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Virulence Factors and Innovative Strategies for the Treatment and Control of Uropathogenic *Escherichia coli*

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Abstract

Urinary tract infections (UTIs) are considered to be the most frequent bacterial infections. *Escherichia coli* is the major factor of community-acquired UTI (80–90%) and a large part of nosocomial UTI (30%), including cystitis, pyelonephritis, prostatitis, and asymptomatic bacteriuria. Uropathogenic *E. coli* (UPEC) shows a variety of virulence factors that allow their transition from the intestinal tract to the urinary tract and causing infection. The virulence factors responsible for pathogenesis outside the gastrointestinal tract belong to various functional groups. Antimicrobial resistance among *E. coli* causing UTIs is increasing in many countries around the world. This paper presents key virulence factors of UPEC such as adhesins, toxins, iron acquisition systems, and biofilm formation by UPEC, which are major problems in patients with long-term catheterization. The resistance of UPEC to antibiotics and innovative strategies of treatment and control of UPEC including drug therapy, preventive vaccines, probiotics, cranberry as source of antimicrobial metabolites, bacteriophages, new therapeutic antibiofilm treatment such as engineered phages, nanoparticles, and plant-derived antibacterial agents are also presented.

Keywords: UPEC, UTI, virulence factors, biofilm, antimicrobial resistance, treatment of UPEC, prevention

1. Introduction

Urinary tract infections (UTIs) are considered the most frequent bacterial infections in humans usually caused by *Enterobacteriaceae*. Among them, *Escherichia coli* is a predominant etiological factor of UTI [1]. The pathogenic *E. coli* strains belong to different pathotypes including enteric *E. coli* and extraintestinal *E. coli* (ExPEC). Seven major pathotypes of enteric *E. coli* cause mainly

gastroenteritis but sometimes are responsible for diseases outside the intestinal tract [2]. Three pathotypes of the ExPEC are able to exist in the gut but do not cause diseases in this place. Whereas, colonization by the ExPEC strains of other host niches including the central nervous system, blood, and the urinary tract leads to illness in human [3]. Among ExPEC, uropathogenic *E. coli* (UPEC) is the most frequently associated with human diseases. UPEC strains cause 80–90% of community-acquired UTIs and more than 30% of hospital-acquired UTIs [4]. Development of UTIs depends on anatomical factors of host, defense mechanisms, and virulence factors of infecting microorganism. Bacterial infections of the urinary tract are important problem, because about 60% of women in the United States will have at least one UTI during their life. About 8 million physician visits per year are related to these often chronic infections, making UTIs a problem of economic and medical significance [5]. UPEC can colonize the bladder and cause cystitis or may ascend into the kidneys, causing pyelonephritis [3]. *E. coli* may also spread from the urinary tract to the bloodstream causing bacteremia in above 30% of cases and the potential sepsis [6]. The presence of high numbers of *E. coli* in the urine without the clinical symptoms is referred as asymptomatic bacteriuria (ABU) and such infection in healthy, nonpregnant women is generally not treated [7]. Infections of the urinary tract occur when *E. coli* enter through the urethra and effectively colonize the bladder. *E. coli* is the most common pathogen causing cystitis, pyelonephritis with the possibility of causing kidney damage and death. This microorganism can induce acute renal failure and in case of complications after renal transplantation, *E. coli* is the most common clinical isolate [8]. It is considered that human intestinal tract is a primary reservoir of UPEC strains, although in some cases, clonal group of UPEC strains can be transmitted by contaminated food [9]. Host inflammatory responses on the breach of the sterile urinary tract by UPEC consist of the production of cytokines and chemokines, neutrophil influx, the exfoliation of infected bladder epithelial cells, and the generation of reactive nitrogen and oxygen species [5]. Genomic differences among UPEC and other *E. coli* show evolutionary adaptations, which enable UPEC to colonize environmental niches within the urinary tract such as epithelia lining the luminal walls of the urethra, bladder, renal pelvis, and collecting ducts of the kidneys [10].

UPEC strains have different virulence factors that enable the bacteria to adhere and colonize the uroepithelial cells and to establish the UTIs. UPEC harbor more genes encoding adhesins, iron acquisition systems, and toxins than K12 strains and commensal *E. coli* isolates. These virulence genes are often encoded on mobile genetic elements called pathogenicity islands [11, 12].

