

Review Article

Importance of Biofilms in Urinary Tract Infections: New Therapeutic Approaches

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Bacterial biofilms play an important role in urinary tract infections (UTIs), being responsible for persistence infections causing relapses and acute prostatitis. Bacterial forming biofilm are difficult to eradicate due to the antimicrobial resistant phenotype that this structure confers being combined therapy recommended for the treatment of biofilm-associated infections. However, the presence of persistent cells showing reduced metabolism that leads to higher levels of antimicrobial resistance makes the search for new therapeutic tools necessary. Here, a review of these new therapeutic approaches is provided including catheters coated with hydrogels or antibiotics, nanoparticles, iontophoresis, biofilm enzyme inhibitors, liposomes, bacterial interference, bacteriophages, quorum sensing inhibitors, low-energy surface acoustic waves, and antiadhesion agents. In conclusion, new antimicrobial drugs that inhibit bacterial virulence and biofilm formation are needed.

1. Urinary Tract Infections

Urinary tract infections (UTIs) are one of the most important causes of morbidity and health care spending affecting persons of all ages, including young women, children, and the elderly. It is estimated that approximately 40% of women have had a UTI at some time in their lives [1].

These infections are traditionally classified based on clinical symptoms, laboratory data, and microbiological findings. UTIs are categorized as cystitis (infection of the lower urinary tract or bladder), pyelonephritis (infection affecting the upper urinary tract or the kidneys), and prostatitis (prostate inflammation) [2]. More recently, however, UTIs have been clinically classified into groups based on clinical factors and their impact on morbidity and treatment [3]. These categories are acute uncomplicated cystitis in young women, recurrent cystitis in young women, acute uncomplicated pyelonephritis in young women, complicated UTI, UTI related to indwelling catheters, UTI in men, and asymptomatic bacteriuria [3].

Sexually active young women are at greater risk of presenting UTIs (especially uncomplicated cystitis) due to their anatomy (short urethra) and certain behavioural factors. Uncomplicated cystitis is limited to a few pathogens, being

the most frequent *Escherichia coli*, causing approximately 80% of cystitis [3].

Recurrent UTIs appear in more than 20% of young women with acute cystitis and are divided into relapse (if all the infections are caused by the same microorganism) and reinfection (if the episodes are caused by different microorganisms). Relapses are categorized as complicated UTIs and require longer courses of antibiotics. Relapses in women have been related to the capacity of the microorganisms to form biofilm [4]. The clinical spectrum of complicated UTIs may range from cystitis to urosepsis with septic shock.

Acute pyelonephritis is a potentially organ- and/or life-threatening infection that often leads to renal scarring. Acute pyelonephritis results from bacterial invasion of the renal parenchyma. Bacteria usually reach the kidney by ascending from the lower urinary tract but may also reach the kidney via the bloodstream. The time of diagnosis and management of this UTI are very important for the impact on patient outcomes.

Acute bacteria prostatitis is a common but important genitourinary infection in men and is presented as a febrile UTI [5]. Acute bacteria prostatitis is most commonly caused by an ascendant UTI, with *E. coli* [6], *Proteus mirabilis*,

Pseudomonas aeruginosa, *Klebsiella*, *Enterococcus* spp., and *Serratia* spp. being the microorganisms most frequently involved [5]. Acute bacterial prostatitis can be caused by a sexually transmitted disease (gonorrhoea), although it is also very common in patients with benign prostatic hyperplasia following a UTI. The incidence of this infection is approximately 1-2 cases per 10,000 males.

Another important type of UTI is the asymptomatic bacteriuria which is defined as the presence of more than 100,000 CFU per mL of voided urine in subjects with no symptoms of UTI and can originate in the bladder or the kidneys [7]. Pregnant and elderly women have the highest rates of incidence of asymptomatic bacteriuria. Treatment is not recommended in the routine practice for asymptomatic bacteriuria, except in pregnant women and individuals undergoing invasive procedures [8]. The microorganisms most frequently found as a cause of asymptomatic bacteriuria are *E. coli*, *P. aeruginosa*, and Gram-positive bacteria such as *Enterococcus* and *S. aureus* [9].

