Such catheters recovered from patients that failed antibiotic therapy were shown to contain *P. aeruginosa*, *E. fecalis*, *E. coli* and *P. mirabilis* [103].

4.1.1. Crystalline biofilms

Foley catheters are commonly used to manage urinary incontinence in elderly patients and those with bladder dysfunction. These devices besides helping the patient also put them under high risk for the development of UTIs. Uropathogens such as *P. mirabilis*, *Providencia stuartii*,

Morganella morganii and *K. pneumoniae* produce urease and form a unique type of crystalline biofilms on catheters. Urease production by these organisms enables them to break down the urea in urine [86] and releases ammonia, which raises the urine pH resulting in calcium and magnesium phosphate crystal formation within the biofilm matrix [149]. Studies have also demonstrated that biofilm formation is a prerequisite for crystal formation since the matrix may act as a nucleation site for crystal development [106]. Stickler and others have shown that *P. mirabilis* biofilm formation on catheter surface starts near the eye-hole in the form of microcolonies [150]. Following this, due to production of urease by these colonies, calcium and magnesium phosphate crystals begin to form and the biofilm extends down the luminal surface. The crystal formation is medically significant because of the blockage of catheters due to crystallization and encrustation, which can lead to bladder distention, urine leakage and pyelonephritis when urine from the distended bladder refluxes into the kidney. Additionally, crystalline biofilms that form on the outside of the catheter can lead to irritation and trauma of the urethral mucosa [58].

4.2. Uropathogen specific factors that contribute to biofilm formation

Uropathogenic *E. coli* (UPEC) are the most common etiology of UTIs [65]. Consequentially, UPEC biofilms are responsible for many CAUTIs [108]. Therefore this section will focus on the specific factors associated with UPEC that aid its biofilm formation. UPEC has several virulence factors such as α-hemolysin, cytotoxic necrotizing factor I, lipopolysaccharide capsule, siderphore aerobactin and enterobactin, proteases and adhesive organelles [109]. The presence of a different repertoire of virulence factors with each UPEC strain could be the reason for the high number of cases associated with UPEC [93]. The single most important virulence factor of UPEC significant to biofilm formation and the associated illness could be type I pili. Type I pili have been shown to play an important role in bacterial adhesion to biotic and abiotic surfaces, and invasion and persistence in the bladder.

Type I pili are pertrichously present on the cell surface of many members of the Enterobacteriaceae, which includes both pathogenic and commensal strains of *E. coli* [179]. Type I pili in *E. coli* is encoded by nine genes of the fim gene cluster which have structural and regulatory roles. The *fimAFGH* genes are structural genes that encode the protein components of the pilus rod and tip [58], whereas FimB and fimE encode the regulatory proteins that control phase variation of type I pili [46]. Phase variation helps *E. coli* to reversibly switch on/off the expression of type I pili, and a stringent regulation of phase variation is critical for successful UPEC infection [138]. The FimH adhesion confers mannose-specific binding property to the type I pili. FimH can recognize the terminal mannose residues on various cell types and secreted glycoproteins such as superficial bladder umbrella cells [39] and CD48 on macrophages and mast cells [136]. Langermann and others reported that FimH is essential for colonization of the murine bladder and immunization with FimH protected the animals from UPEC colonization and infection [80, 81]. Scanning electron microscopy (SEM) revealed that type I pili are in close contact with uroplakin-coated superficial bladder membrane [99]. Uroplakins are proteins that cover the apical surface of superficial umbrella cells and give strength to the bladder epithelium to create a permeability barrier [152]. *In vitro* studies using mouse uroepithelial plaques

and recombinant FimH have shown that uroplakin UP1a is the unique bacterial receptor for FimH adhesion [180]. It has been shown that commensal and pathogenic *E. coli* contain type I pili and bind to trimannose receptors via FimH adhesion [139]. However, type I pili in UPEC strains also have a high affinity for binding monomannose units [180], which potentially provides a selective advantage during pathogenesis by increasing specific binding on the uroepithelium.