This paper describes key virulence factors of UPEC, the role of biofilm formation by UPEC in development of UTIs and in catheter-associated UTIs. The resistance to antibiotics and new therapeutic approaches of treatment and control of UPEC will be also discussed.

2. Virulence factors of UPEC

2.1. Adhesins

Adhesive proteins as the most important determinants of pathogenicity of UPEC strains are arguable [13], but based on many observations of ABU strains, it was found that these strains are nonadherent and nonhemolytic [14]. UPEC adhesins activate host signaling

pathways that promote bacterial invasion [15]. Bacterial adherence to urothelium is important in the development of UTI because it allows the bacteria to persist in the urinary tract against flushing by urine flow. Function of type 1 fimbriae as virulence factors in human pathology remains unclear because they are expressed in both commensal and pathogenic *E. coli* strains [16, 17]. The type 1 fimbriae are heteropolymeric surface organelles that consist of several subunits. These fimbriae bind *E. coli* cells to the urothelial mannosylated glycoproteins uroplakin by subunit FimH, which is located at the distal tip of the type 1 fimbriae. UPEC commonly expresses FimH that efficiently bind monomannose- and trimannose-containing glycoprotein receptors. Whereas, commensal *E. coli* strains usually bind to trimannose residues [18]. Binding of FimH to uroplakins that are expressed in the differentiated urothelium of the bladder and urethra causes adhesion and cellular invasion of *E. coli* and promotes formation of intracellular bacterial communities which leads to the acute stage of infection [19, 20]. FimH adhesin enables UPEC to escape before the immune response by internalization within urothelial cells. Inside infected urothelial cells, *E. coli* is harbored within vesicles [21, 22]. Blocking of FimH adhesin with antibodies or inactivity of the *fimH* gene has a negative effect on the ability of UPEC to colonize the bladder epithelium [5]. *fimH* gene is the most commonly identified virulence gene in the isolates causing UTI [17].

About 80% of UPECs express P fimbriae that are frequently associated with acute pyelonephritis [23]. P fimbriae are encoded by *papA-K* gene operon which can be localized on one or more pathogenic-associated islands [24]. The P-fimbrial-tip adhesins (PapG adhesins) bind to Gal α (1–4) Gal in glycosphingolipids of the membrane of urothelial cells localized in the kidney. The PapG adhesins are encoded by four classes of *papG* genes but only two of them are associated with uropathogenicity. Class II adhesin genes are predominant among the isolates from pyelonephritis and from renal transplant patients, while class III genes are found more frequently among cystitis isolates [25–27]. Attachment of P fimbriae to receptors leads to activation of the immune cell response and to the development of inflammation- and pain-associated with UTIs. P fimbriae improve bacterial colonization of the tubular epithelium that can adversely affect renal filtration leading to total obstruction of the nephron and consequently contributes to the full pathophysiology of pyelonephritis [14].

S fimbriae of *E. coli* bind to sialyl galactosides occurring in the receptors of erythrocytes and renal tubular epithelium cells, and are also involved in UTIs development. S fimbriae show binding to epithelial cells of lower urinary tract and kidney and may facilitate bacterial dissemination within host tissues [15, 28].

E. coli strains harboring operons coding fimbrial Dr and afimbrial Afa adhesins are also associated with UTIs. Dr adhesins bind to decay-accelerating factor (DAF) which is widely distributed along the urinary tract and plays an important role in colonization of urinary tract by Dr adhesin-producing *E. coli* [29]. UPECs with Afa adhesins have a tropism to renal tissue and have the ability to induce chronic or recurrent infection [30]. The research recently conducted by Muenzner et al. [31] showed that uropathogenic *E. coli* strains, which express the Dra/AfaE adhesins, bind to CEACAMs (carcinoembryonic antigen-related cell adhesin molecules) present on epithelial cells. The interaction of CEACAMs with Dra/AfaE adhesins causes increase of integrin activity, promote matrix adhesion, and suppress epithelial exfoliation, which promotes host infection.