Urinary catheters are a route of entry for bacteria. Between 10 and 20% of hospitalized patients are catheterized. Catheter-associated UTIs account for 40% of all nosocomial infections and are the most common source of Gram-negative bacteremia in hospitalized patients [10]. The role of biofilm forming pathogens in catheter-associated UTIs is explained in the present review. The pathogens most frequently found in this type of UTI are *E. coli*, *Proteus*, *Enterococcus*, *Pseudomonas*, *Enterobacter*, *Serratia*, and *Candida* spp. [11], being normally acquired exogenously via manipulation of the catheter and drainage device.

2. Bacterial Biofilms

Biofilms are currently estimated to be responsible for over 65% of nosocomial infections and 80% of all microbial infections [12].

Biofilm is defined as a microbiologically derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or each other and embedded in a matrix of extracellular polymeric substances (EPS) that they have produced. This matrix accounts for about 90% biomass [13], exhibiting an altered phenotype with respect to growth rate and gene transcription [14, 15]. Environmental changes are responsible for the transition from planktonic growth to biofilm [16] and cause changes in the expression of surface molecules, virulence factors, and metabolic status, allowing the bacteria to acquire properties that enable their survival in unfavourable conditions [17, 18].

Biofilms are ubiquitous and can be found in a wide variety of sites or niches. They can be formed by one or multiple bacterial species forming complex structures.

Biofilm formation is carried out in five steps which are represented in Figure 1 [19].

(i) *Reversible attachment of planktonic bacteria to surfaces.* The first attachment of the bacteria is influenced by attractive or repelling forces that vary depending on nutrient levels, pH, and the temperature of the site or niche [14]. In this step, flagella [20, 21] and

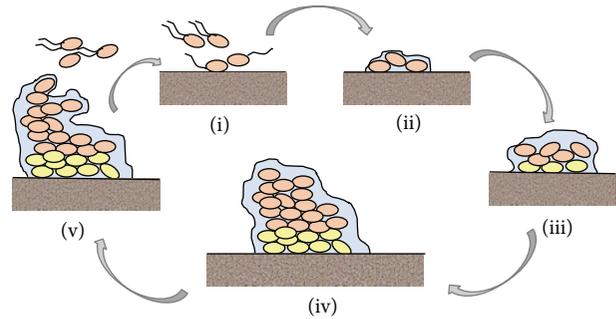


FIGURE 1: Biofilm formation steps. (i) Reversible attachment of planktonic bacteria to surfaces. (ii) Irreversible attachment to surfaces. (iii) Formation of the external matrix. (iv) Biofilms acquire a three-dimensional structure. (v) Biofilm detachment.

chemotaxis play an important role avoiding the action of the hydrodynamic and repulsive forces as well as selecting the surface [22], respectively.

- (ii) *Irreversible attachment to surfaces.* In the case of *E. coli*, it is mediated by type 1 pili, curli fibres, and antigen 43 that also favours the interbacterial interactions [23–26]. In the case of *P. aeruginosa* as well as other *Pseudomonas* species, transition from reversible to irreversible attachment has been well studied. It has been observed that *P. fluorescens* requires an ATP-binding cassette (ABC) encoded by the *lap* genes for carrying out this process [27]. On the other hand, *P. aeruginosa* requires the SadB protein and the two-component regulatory systems BfiSR for irreversible attachment [28, 29].
- (iii) *Formation of a complex layer of biomolecules [30] and EPS secretion that constitute the external matrix.* Production of polysaccharides in biofilm forming strains facilitates aggregation, adherence, and surface tolerance, allowing better surface colonization [31]. The *E. coli* matrix is composed of cellulose [32], polyglucosamine, and colonic acid [33]. The *P. aeruginosa* matrix is composed of two types of polysaccharides: the capsular and aggregative polysaccharides. Alginate is the main and most studied capsular polysaccharide produced by *P. aeruginosa* [34] and maintains the characteristics of protective dynamic polymers that present one or more cells. On the other hand, aggregative polysaccharides confer structural integrity to the biofilm [35]. Nucleic acids, such as DNA, proteins, surfactants, lipids, glycolipids, membrane vesicles, and ions such as calcium can also be found forming part of the matrix composition and may play an important role in the characteristics that biofilm structure confers to the cells.
- (iv) Biofilms acquire a three-dimensional structure when they reach maturity. These three-dimensional structures with macrocolony morphology depend on self-produced extracellular matrix components. EPS, adhesins, amyloid-forming proteins, and exopolysaccharides (all included in biofilm matrix) are required

to generate these structures in which gradients of nutrients, water, signaling compounds or waste products are present along the different areas of biofilm [36], conditioning the metabolism of the cells.