In addition to their role in adherence, type I pili are also essential for the invasion of bladder epithelial cells by UPEC. TEM and SEM imaging have revealed that bladder cells internalize UPEC through interactions between FimH and UP1a [99]. Other studies have also demonstrated that type I pili carrying bacteria interact with plasma membrane micro domains knows as lipid rafts [39]. More specifically, caveolae, a subtype of the lipid rafts with a cave-like appearance have been shown to associate with intracellular bacteria during UPEC invasion. Besides the bladder cells, UPEC can also bind and invade macrophages [10] and mast cells [136], thereby serving as a source of chronic UTIs. The ability of UPEC to invade macrophages allows the bacteria to survive within them and evade phagocytosis. Besides tiding over phagocytosis, ability to survive inside bladder cells also helps to avoid host defenses, including urine flow, secretion of adhesion-binding competitors such as Tamm-Horsfall protein, IgA, chemokines, and exfoliation of superficial bladder cells [113, 155]. UPEC sequestered within the bladder cells are also protected from antibiotic treatments that sterilize the urine, and are provided a rich environment in which the bacteria replicate [100]. UPEC has the ability to form biofilms on abiotic surfaces such as polypropylene, polyvinylchloride, polycarbonate and borosilicate glass when grown statically [120]. Using transposon mutagenesis, Pratt and Kolter demonstrated that Fim mutants were defective in initial attachment and biofilm formation was severely impacted. This indicates that type I pili are essential for the initial attachment of UPEC to abiotic surfaces. Besides type I pili, motility also plays an important in biofilm formation. Non motile strains were severely defective in the initial attachment and consequently in biofilm formation [120].

4.3. Biofilm formation in urinary tissues

UPEC are capable of attaching and invading uroepithelial cells, persisting and forming intracellular reservoirs that help them escape host defenses [100]. Anderson and coworkers [2003; 7] hypothesized that UPEC reservoirs are established by the formation of biofilm-like pods or intracellular bacterial communities (IBC) within the bladder cells. Replication of UPEC in the superficial bladder cells leads to the formation of tightly packed biofilm-like pods that protrude into the lumen. Bacteria inside these pods undergo continuous development leading to the maturation of the IBCs. The development of IBC can be divided into four phases. The first phase begins 1-3 h after infection. The type I pili bind and invade the superficial bladder epithelial cells [74]. At this stage the bacteria are non-motile and divide rapidly and by 8 h post infection, they form loosely organized colonies that resemble microcolonies of abiotic biofilms, known as early IBC. The next phase leads to the formation of middle IBCs, which is characterized by a reduction in cell proliferation and cell size. Each pod corresponds to a single epithelial cell tightly packed with bacteria forming an intracellular biofilm. Within the pods,

a polysaccharide matrix surrounds the bacteria [7, 74]. At around 12 h post infection, late IBCs are formed, when UPEC regain their rod shape and motility and flux out of the bladder cells. Fluxing aids UPEC in infecting neighboring cells [74]. The last phase of IBC formation results in UPEC filamentation which occurs 24 to 48 h post infection, where filamentation helps UPEC evade host immune responses. The filamentous bacteria can also separate to form rod-shaped daughter cells. The appearance of filamentous cells also coincides with the appearance of small groups of UPEC on newly infected healthy cells [74].

4.3.1. Pathogenesis of catheter-associated biofilm

The pathogenesis of CAUTI depends on the physicochemical properties of the catheter material and its susceptibility to bacterial colonization. Bacterial binding to the bladder mucosa triggers an inflammatory response that leads to neutrophil influx and sloughing of the infected epithelial cells [78]. This helps to clear the bacteria from the mucosal surface. In the case of a catheter, besides the absence of inherent defense mechanisms, they also provide a survival advantage to the bacteria which become difficult to eradicate. The advantages include resistance from being swept away by the urine flow, resistance to phagocytosis and antimicrobials [167]. In addition to the catheter providing an environment for biofilm formation, the presence of a catheter helps to weaken many normal defenses of the bladder. The catheter helps to connect the heavily colonized perineum with the sterile bladder, thus providing a route for bacterial entry into the bladder. Urine pools in the bladder or in the catheter and the resulting urinary stasis promote bacterial growth. Additionally, the catheter also damages the bladder mucosa by triggering inflammatory response and mechanical erosion [175]. Once bacteria gain entry into the urinary tract, low level bacteriuria progresses within 24 to 48 h in the absence of an antimicrobial therapy [145].