Curli are highly adhesive extracellular amyloid fibers produced by UPEC and other *Enterobacteriaceae* [32]. The major subunit of curli is the CsgA [33]. Curli promote adherence to epithelial cells and resistance against the human antimicrobial peptide LL-37, and also cause induction of the proinflammatory cytokine IL-8. They exhibit exclusive role in promoting UPEC biofilms and represent one of the major biofilm components [34]. Curli are produced at limitation of nutrients and salts, at reduced oxygen tension and at temperature below 30°C. However, it is believed that many pathogenic bacteria and commensal strains can also express curli at 37°C during infection in humans [35]. Curli fimbriae interact with serum proteins and this might promote bacterial dissemination in host. UPEC strains-producing curli are more likely to cause urosepticaemia than strains which do not produce curli [36].

2.2. Toxins

Production of toxins by UPEC is an important virulence factor because they may induce an inflammatory response and lead to symptoms of urinary tract infections. The most important virulence factor of UPEC is α -hemolysin (HlyA). This toxin is strongly proinflammatory and leads to secretion of IL-6, IL-8, and chemotaxins that increase clinical severity in UTI patients [27, 37]. HlyA belongs to the family of RTX (repeats in toxin) [38]. HlyA is a lipoprotein of 110 kDa that forms pores in host cells, leading at high concentrations of HlyA to cell lysis, that enable UPEC to defeat mucosal barriers, damage effector immune cells, and gain access to nutrients and iron [39]. At sublytic concentrations, HlyA implicates the inhibition of chemotaxis and bacterial killing by phagocytes and induces apoptosis of neutrophils and renal cells, and also promotes the exfoliation of bladder epithelial cells [40]. Hilbert et al. [41] found that cytotoxicity, cytokine suppression, and HlyA production were tightly linked in clinical strains, and that *E. coli* utilizes HlyA to inhibit epithelial cytokine production *in vitro*. HlyA is responsible for about 50% of UTIs cases which leads to renal complications [27].

Cytotoxic necrotizing factor 1 (CNF1) is produced by approximately one third of UPEC [14]. The toxicity of this protein is linked with its ability to constitutive activation of the Rho GTPases that affect numerous cellular functions such as the formation of actin stress fibers and membrane ruffle formation. The result is the entry of *E. coli* into urothelial cells [42]. CNF1 promote apoptosis of bladder epithelial cells, probably stimulating their exfoliation and increasing bacterial entry to underlying tissue [43]. Besides, CNF1 inhibits activities of neutrophils, reducing phagocytosis and antimicrobial activity [44].

Secreted autotransporter toxin (Sat) is referred to as serine protease autotransporter and is associated with pyelonephritic *E. coli* strains. Sat is considered a virulence factor because it has toxic activity against cell lines of bladder or kidney origin. Sat induces elongation of cells and loosening of cellular junctions in cell lines of kidney. Furthermore, Sat triggers vacuolation within the cytoplasm of both human bladder and kidney cell lines [45]. Another secreted toxin called Vat (vacuolating autotransporter toxin), often expressed by UPEC strains, shows the ability to induce a variety of cytopathic effects in target host cells, including swelling and vacuolation. However, the role of Vat in UTI pathogenesis has not been thoroughly studied [46].

2.3. Iron acquisition systems

Limiting iron availability in the urinary tract is an important host defense against bacterial pathogens. For growth and metabolic activity, bacteria require a cytoplasmic iron concentration of about 10^{-6} M, while free iron concentrations in the mammalian host are extremely low (10^{-25} M in the blood and lower at other sites of organism) [47]. Consequently, pathogenic bacteria have to be equipped with systems for acquisition of iron from the host. Bacteria produce siderophores, low-molecular-weight molecules that bind and transport iron (Fe^{3+}) through the bacterial membrane into cytosol where the iron is released. Iron bound siderophores are transported through (with) specific receptors at the outer membrane that facilitate carrying of siderophore-iron complexes through the bacterial membrane. Common siderophore system is enterobactin and its receptor FebA, which is expressed by both pathogenic and K12 *E. coli* strains, although in the context of infection and also other siderophore systems (salmochelin and Iron, aerobactin and IutA, and yersiniabactin and FyuA) have been observed in UPEC [3]. The occurrence of these systems in UPEC strains difficult to identify certain systems as virulence factors of UPEC [48].