- (v) When biofilms are fully mature, detachment may occur. Detachment allows cells to again take on a planktonic state and can thereby form biofilm in other settings. It has been proposed that bacteria detachment could be caused by active mechanisms initiated by the bacteria themselves such as enzymatic degradation of the biofilm matrix and quorum sensing in response to environmental changes related to nutrition levels and oxygen depletion [37] and by passive mechanisms mediated by external forces and erosion [38–41]. Biofilm dispersal is an important step in a high number of bacterial species, allowing their transmission from environment to human host, between hosts, and even within a single host spreading the infection [39]. The role of c-di-GMP levels in the biofilm dispersion has recently been determined, being a second messenger used in signal transduction in a high number of bacteria species [42]. Thus, it has been proposed that high levels of c-di-GMP increase the sessile behaviour of the bacteria, while low levels increase the motility of the bacteria [43]. c-di-GMP affects EPS production, biofilm formation, cell length, and swimming motility in *E. coli* [44]. Nowadays, this second messenger is the subject of further research (for further review see [45, 46]).

Biofilms can also be found inside the host cells forming intracellular structures. The first report of intracellular bacterial communities (IBC) with biofilm-like properties was described in uropathogenic *E. coli* (UPEC) [24, 46]. It has been observed that a high number of IBC are associated with the development of chronic cystitis [47, 48]. The presence of IBC has also been described in children with recurrent urinary infections by light and confocal laser scanning microscopy. These structures have been associated with an *E. coli* strain presenting type 1, P, and S/F1C fimbriae and K1 capsule genes [49], indicating the important role of adhesion structures in biofilm formation.

3. Biofilms and Urinary Tract Infections

As previously commented, bacterial biofilms play an important role in medicine. According to the NIH, biofilm forming bacteria involved up to 80% of all infections [19], with urology being one of the main fields in which biofilm can become a serious problem. Biofilm can be found in the urothelium, prostate stones, and implanted foreign bodies [50].

Bacteria adhered to the uroepithelium and forming biofilm can invade the renal tissue causing pyelonephritis [51] and even be responsible for chronic bacterial prostatitis. In the latter case, an additional problem is the difficulties to diagnosis this prostatitis because the colonized bacteria may not be present in the prosthetic secretion or the urine samples [52].

Biofilms can not only develop into urethral stents but they can also form on catheters causing their blockage. Thus, catheter-associated UTI (CAUTI) is one of the most common care-associated infections around the world [53]. Several reports have associated CAUTI with more than 40% of health-care-associated infections in the United States [53]. Commensal perineal flora is involved in most CAUTI cases. More than 90% of these infections are monomicrobial with *E. coli*, *Pseudomonas aeruginosa*, enterococci, *Candida*, *Klebsiella*, or *Enterobacter* spp. being the most frequently isolated pathogens [54]. The environmental conditions created on the catheter surface make it an ideal site for bacterial attachment and formation of biofilm structures [55]. In this type of medical device, microorganisms producing urease, an enzyme that hydrolyzes urea to ammonium ions, can cause encrustation, formation of infected bladder calculi, and urinary obstruction. The formation of ammonium ions increases the pH of the urine, finally causing the precipitation of magnesium and calcium phosphate crystals [56, 57]. The pH value at which precipitation occurs is called nucleation pH [58]. These crystals can form a layer that protects bacteria from the antimicrobial effects of compounds used for coating or impregnating the catheters [59]. *Proteus mirabilis* is the main source of this problem in urinary infections [60] and presents several virulence factors that allow it to form biofilm such as mannose-resistant fimbriae, capsules, and urease [61]. Other microorganisms such as *Proteus vulgaris* and *Providencia rettgeri* also have the capacity to produce crystalline biofilms [56].

In addition, biofilm formation may even result in the increased ability of strains causing acute prostatitis to persist in the prostatic secretory system and lead to the recurrent UTIs characteristic of chronic bacterial prostatitis [62]. In fact, it has been shown that after an episode of acute prostatitis cultures of expressed prostatic secretions are still positive 3 months after the end of a 6-week therapeutic regimen in one-third of men [63]. It has been reported that 63% of *E. coli* strains collected from patients with prostatitis were “*in vitro*” biofilm producers in contrast to 40% of *E. coli* strains causing cystitis and pyelonephritis [62]. Biofilm formation may be the reason why bacterial prostatitis is so difficult to eradicate using conventional treatments.