4.4. Biofilm related UTIs

Chronic bacterial prostatitis: The prostatic ducts and acini provide a safe environment for bacteria to multiply and induce host response. If the bacteria are not eradicated by the immune response, it leads to their persistence and formation of bacterial microcolonies. The presence of microcolonies induces persistent immunological stimulation and chronic inflammation [105].

Recurrent cystitis: UPEC binds to superficial bladder epithelial cells resulting in neutrophil recruitment and influx into the bladder lumen. Neutrophil recruitment occurs due to the recognition of bacterial LPS by the toll-like receptors. Additionally, interaction between type I pili and the uroepithelium results in exfoliation of the superficial epithelial cells causing pathogen shedding into the urine [129]. When IBCs form in the epithelial cells, they persist as a chronic reservoir, which leads to recurrent cystitis.

Pyelonephritis: Once the bacteria reach the kidney, they adhere to the uroepithelium and form thin biofilms before invading the renal tissue [106]. Additionally encrustation and obstruction to the catheter flow due to formation of crystalline biofilms leads to bladder distention, urine

leakage and pyelonephritis when urine from the distended bladder refluxes in to the kidney [162].

Infected urinary caliculi: In case of urease positive bacteria, biofilm formation is accompanied by the deposition of calcium and magnesium crystals. This crystallization occurs only after the biofilm is formed, since the biofilm serves as a nucleation site [106].

5. Control strategies to prevent CAUTI

CAUTI is the most common hospital acquired infection and accounts for up to 40% of all health care associated infections in the United States [102, 156]. About 15-25% of hospitalized patients have an urethral catheter in place during some point of their stay. It is estimated that around 30 million bladder catheters are placed annually in the United States, resulting in several hundred thousand cases of CAUTI [156]. A systemic review of the proportion of health care associated infections that can be prevented revealed that CAUTI was the most preventable nosocomial infection [170]. An estimate of the number of avoidable cases ranged from 95,483 to 387,550 per year and associated lives saved ranged from 2225 to 9031 annually. This prevention could also avoid the annual cost of these illnesses which is estimated at $1.8 million to $115 million [170]. This underscores the need for control strategies to prevent CAUTI. Prevention of CAUTI is primarily based on reviewing the criteria for appropriate placement and early removal of catheters. The advances in our understanding of the pathogenesis and key factors that influence the onset of infection are also critical in the development of adequate and effective control strategies [137]. Several protective strategies have been suggested for CAUTI, some of which are already in place for patient care, whereas others are still in development. The control strategies include:

5.1. Need for and duration of catheterization

It is estimated that about 21-50% of catheters are placed without justified need and catheters are inappropriately retained for 33-50% of total device days [73, 101]. The most effective ways for the preventing CAUTI are by reducing the duration of catheterization and its early removal [51]. Use of interventions such as nurse prompted removal suggestions and computer based reminders to the patients have resulted in a decline in catheter retention and a concomitant reduction in bacteriuria [164]. Thus, it is important to refrain from using an indwelling catheter without an appropriate indication. A study conducted in an emergency department indicated that use of pre-insertion checklists have led to an improved adherence to indications for placement resulting in the increase in the number of appropriately placed catheters from 37% to 51% [50].

5.2. Catheter placement and management

Since the catheter provides a connection between the highly colonized perineum and the sterile bladder, sterility during catheter handling and placement is of greatest importance. In this regard, hand hygiene plays a vital role in the prevention of CAUTI [16]. Insertion of a catheter

in the emergency room rather than an operating room has been shown to be associated with higher rates of catheter associated bacteriuria (CAB; 158). Use of an aseptic insertion technique reduces the risk of acquiring resistant organisms in the hospital [63]. A randomized study conducted by Platt and others [1983; 118] demonstrated that hospitalized patients intubated with a catheter without a pre-sealed junction were 2.7 times more likely to develop CAB than patients with pre-connected catheter drainage bags and sealed junctions. Therefore, the use of closed catheter drainage systems universally is recommended [63]. Similarly, any breach in the closed drainage system would also increase the risk for CAB. Any manipulation of the indwelling catheter should be avoided so that breaches in the closed drainage and shear trauma can be minimized [25].