3. Biofilm formation by UPEC

Currently biofilm is defined as a structured bacterial community embedded in a self-produced matrix and attached to an abiotic or living surface [49].

The biofilm matrix is composed with exopolysaccharides, which form a hydrated viscous layer and protects enclosed bacterial cells against dehydration, toxic molecules such as antibiotics, and from immune system of host [50]. Bacteria within the biofilm differ in gene expression resulting in a phenotype different from the planktonic bacteria. The slow growth of pathogens in biofilms is the major factor conferring resistance to antibiotics [51]. The ability of bacteria to form biofilm is associated with pathogenesis of numerous diseases. Biofilm formation results in chronic, persistent infections that are difficult to eradicate with antimicrobial treatment. It is believed that biofilms occur in up to 60% of human infections [52]. UPEC can persist within the bladder tissue in underlying epithelial cells or create biofilm-like pods in the recurrent cystitis [53]. Biofilm of *E. coli* may form on the urothelium and is involved in infections associated with biomaterials such as catheters or prostheses. UPEC strains are frequently isolated from biofilms formed in the lumen of catheters and showing resistance to antibiotic treatment [54]. Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection, and approximately 80% of UTIs acquired in the hospital are associated with catheterization [55]. The insertion of indwelling catheter into the bladder increases the susceptibility of patients to UTIs, because these devices are the initiation site of infection by introducing opportunistic organisms into the urinary tract [56]. UPEC strains are capable of colonizing the intestinal and vaginal tracts, and these sites are potential reservoirs of microorganisms for UTIs and CAUTIs [57]. The urinary catheter connects the colonized perineum with the sterile bladder providing a route for bacterial entry along the catheter lumen or the external surface of the catheter [58]. CAUTI is related to the susceptibility of catheter material to microbial colonization. The initial

stage of biofilm formation on a urinary catheter includes deposition of conditioning film of host urinary components, such as proteins, electrolytes, and other organic molecules [59]. These molecules on the surface of the urinary catheter may change its surface and neutralize any antiadhesive properties [60]. Planktonic bacteria are attached to the surface of the urinary catheter through hydrophobic and electrostatic interaction [61]. Development of biofilm on surface of the catheter occurs through the division of binding bacterial cells, appending additional planktonic bacteria and secretion of extracellular matrix. Detachment of single cell or group of bacterial cells from the biofilm may result in the passage of pathogens into the urine [51]. For this reason, biofilm formation on the urinary catheters is critical for initiating and maintaining of CAUTIs and is a reservoir of resistant pathogenic bacteria [62]. Several factors contribute to the formation of biofilm by *E. coli*, e.g. fimbriae, curli, and flagella. Type 1 fimbriae involved in biofilm formation may also support the colonization of urinary catheter surface [15]. The risk of CAUTI depends on the duration of catheterization, the quality of catheter care, and host susceptibility. Prolonged catheterization is the most important risk factor associated with CAUTI [62]. Long-term urinary catheter use (more than 30 days) causes permanent bacterial colonization of the urine in 100% cases [63]. Examination of people in a nursing home showed that long-term catheterization was significantly related with bacteriuria, pyelonephritis, and renal inflammation [58]. Forming of biofilm on the urinary catheters is a public health problem for patients who need these medical devices. It is recommended that patients who are chronically catheterized were treated with 5–10 days of targeted antibiotic therapy [64].

4. Antimicrobial resistance of UPEC

Antimicrobial resistance in UPEC is a clinical problem in patients with UTIs, in particular in women with recurrent UTI. The empirical antimicrobial treatment in case of recurrent UTIs exerts significant resistance pressure on the uropathogens and the fecal flora, which serves as resistance reservoirs for potential uropathogens [65–67]. Antimicrobial resistance among *E. coli* causing UTI is increasing in many countries around the world and shows considerable variations during different time periods and in different areas [68, 69].

The level of resistance of UPEC strains from hospitalized patients in Poland and Turkey to ampicillin was 56% [70, 71], while above 85% of UPEC strains from patients in India were resistant to this antibiotic [68]. High percentage (67.3%) of *E. coli* strains resistant to tetracycline was isolated from people with UTI from different parts of India [68].