4. Biofilms and Persistent Infections

Acute UTI caused by bacteria can lead to recurrent infection, which is defined as a “reinfection” when it involves a strain other than that causing the original infection, or it is defined as a “relapse” when it is caused by the same strain as that involved in the original UTI. Recurrent UTIs are common among young, healthy women, despite their urinary tracts generally being anatomically and physiologically normal [64]. Approximately 25% of women with an episode of acute cystitis later develop recurrent UTI, which represents a substantial burden to the healthcare system. Consequently, the number of studies to elucidate the factors predisposing recurrent UTI in order to develop effective methods of prevention and therapy is encouraged to be increased [65].

Several studies observed that most of isolates collected from patients with relapse infections were biofilm producers “*in vitro*” [66]. Relapse by uropathogenic *E. coli* (UPEC) has been related to the ability of pathogenic strains to form biofilm. In these cases, biofilm production may be the key determinant for the persistence of UPEC in the vaginal reservoir, the bladder epithelial cells, or both. Thus, in a study carried out in the Hospital Clinic of Barcelona, 43 ambulatory female patients ≥ 18 years of age were included following an index episode of cystitis or pyelonephritis, and they were clinically followed for at least 6 months, collecting urine cultures every month. Eighty *E. coli* strains were collected, 27 causing relapses and 53 causing reinfections. Among them, 74% and 42% were “*in vitro*” biofilm producers, respectively, demonstrating a relationship between persistence, relapse, and biofilm formation [4].

5. Biofilms and Antimicrobial Resistance

One of the most important advantages of biofilm status is the antimicrobial resistance shown by these structures. Biofilm can be up to 1000-fold more resistant to antibiotics than planktonic cells due to several mechanisms [67–71].

- (i) *Limitation of antibiotic diffusion through the matrix.* Some antimicrobial agents are unable to diffuse through the matrix or sometimes the time required for the antibiotic to penetrate into biofilm is longer than the duration of treatment or the antibiotic lifetime. Thus, for example, aminoglycosides penetrate more slowly through the matrix than β -lactams.
- (ii) Transmission of resistance genes within the community can occur. Thus, plasmids, transposons, and other mobile genetic elements can be transmitted between cells forming biofilm by their close relationship, spreading resistance markers.
- (iii) Expression of efflux pumps is also considered a mechanism for antimicrobial resistance not only in planktonic cells but also in biofilms structures [72, 73].
- (iv) *Inactivation of the antibiotic by changes in metal ion concentrations and pH values.* Antibiotics able to diffuse can be inactivated by the pH inside biofilm. This change in the pH could antagonise the activity of the antibiotic.
- (v) The presence of metabolically inactive cells denominated persister cells. Persisters are dormant variants of regular cells, not mutants, which may form small colony variants that are high tolerant to extracellular stresses. They are highly tolerant to antibiotics forming a reservoir of surviving cells [74] able to rebuild the biofilm population [74–76]. The tolerance to antibiotics could be explained by their reduced metabolism and their ability to switch off the antibiotic targets, such as protein synthesis or DNA replication. The acquisition of this persister status is mediated by toxin-antitoxin modules [77]. Taking into account that several antimicrobial agents,

such as penicillin, only kill actively growing bacteria, persister cells are a problem for biofilm eradication. Proteins required for maintaining persisters may represent excellent targets for the discovery of compounds capable of effectively treating chronic infections and biofilm-related infections.

The level of resistance depends on biofilm stage. Thus, in the reversible attachment step, antibiotics and antibiofilm are the most effective, because the bacteria have not connected themselves in the matrix and are vulnerable to the action of antibiotics and host immune system [19].