5.3. Catheter design

Catheter design has not changed significantly since the inception of the Foley catheter in the 1930s [97]. In addition to the catheter design, biocompatibility of the material is crucial. Catheter material can also impact the rate of biofilm formation. Scanning electron microscopy imaging of latex catheters revealed that presence of more uneven surfaces on it than other silicone counterparts which can promote bacterial adhesion [150]. Additionally latex has been associated with toxic effects *in vitro* and proinflammatory reactions *in vivo* leading to polypoid cystitis on chronic exposure [49]. Moreover, silicone catheters are more popular to avoid allergic reactions associated with latex use. Besides being hypoallergenic, silicone catheters have a larger lumen and are minimally prone to encrustation by crystalline biofilms [36]. A newly engineered silicone catheter with a trefoil cross-section was shown to reduce CAB and inflammation when compared to a standard urinary catheter [153]. The trefoil conformation helps to minimize the surface area of contact between the catheter and the urethra, thereby decreasing friction and trauma and increasing drainage of urethral secretions [137].

5.4. Hydrogel coated catheters

Cross linked insoluble polymers that are hydrophilic and trap water are known as hydrogels. Use of hydrophilic coating on catheters has been shown to improve patient comfort, reduce bacterial adherence and encrustation. The presence of hydrogels also increases lubrication and decreases bacterial adhesion to the interface of the tissue and the catheter [11]. However, conflicting data exist on the ability of hydrogel coated catheters to reduce CAUTI, which could be attributed to the type of hydrogel incorporated. Tunney and Gorman [2002; 169] used *in vitro* models to demonstrate that Poly(vinyl pyrollidone)-coated polyurethane catheters had a lower rate of encrustation when compared to uncoated polyurethane and silicone catheters. Another study showed that the use of poly(ethylene oxide)-based multiblock copolymer and segmented polyurethane increased the time to encrustation and catheter blockage from 7.8 h to 20.1 h [116]. These findings collectively suggest that the type of hydrogel coating can affect the rate of encrustation and the resulting catheter blockage.

5.5. Antimicrobial coating

Antimicrobial modification of catheters is achieved by coating, matrix loading and immersion in an antimicrobial solution. The primary objective behind the incorporation of antimicrobial on a catheter is to reduce bacterial attachment and biofilm formation. Additionally, release of antimicrobials from the catheters into the milieu is also another potential approach to control planktonic cells of uropathogens [56].

5.5.1. Nanoparticles and iontophoresis

Nanoparticles by virtue of their small size have the ability to penetrate bacterial cells, disrupt cell membranes and bind to the chromosomal DNA. Lelouche and others [2009; 84] demonstrated that glass surfaces coated with magnesium fluoride nanoparticles inhibited biofilm formation by *S. aureus* and *E. coli*, whereas magnesium fluoride solutions did not affect biofilm formation. This highlights the size dependent effect of nanoparticles.

The application of low intensity direct current (Ionotophoresis) *in vitro* has been shown to increase the antimicrobial activity of antibiotics on bacteria embedded in biofilms [27]. Chakravarti and others [2005; 21] used a urinary flow model to test the *in vitro* antibiofilm efficacy of iontophoretic silver wire containing silicone catheters. These catheters were challenged with *P. mirabilis* and then exposed to a steady current of 150 μA. It was observed that application of the electric field increased the time to blockage from 22 h to 156 h, and reduced the viable count from 10^9 CFU/ml to 10^4 CFU/ml. Similar *in vivo* study in sheep intubated with catheters containing platinum electrodes showed a decline in pathogen count from 10^7 CFU/ml to 10^3 CFU/ml on application of a direct current of 400 μA [33].