Sanchez et al. [72] suggested that the increase of resistance of UPEC to ciprofloxacin is a result of widespread use of this antibiotic in the treatment of uncomplicated UTIs in the early 2000s. The most recent published data suggested that the level of resistance to trimethoprim-sulfamethoxazole increased and in different countries was over 21–24.2% [71–73]. This trend has continued for decades and the increasing resistance of *E. coli* to trimethoprim-sulfamethoxazole can be explained by frequent use of this antimicrobial agent because it is recommended as the second-line drug in treating acute uncomplicated cystitis in women. Authors reported low resistance of *E. coli* to nitrofurantoin (0.85–1.6%) and no increase in resistance in the last decade was observed [71, 72].

The extended spectrum of β -lactamases (ESBLs) produced by *Enterobacteriaceae* is responsible for resistance of amino and ureido penicillin, oxyimino cephalosporin, and monobactams, but not to 7- α -substituted β -lactam [74]. The production of ESBLs by UPEC strains complicates treatment because these strains are resistant not only to β -lactam antibiotics but often are also resistant to other classes of antibiotics-like aminoglycosides, quinolones, and cotrimoxazole, such as gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole, respectively [75–77]. This reduces the treatment options to a limited number of antibiotics and empirical therapy with cephalosporins and fluoroquinolones often fail in patients with UTI [78]. Hoban et al. [79] found that these resistant microorganisms are more susceptible to the carbapenems, imipenem, and ertapenem, than to other antibiotics. ESBL-producing microorganisms were primarily considered multiresistant organisms originating in hospitals, but in recent years, the number of ESBL producers increased also among outpatients, especially related with UTIs. The authors reported 21 and 21.4% ESBL-producing *E. coli* found in community-acquired UTIs in Turkey [80] and in North India [81], respectively, while in Mexico, 31% of uropathogenic *E. coli* isolated from hospitalized patients [77] and 17.6% *E. coli* from hospitalized European UTI patients [79] were producers of ESBLs. UTIs complicated by ESBL producers tend to lead to uncertain outcomes and prolong hospitalization, especially that these organisms tend to be multidrug resistant [74]. Among ESBLs, the CTX-M enzymes are the most prevalent among isolates of UPE from inpatients and outpatients leading to serious problems for the antimicrobial management of these infections [82, 83]. There is a need for new therapy of UTI caused by multiresistant ESBL-producing UPEC.

5. Treatment and control of UPEC

Currently, the antibiotic therapy is an important part of the therapeutic strategy for UTI. The increased antibiotic resistance in recent years suggests that the choice of antibiotic should be guided by the results of sensitivity assay, although in cases of community-acquired UTI, an empirical therapy is often used [23]. The drugs of first-line choice for empirical treatment of uncomplicated UTI in all European countries are fosfomicin trometamol, pivmecillinam, or nitrofurantoin macrocrystals [84]. Trimethoprim-sulfamethoxazole is also used in countries where resistance to this chemotherapeutic is low. Higher rates of side effects in comparison with other drugs limit the use of quinolones as second-line therapy. Moreover, in many countries in Europe, high resistance rates of *E. coli* strains to nalidixic acid were observed [85], and thus aminoglycosides and carbapenem are the drugs of choice. In patients with recurrent infections of the urinary tract, the antibiotics may be recommended prophylactically. It is believed that two recurrences of UTI within 6 months after therapy or three episodes per year could be considered an indication to establish prophylaxis after treatment. The drugs for this purpose are nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomicin trometamol, and cotrimoxazole at lower doses than therapeutic [86]. However, repeated antibiotic treatment of UTI and prophylactic use of antibiotics frequently results in a rise in resistance to antibiotics and adversely affects microbiota of patients which may lead to secondary infections posttreatment, such as gastrointestinal infection and vaginal yeast infection [87, 88].