Once the bacteria begin to secrete EPS and the attachment becomes irreversible, biofilm is more resistant to antibiotics and host immune responses [78]. The matrix protects the cells within it from exposure to innate immune defences and antimicrobial treatments [79, 80] and facilitates communication among them through biochemical signals. Some biofilms have been found to contain water channels that help to distribute nutrients and signalling molecules [81]. Other studies suggest that resistance of bacteria in biofilm to a high number of antibiotics can be due to the density and physiological state of the culture rather than their residence within biofilm [82]. In addition, the spread of resistance markers and virulence factors can be promoted through their structure [83]. It has been demonstrated that the mode of growth of biofilm increases the ability of *S. aureus* to disseminate plasmid-borne antibiotic resistance determinants by both conjugation and mobilization of these mobile genetic elements [84]. This phenomenon could be facilitated by the close cell-to-cell contact inside biofilms and also by the stabilization of these contacts that may be favored by the biofilm matrix.

6. Antimicrobial Treatment of Biofilms

Treatment of biofilm-associated infections is a field that requires further study, in part due to the high levels of antibiotic resistance exhibited by biofilm structures conferred in part by the exopolysaccharide matrix. Several studies recommend combination therapy as the treatment of choice in biofilm-associated infections, with macrolides being one of the first antibiotics chosen [85]. Macrolides (erythromycin, clarithromycin, and azithromycin) present high “*in vitro*” and “*in vivo*” antibiofilm activity against biofilm-associated infections caused by Gram-negative bacteria inhibiting the production of a key component of the matrix, alginate [85]. Macrolides have been shown to be effective against *P. aeruginosa*, another Gram-negative bacteria, and more recently against *Staphylococcus* spp. biofilms [86]. This antibiofilm activity was first described “*in vitro*” exposing *P. aeruginosa* sessile cells to clarithromycin and erythromycin [86]. The antibiotic combination, clarithromycin plus vancomycin, demonstrated the ability to eradicate both biofilm and planktonic cells [87] as well as to eradicate biofilm on the titanium washers used in animal experiments [88]. Roxithromycin plus imipenem favour a higher penetration of neutrophils into biofilm structure destabilizing the biofilm [89]. Conversely, macrolides have been shown to enhance biofilm

formation in Gram-positive bacteria due to an increase in the expression of biofilm-related genes such as *icaA*, *atlE*, *fruA*, *pyrR*, *sarA*, and *sigB* [90]. This fact has an important clinical implication because the macrolide levels needed for enhancing biofilm formation could be found in clinical niches or settings.

Another approach using antimicrobials consists in coating and impregnating the catheters with these antimicrobial agents. The aim of this procedure is to avoid bacterial attachment to the catheter surface and the posterior development of biofilm [91]. In this sense, the silver has also been used to coat catheters because it has bactericidal actions. Silver has broad-spectrum antimicrobial activity. The antimicrobial action of silver compounds is proportional to the bioactive silver ion released and its availability to interact with bacterial or fungal cell membranes. It has been observed that silver alloy coating prevents adherence and the growth of biofilm-embedded bacteria by 50% [92, 93]. Synthetic cationic peptide variants derived from natural peptides have been used as strategy to target biofilm [94].

More recently, some substances showing antibacterial properties, such as gentine (gentian violet plus chlorhexidine), nitrous oxide, and nitrofurazone (nitrofurantoin), have been used to modify the surface of urinary catheters. However, the risk of using antibiotics to treat the catheter surface may lead to the development of antimicrobial resistance when the drug levels become subinhibitory [60].

7. New Trends in Antibiofilm Treatments

Biofilms eradication is difficult due to the high level of antimicrobial resistance showed by these structures. In spite of the previously commented approaches, new therapeutic options are being studied as an alternative to treatments with existing antibiotics in order to avoid not only biofilm formation but also the emergence of resistant bacterial populations in underlying tissues. Here a review of these new approaches is provided.

7.1. Catheters Coated with Hydrogels or Antibiotics. Hydrogels are cross-linked, insoluble, hydrophilic polymers that trap water. This characteristic provides the catheter with an increase in surface lubrication which consequently decreases the bacterial adhesion to this surface and demonstrates a role in the reduction of encrustation of catheters. However, the ability of these hydrogels to prevent CAUTI remains unclear [95]. Kazmierska et al. [96] observed that a hydrogel layer increased the aggregation of planktonic cells, causing an increase in nucleated crystals, provoking more rapid catheter blockage in comparison with the uncoated silicone. However, this negative effect was suppressed when active agents were added to the hydrogel.