5.5.2. Antimicrobials

A variety of antimicrobials applied on urinary catheters have been investigated for their efficacy in controlling UTIs using *in vitro* and *in vivo* models.Nitrous oxide is known to exhibit bactericidal activity [123]. Urinary catheters impregnated with gaseous nitrous oxide, a known antimicrobial, and challenged with *E. coli* resulted in the slow release of nitrous oxide into the urine for over 14 days, and decreased biofilm formation by *E. coli*. Chlorhexidine is a common antimicrobial used against oral plaques. *In vivo* studies in rabbits intubated with genidine (combination of chlorhexidine and gentian violet) coated silicone catheters showed a reduction in biofilm formation by *E. coli*, *E. faecium*, *P. aeruginosa*, *K. pneumoniae* and *Candida* in comparison to silver coated and uncoated catheters [54]. Catheter associated bacteriuria was noticed in 60% and 71% of the rabbits with uncoated catheters and silver hydrogel coated catheters, respectively, whereas CAB did not occur in any of the rabbits with genidine coated catheters. Similar to chlorhexidine, triclosan is another antibacterial ingredient in toothpastes and cleaners used in health care settings. Triclosan exerts its antibacterial effect by inhibiting bacterial fatty acid synthesis [147]. Incorporation of triclosan in the balloon of catheters resulted in its release and diffusion through latex and silicon catheter balloons. The balloon served as a reservoir and the membrane helped in controlled release of triclosan. This in turn slowed encrustation and maintained the lumen patent for 7 days as compared to 24 h in saline-filled

catheters [150]. Another antibacterial shown to possess antibiofilm effect is nitrofurazone, which interferes with bacterial ribosomes, DNA and cell wall. When nitrofurazone coated catheters were compared with standard catheters, it was observed that nitrofurazone significantly reduced CAB [133]. Besides nitrofurazone, norfloxacin coated catheters were also shown to inhibit the growth of *E. coli*, *K. pneumoniae* and *P. vulgaris* for up to 10 days [115]. Similarly, gentamicin coated catheters were also effective in reducing CAB in rabbits [23]. Another study demonstrated that sparfloxacin coated and heparin coated catheters reduced colonization by *S. aureus*, *E. coli* and *S. epidermidis* for greater than 26 days compared to control catheters [79]. However, the use of antibiotics on catheters to control bacterial biofilms could potentially lead to the emergence of antibiotic resistant bacteria [126]. Repeated use of antibiotics for treating UTIs has been linked to the emergence of antibiotic resistant UPEC [41, 126]. Therefore, there is an increasing interest in the use of natural antimicrobials for controlling microbial infections, including UTIs.

5.5.3. Plant molecules

Plants are capable of synthesizing a large number of molecules [47], most of which are produced as a defense mechanism against predation by microorganisms and insects. A variety of plant-derived polyphenols are active components in traditional medicines [178]. A significant body of literature exists on the positive effects of dietary intake of berry fruits on human health, performance and disease [134]. Cranberry products such as its juice and tablets have been used as an alternative medicine to prevent UTIs in humans for decades. Clinical and epidemiological studies support the use of cranberry in maintaining a healthy urinary tract [117]. Although several studies have tested the antimicrobial effect of cranberries against multiple uropathogens, it was found to be most effective against UPEC.

Cranberries exert anti-adhesive effects on certain uropathogens [112] and this effect is specific to certain components of cranberry [110]. Cranberries contain three different flavonoids (flavonols, anthocyanins and PAC), catechins, hydroxycinnamic and other phenolic acids and triterpenoids. The anthocyanins are absorbed in the human circulatory system and transported without any chemical change to the urine [117]. Cranberry products do not inhibit bacterial growth, but reduced bacterial adherence to uroepithelial cells, thereby decreasing the development of UTI. The anti-adhesive effects of p-fimbriated UPEC to uroepithelial cells are related with A-linked PAC as compared with lack of anti-adhesion activities of B-linked PAC from grape, apple juice, green tea and chocolate [67]. The A-type PAC in cranberries enhances the anti-adhesive effects *in vitro* and in urine. PAC binds to lipopolysaccharide in gram-negative bacteria. When *E. coli* was grown in the presence of cranberry components, the bacterial morphology changed to a more spherical cell-like form. These changes cause them to be repelled by the human cells [88]. Similar study by Tao and others [2011; 159] have also demonstrated that consumption of cranberry juice cocktail reduced the adhesion of UPEC to a silicon nitride probe.