For this reason, alternative or additional prophylactic strategies have been investigated. One of them is improving the management of UTI by the development of preventive vaccines. Effective vaccine for UTI will need to generate a strong mucosal immune response in the urinary tract. Designing a UTI vaccine that would be effective against UPEC is difficult due to heterogeneous nature of the UPEC population. UTI vaccine should be designed based on more than one antigen because not all strains express the exact set of virulence genes during infections. A vaccine based on the multiple virulence factors, such as fimbrial adhesins or iron receptors, could be clinically effective against UTI [89]. The vaccine with whole or lysed fractions of inactivated bacteria can be effective to generate protective immunity. Urovac[®] is one of such vaccines (Solco Basel AG, Birsfelden, Switzerland, and Protein Express, Cincinnati, OH, USA) containing ten heat-killed uropathogens, including six UPEC strains. The UPEC strains in the Urovac[®] show different virulence factors, such as hemolysin, type 1, P, and S fimbrial adhesins, CNF-1, siderophores, and the *E. coli* CFT073 pathogenicity island marker and many different O and H antigens. Evaluating the efficacy of vaginally administered Urovac[®] found that the immunization did not ensure significant long-term protection from UTI or an increase in mean levels of UPEC antibodies in serum, vagina, or urine [90]. However, among the women receiving Urovac, 72% were free from UTIs, while only 30% of women given placebo remained free from UTIs caused by *E. coli*. Moreover, in the Urovac vaccinated group, the number of *E. coli* caused UTIs was significantly lower compared to the control group [91]. Another vaccine which is used in Switzerland since 1988 and sold in other countries worldwide is OM-89/Uro-Vaxom[®] (OM Pharma, Myerlin, Switzerland). Uro-Vaxom is an oral capsule containing a lyophilized mix of membrane proteins from 18 UPEC strains. The clinical studies showed that Uro-Vaxom was significantly more effective than placebo in preventing recurrent UTI [92].

Other prophylaxis method is use of different *Lactobacillus* species in the form of probiotics which reduced the risk of UTI and vaginal infections. Use of *Lactobacillus* species maintains low pH and produces hydrogen peroxide that inhibits growth of *E. coli* in urinary tract but also activates Toll-like receptor-2 and therefore leads to reduced inflammatory reaction [93]. Beerepoot et al. [94] conducted study in which postmenopausal women with recurrent UTI prophylactically received trimethoprim-sulfamethoxazole or oral capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14. After 12 months of treatment, the reduction in recurrence was more than 50% in both groups. However, in group that received trimethoprim-sulfamethoxazole, the two-fold increase in resistance was observed.

Research on dietary supplementation showed that cranberry juice and its extracts reduced UTI recurrences. The active metabolite of cranberry, proanthocyanidin A prevents bacterial adhesion to the urothelial layer by inhibiting P fimbriae expression [95]. The minimum daily dose of proanthocyanidin A, which is able to reduce significantly the number of urinary *E. coli* to be 36 mg [96]. The study conducted by Wojnicz et al. [97] showed that cranberry extract Żuravit S.O.S.[®] reduced motility and adhesion to epithelial cells in *E. coli* strains isolated from urine of patients with pyelonephritis and also limited the ability of these strains to form biofilm.

Bacteriophages are highly specific and very effective in lysing bacteria. The use of lytic phages that are able to pass through the extracellular matrix against *E. coli* biofilm causes a reduction of bacteria number in biofilm and also prevents biofilm formation on catheter coated

with hydrogel containing bacteriophages [98, 99]. Biofilm-associated UTIs are difficult to treat due to the high level of antimicrobial resistance showed by biofilm structures. Many authors recommend macrolides (erythromycin, clarithromycin, and azithromycin) as the treatment of choice in biofilm-associated infections because these antibiotics inhibit the production of primary component of the matrix, alginate [100, 101]. Ciprofloxacin, norfloxacin, gentamicin, or nitrofurazone are often used as components in coating and impregnating the catheters in the aim to inhibit bacterial attachment and development of biofilm [55, 102]. New therapeutic antibiofilm treatments are studied as alternative to antibiotics in order to inhibit biofilm formation and also to avoid the emergence of resistant bacterial populations. The silver showed antimicrobial activity by interacting with bacterial cell membrane and is used to coat catheters. The study showed a statistically significantly lower frequency of bacterial infection in patients treated with a silver alloy-coated catheter compared to those treated with uncoated catheter. Schaeffer et al. [103] reported that bacteriuria was present in 27% of patients with the silver-coated silicone catheter and in 55% of group with uncoated silicone catheter. It was also demonstrated that silver alloy used in hydrogel-coated urinary catheter reduced of up 45% of CAUTI [104]. However, the study conducted by Desai et al. [105] showed that *E. coli* adherence was not significantly lower on silver-impregnated silicone or latex catheters compared to adherence of *E. coli* on catheters without silver.