In this sense, a high number of antimicrobial agents and other chemical compounds have been used to coat catheters. Silver alloy has been used in hydrogel-coated urinary catheter observing a decrease of up to 45% of CAUTI [97, 98]. Minocycline-rifampicin-coated catheters have been shown to

inhibit the biofilm formation of Gram-positive and Gram-negative pathogens, except *P. aeruginosa* and *Candida* spp. [99]. However, one problem with this may be the possible development of resistant phenotypes among the bacteria [100]. However, no silver-resistant mutants were collected in the aforementioned studies.

7.2. Nanoparticles. A nanoparticle is a microscopic particle with a dimension of less than 100 nm. Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical, and electronic fields. These particles have the capacity to attach and penetrate into bacterial cells, disrupt the bacterial membrane, and interact with chromosomal DNA [101].

Nanoparticles of MgF have been used for coating glass surfaces observing an inhibition of biofilm formation by both, *E. coli* and *S. aureus* [101]. Catheters have also been coated with these nanoparticles and a significant reduction of bacterial colonization was observed over a period of 1 week in comparison with the catheter uncoated catheter control. This group also demonstrated the antibacterial and antibiofilm activity of yttrium fluoride (YF₃) nanoparticles which showed low solubility and provided extended protection. In addition, another advantage of these nanoparticles was their low cytotoxicity [102].

Microwave irradiated CaO nanoparticles (CaO-NPs) have also shown the potential to inhibit biofilm formation against Gram-negative and Gram-positive bacteria [103].

Silver nanoparticles have also been used for impregnating medical devices due to the silver antimicrobial properties previously commented in this review [104]. These nanoparticles have been used in medical and pharmaceutical nano-engineering applied to the delivery of therapeutic agents, diagnostic approaches, and as part of biosensors [104]. Several studies have demonstrated the “*in vivo*” and “*in vitro*” inhibition of biofilm formation by numerous bacterial species and using determined nanoparticle concentrations. However, the mechanism of action of silver nanoparticles remains unknown [105].

Another aspect related to silver nanoparticles is the toxicity to eukaryotic cells which remains uncharacterized.

7.3. Iontophoresis. Iontophoresis is a physical process in which ions flow diffusively in a medium driven by an applied electric field. This method enhances the efficacy of antibiofilm agents “*in vitro*” [106]. Thus, it has been observed that low electrical currents enhance the activity of tobramycin and biocides against *P. aeruginosa* biofilm. However, this effect has only been observed among those antibiotics that are effective against planktonic cells [107]. Iontophoresis has also been studied to prevent biofilm formation and encrustation by *P. mirabilis* showing that the application of electric current to these catheters fitted with silver electrodes significantly decreased their encrustation [108]. Nevertheless, “*in vivo*” studies have yet to be performed in this respect.

7.4. Enzyme Inhibitors. Urease, the enzyme that allows *P. mirabilis* to hydrolyze urea to ammonium ions, has been

an important target in the study of new antibiofilm compounds. In this sense, fluorofamide has been a candidate molecule because it is able to prevent the increase in pH by *Proteus mirabilis* “*in vitro*”, thereby inhibiting the formation of urea crystal and the subsequent encrustation and catheter obstruction [109, 110]. Other natural compounds, such as vanillic acid [111], natural plum juice [112], and germa- γ -lactones [113], among others, presented the ability to strongly inhibit bacterial growth as well as the formation of crystals in catheters by the inhibition of the urease enzyme.

In one study Lu and Collins [114] generated a bacteriophage which expressed a biofilm-degrading enzyme during infection. The enzyme associated with the bacteriophage was DspB and it is produced by one species of *Actinobacillus*. DspB hydrolyses a crucial adhesion needed for biofilm formation and integrity in both *E. coli* and *Staphylococcus* [115] and attacks the bacterial cells in the biofilm and the biofilm matrix simultaneously. The percentage of eradication using this bacteriophage-enzyme combination was about 99.9% [114].

In recent years, the second messenger, c-di-GMP, has been studied in depth because it is highly conserved among bacterial species, being an important candidate for studies on biofilm inhibition. c-di-GMP is synthesized via diguanylate cyclases (DGC). Inhibition of DGC activity leads to a reduction in biofilm formation by a decrease in the intracellular levels of c-di-GMP [116]. Several molecules have been shown to inhibit biofilm formation on urinary catheters by *P. aeruginosa* via an inhibition on the DGC WspR enzyme and they have the ability to disperse formed biofilm of *P. aeruginosa* and *A. baumannii*. These small molecules are denominated LP 3134, LP 3145, LP 4010, and LP 1062 [117].