Cranberry has undergone extensive evaluation in the management of UTIs. However, currently there is no evidence that cranberry can be used to treat UTIs. Hence, the focus has been on its use as a prophylactic agent in the prevention of UTIs [52]. The consumption of

cranberry juice can help to prevent the adhesion of UPEC to the uroepithelium and thereby help reduce the incidence of UTIs. With rising concerns of antibiotic resistance among UPEC, cranberry could serve as an effective alternative in controlling UTIs.

Trans-cinnamaldehyde (TC) is a major component of the bark extract of cinnamon [1]. It is a generally recognized as safe (GRAS) molecule approved for use in foods by the Food and Drug Administration (FDA). The U. S. Flavoring Extract Manufacturers' Association reported that TC has a wide margin of safety between conservative estimates of intake and no observed adverse effect levels, from sub-chronic and chronic studies [1]. The report also indicated no genotoxic or mutagenic effects due to TC. Although, cinnamon or cinnamon oil has been used for ages in the treatment of UTIs, no scientific study was undertaken to investigate its antimicrobial efficacy against uropathogens. Amalaradjou and group [2010; 4] investigated the efficacy of TC for controlling UPEC biofilm formation. They observed that TC as a catheter lock solution or as a coating significantly inactivated UPEC and prevented biofilm formation when compared to untreated catheters. In a follow up study, these researchers reported that TC decreased the attachment and invasion of UPEC in cultured urinary tract epithelial cells by down-regulating several virulence genes in the pathogen [5].

Besides the use of cranberry and TC, other plant derived natural antimicrobials have also been shown to be effective against uropathogens. Sosa and Zunino [2009; 141] demonstrated that *Ibicella lutea* (Devils claw or Rams horn) extracts had an effect on bacterial growth rate and morphology of *P.mirabilis* by affecting its swarming differentiation, hemagglutination and biofilm formation on glass and polystyrene. Similarly, the use of *Coccinia grandis* (Ivy gourd) plant extracts have been reported to inhibit growth of UPEC *in vitro* [119]. Several other herbs that are used for the treatment of UTIs, but lacking scientific basis include *Agrimonia eupatoria* (agrimony), *Althea officinalis* (marshmallow), *Apium graveolens* (celery seed), *Arctium lappa* (burdock), *Elymus repens* (couchgrass), *Hydrangea aborescens* (hydrangea), *Juniperus communis* (juniper), *Mentha piperita* (peppermint*), Taraxacum officinalis* leaf (dandelion), *Ulmus fulva* (slippery elm) and *Zea mays* (corn silk; 3).

5.5.4. Silver coated catheters

Silver is a well-known antimicrobial exerting its bactericidal action by inactivating bacterial enzymes and causing cell wall damage [96]. Silver alloy and silver oxide coatings on catheters were investigated for reducing CAB, where silver alloy coating was found to be more effective [131]. In addition to reducing CAB, other studies also demonstrated the ability of silver alloy to decrease CAUTI compared to silver oxide or latex catheters [143]. However other researchers have observed conflicting results with no difference in antibiofilm effect of silver alloy and silver oxide [122, 143].

5.6. Enzyme inhibitors

Urease producing bacteria are known to produce crystalline biofilms and encrustation on catheters. Use of urease inhibitors such as acetohydroxamic acid and fluorofamide have been reported to reduce encrustation and thereby prevent CAB [98]. These urease inhibitors have

been also shown to prevent urea break down and pH increase *in vitro* by *P. mirabilis* besides decreasing the associated encrustation. Another enzyme target is N-acetyl-D-glucosamine-1-phosphate acetyltransferase, which is essential for peptidoglycan, lipopolysaccharide and adhesion synthesis. Inhibitors of the enzyme belonging to the N-substituted maleimide family have produced antibiofilm activity against *P. aeruginosa* and *S. epidermidis* compared to silver hydrogel coated catheters [17].