7.5. Liposomes. The use of liposomes could be one method for improving the effectiveness of antibiotics [118]. They act as carriers of drug molecules, increasing their length of life [119] and reducing toxicity in the host [120, 121]. Liposome-encapsulated antimicrobial agents have been successfully tested in humans and in animal models, being directed to eradicate protozoa, fungal, and bacterial infections [122, 123]. Liposomes can be applied in the eradication of formed biofilm because when the antibiotic is encapsulated in a liposome carrier it does not interact with the EPS, improving its antibiofilm effect, and it is protected from degradation by antibiotic-inactivating enzymes (such as β -lactamases) which can appear in the biofilm matrix [124]. Thus, liposomal containing tobramycin and bismuth reportedly penetrated and killed bacteria in the core of the *P. aeruginosa* biofilms, in contrast to both free compounds that only killed and detached bacteria from the biofilm surface [125]. Liposomes containing clarithromycin have been tested against biofilm-forming *P. aeruginosa*, observing a significant reduction in biofilm production as well as in bacterial twitching, swarming, and swimming motility. In addition, clarithromycin-entrapped liposomes showed less cytotoxicity than the free drug [126]. In spite of the excellent results obtained, more studies are needed in CAUTI and other biofilm-related infections.

7.6. Bacterial Interference. This method is related to the antagonism between different bacteria species during the colonization of surfaces and biofilm formation. Briefly, the colonization of a surface by nonpathogenic bacteria could prevent the adherence of pathogenic bacteria thereby avoiding infection [60]. Several avirulent strains of *E. coli* have been used as a method to reduce urinary catheter colonization by a wide variety of pathogens [127, 128]. Thus, the *E. coli* HU2117 strain, derived from *E. coli* 83972, that causes persistent colonization without symptomatic infection [129–131], has been used for coating urinary catheters, observing a reduction of biofilm formation by other pathogens [128]. This strain presented a deletion of the *papG* gene resulting in a lack of P-fimbriae. The *E. coli* 83972 strain has also been used for coating urinary catheters, demonstrating a reduction in the development of UTIs in persons undergoing an intermittent catheterization programme [132]. A study performed among catheterized patients with spinal cord injury who were inoculated with a nonpathogenic *E. coli* strain in the bladder showed that these patients had less probability of developing an episode of UTI during the one-year follow-up period [133].

7.7. Bacteriophages. Bacteriophages are the natural predators of bacteria. They are viruses that specifically infect bacteria. Among them, lytic phages are able to disrupt the normal bacterial metabolism, favouring viral replication [134]. Phages have been used for treating some infectious diseases in humans mainly related to *S. aureus* [135] due to their bactericidal activity. The phage characteristics that allow them to control biofilm are the capacity to replicate at the site of infection, the production of enzymes (depolymerases) that degrade the EPS of the biofilm matrix [136–139], and their capacity to propagate through the biofilm [140]. These phages have been incorporated into hydrogel-coating catheters, and a reduction has been observed in biofilm formation by *Staphylococcus epidermidis* and *P. aeruginosa* [141, 142]. In addition, the use of lytic bacteriophages against established biofilm of *P. mirabilis* and *E. coli* caused a reduction of three to four log cycles [134]. These lytic phages also prevented biofilm formation on catheters coated with hydrogel containing bacteriophages. The reduction of formation observed was about 90% [134].

7.8. Quorum Sensing Inhibitors. Quorum sensing (QS) is a cell-density-dependent chemical signalling system that allows individual cells to release small signal molecules to the surroundings to make their presence known [143]. The small signal molecules are known as autoinducers and coordinate cell-density-dependent gene expression [144]. QS is used to coordinate gene expression and regulate numerous processes that are involved in virulence such as motility and biofilm formation [145] being necessary for planktonic bacteria to adopt the biofilm phenotype.

An efficient quorum sensing inhibitor (QSI) should have the following characteristics [146]:

- (1) have a low molecular mass able to inhibit the expression of genes related to QS,

- (2) be highly specific for the QS-regulators,
- (3) not show toxicity to the eukaryotic hosts,
- (4) not interfere with the basal metabolic processes of bacteria in order to avoid the development of resistances,
- (5) be chemically stable, resistant to host metabolism, and able to reside in the host for a sufficient long time.

Several QSI have been identified to date, many having been isolated from nature [147–151]. For example, the pyrimidinone compound inhibits biofilm formation and disrupts and removes the biofilm deposited. HSL analogues are compounds analogous to the QS signal and compete with the native signals for binding to the receptor, blocking QS, and inhibiting biofilm formation in *S. aureus* [152]. Garlic extract was found to enhance the susceptibility to tobramycin by altering the architecture of the bacterial biofilms [150]. Peptides also show QSI activity. Thus, the RNAIII inhibiting peptide was able to inhibit *agr*-mediated biofilm formation in drug resistant *S. epidermidis* [153, 154].

7.9. Low-Energy Surface Acoustic Waves. It has been demonstrated that surface acoustic waves (SAW) interfere with adhesion of planktonic microorganisms to cellular surfaces [155]. SAW reduces biofilm bioburden on catheter segments in suspensions with several Gram-negative [156] and Gram-positive bacteria as well as fungi indicating its efficacy against a broad spectrum of microorganisms. Power intensities of 0.1 and 0.2 mW/cm², generating vibration frequencies of 95 KHz and 220 kHz with acoustic pressure amplitudes of 0.1 and 0.22 kPa, respectively, were the conditions used in the “*in vitro*” experiments on avoiding adhesion [157].

The efficacy of this approach was studied in a rabbit model, and it was observed that catheter-associated vibrating activators were found to maintain urine sterile for 7 days, whereas control catheters (without vibrations) resulted in bacteriuria within 1.5 days [157]. This effect was observed against *E. coli*, *Enterococcus faecalis*, *Candida albicans*, and *P. mirabilis*.

7.10. Antiadhesion Agents. The prophylaxis of UTIs using antiadhesive compounds/molecules is currently an important objective in clinical research [158].

The main characteristic of an antiadhesive compound is that it should specifically interact with the adhesins of the pathogen, inhibiting the union between pathogen and eukaryotic cell [159, 160]. These antiadhesive compounds cause a decrease in invasion or infection of host epithelial cells, also avoiding recurrence. One of the compounds most frequently studied is cranberry extract [161]. The antiadherence effect of cranberry against uropathogenic *E. coli* (UPEC) is due to the presence of A-type proanthocyanidin trimers in the cranberry extract [162, 163] that acts as an antiadhesion agent. Other antiadhesion agents are those denominated mannosides, curlicides, and pilicides. These agents inhibit the biogenesis of adhesins required for biofilm formation and adhesion to epithelial cells. The most studied agents are the mannosides that inhibit FimH attachment to host receptors.

FimH is the tip of the type 1 fimbriae of *E. coli* that mediates the first step in biofilm formation. Mannosides seem to have a good prophylactic role in UTIs caused by *E. coli* since they not only interfered with adherence but also enhance the effect of the antimicrobial agent cotrimoxazol [164]. In this sense, nanodiamond particles, covalently modified with mannose moieties, are able to efficiently inhibit *E. coli* type 1 fimbriae-mediated adhesion to eukaryotic cells [165].

Salicylate is a member of a large group of pharmaceuticals referred to as nonsteroidal anti-inflammatories and it is the active component of the analgesic aspirin. Salicylate has shown to decrease biofilm formation of UPEC inhibiting type 1 fimbriae expression. In addition, the effect of salicylate in biofilm reduction could be intensified by the decrease of OmpA expression that causes a decrease in the extracellular matrix [166].

In addition, bacterial biofilms seem to be reservoir for molecules that act as antagonists of bacterial adhesion. An example is a polysaccharide produce by *E. coli* that excludes *S. aureus* from mixed *E. coli* and *S. aureus* biofilms [167].

In conclusion, the possible patient outcomes related to biofilm-related infections make the in-depth search for compounds with antibiofilm properties necessary in order to prevent the formation of and/or disrupt the development of biofilm. The ideal situation is a compound or a group of compounds that present not only antibiofilm activity but also the capacity to eradicate multidrug-resistant bacteria. It is also important to study the antibiofilm activity of new combinations of therapeutic strategies including new ones and old antibiotics. Virulence factors should be considered important targets for developing antivirulence compounds that may be applied in the prevention and treatment of infectious diseases.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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