5.6.1. Bacterial interference

Use of nonpathogenic microorganisms to counteract pathogenic bacteria is known as bacterial interference [137]. Colonization of catheter surfaces with nonpathogenic bacteria can prevent adhesion and colonization by pathogens. The nonpathogenic *E. coli* 83972 has been extensively investigated both *in vitro* and *in vivo* in bacterial interference protocols [68]. Initially, studies with this nonpathogenic strain were done by instilling the bacteria into the bladder of patients. Colonization by *E. coli* 83972 protected these patients from symptomatic UTI. To reduce the need for instillation of bacteria into the bladder of patients, experiments were later conducted with catheters coated with the nonpathogenic strain [168]. This study also revealed that *E. coli* 83972 was effective in reducing symptomatic UTI similar to previous experiments with direct infusion of the bacteria.

5.6.2. Bacteriophages

Another potential approach investigated for controlling CAUTI is the use of bacteriophages. Catheters coated with T4 bacteriophage against *E. coli* and coli-proteus bacteriophage active against Proteus were exposed to *E. coli* ATCC 11303, *P. mirabilis* or saline. It was observed that phage treatment of catheters led to approximately 90% reduction in biofilm formation compared to control catheters [19]. It was also observed that the application of phage cocktail on catheters was more effective against bacteria than the use of a single phage [19]. When hydrogel coated catheters were pretreated with a five-phage cocktail, *P. aeruginosa* biofilm formation was reduced by 99% after 48 h [45].

5.6.3. Liposomes

Liposomes are carrier or delivery vehicles that can carry both hydrophilic and hydrophobic molecules to their target site for delivery. This helps to increase the half life of the drugs besides protecting them from the environment. Liposomes containing ciprofloxacin embedded in a hydrogel coated catheter were evaluated in a rabbit model to investigate its antibiofilm effect against *E. coli* induced CAUTI [121]. The results from this study revealed that liposomal ciprofloxacin treated group had a delayed onset of positive urine cultures compared to the control group.

5.6.4. Quorum sensing inhibitors

Quorum sensing between bacterial cells in a biofilm have been shown to be essential for biofilm formation and maintenance. Inhibition of quorum sensing could therefore provide a potential

route for the control of biofilms. *Delisea pulchra*, an algal species has been shown to produce furanones that interfere with autoinducer signaling and biofilm formation [92]. *In vitro* and *in vivo* sheep experiments using furanone containing catheters have been evaluated against *S. epidermidis* [35]. Similarly, use of azithromycin has been shown to inhibit the production of quorum sensing signals, swimming, swarming and twitching motilities, and biofilm formation *in vitro* [9].

5.6.5. Surface vibroacoustic stimulation

Catheters containing peizo elements can generate low energy acoustic waves that can lead to the formation of a vibrating coat along the catheter and prevent bacterial attachment and biofilm formation [60]. Scanning electron microscopy studies demonstrated that application of surface acoustic waves led to reduced biofilm formation by *E. coli*, *E. faecalis*, *Candida albicans* and *P. mirabilis*. An *in vivo* study in rabbits demonstrated that peizo element containing catheters with acoustic vibration led to a delayed positive urine culture compared to control animals [60]. The acoustic waves generated resulted in bacterial vibration at the same frequency, thereby preventing bacterial attachment and eventual biofilm formation.

6. Conclusion

Catheter associated urinary tract infections are the most common nosocomial infections and a vast majority of them are caused by biofilms formed on catheters. The complications caused by biofilms can undermine the patient's quality of life and threaten their health. The high incidence of CAUTI and the consequent complications warrants the development and application of effective control strategies. Prevention is predominantly based on enforcing guidelines for appropriate catheter placement and early removal. However, a comprehensive understanding of bacterial biofilm formation, pathogenesis and other key factors essential for development of UTIs would help in the development of novel and effective control strategies.

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