The new antibiofilm strategy is phage therapy using engineered bacteriophages that have biofilm-degrading enzymatic activity. It was demonstrated that engineered phages that express biofilm-degrading enzymes are more efficient in removing bacterial biofilms than nonenzymatic phage alone. Lu and Collins [106] generated bacteriophage which expressed biofilm-degrading enzyme (DspB) during infection. The DspB showed simultaneous action against both bacterial cells in the biofilm and the biofilm matrix. The engineered enzymatic phage reduced bacterial biofilm cell in 99.9%. One of the new ways of eliminating biofilm is the use of nanoparticles. Water-based synthesis of yttrium fluoride (YF₃) nanoparticles that showed antibacterial properties against *E. coli* was described. The minimal inhibitory concentration was observed at 0.01 mg/mL. In addition, YF₃ nanoparticles-coated catheters were able to significantly reduce bacterial colonization compared to the uncoated surface, which provides the potential to develop the concept of utilizing yttrium fluoride nanoparticles as novel antimicrobial and antibiofilm agents [107].

The alternative strategies to decrease UPEC infection include the use of plant-derived antibacterial agents containing different functional groups in their structure and development of resistance in bacteria to these antimicrobials is less frequent [108]. Borges et al. [109] showed that phenolic acids such as gallic and ferulic acid have prevented biofilm formation and show potential to reduce the mass of biofilms formed by the Gram-negative bacteria including *E. coli*. The antibiofilm effect of trans-cinnamaldehyde (TC) on UPEC was reported by Amalaradjou et al. [110]. These authors showed that TC was effective against UPEC biofilm on polystyrene or latex, and the expression of *E. coli* genes encoding attachment and invasion of bladder cells was significantly decreased by TC [111]. Phytochemicals as alternative antimicrobials in preventing and inactivating *E. coli* biofilm on urinary catheters were also assessed. It was demonstrated that TC at the concentration of 0.5% was highly effective for preventing *E. coli* biofilm formation in the lumen of urinary catheter and after 1 day of completely inhibited biofilm formation. Whereas, completely inactivated biofilm after 1 day was observed at 1.25%

and 1.5% TC solution. *p*-Coumaric and ferulic acids have preventive action on *E. coli* biofilm formation on urinary catheter but complete inactivation of the biofilm formed at presence of these phytochemicals was not observed [112]. Recently showed that two alkaloids, piperine from black pepper and reserpine from Indian snakeroot, decreased swarming and swimming motilities of the uropathogenic *E. coli* CFT073. Additionally, piperine increased penetration of ciprofloxacin and azithromycin in to biofilm of *E. coli* CFT073. Authors suggest that these substances can affect on bacterial colonization by inhibition bacterial motility and also may help in treatment of infection by strengthening the penetration of antibiotic in biofilms [113].

One of the other strategies to prevent colonization, invasion, and biofilm formation by UPEC is inhibition of the assembly of pili by family of bicyclic 2-pyridones, termed pilicides.

The activity of pilicides was evaluated in two different pilus biogenesis systems in UPEC. Hemagglutination mediated by either type 1 or P pili, adherence to bladder cells, and biofilm formation mediated by type 1 pili were all reduced by 90% in laboratory and clinical *E. coli* strains [114]. Pilicide ec240 was found to disrupt type 1 pili, P pili, S pili, and flagellar motility [115]. Other pilicides also inhibit the production of Dr pili that are important in pyelonephritis [116]. Mannosides are FimH receptor analogues and bind to this pilus with high affinity, which results in blocking FimH binding to mannosylated receptors. The use of mannosides is considered a new strategy in treating and preventing UTIs because they prevent bladder colonization and invasion and are effective against multidrug-resistant UPEC and against established UTIs [117].

6. Conclusions

UTIs belong to the most common bacterial infections. *E. coli* is the major factor of community-acquired UTIs and a large part of nosocomial UTIs is also caused by this microorganism. UPECs have a wide range of virulence factors and spread of antimicrobial resistance that threaten effective treatment of UTIs using antibiotics. Intensive research that can identify essential virulence mechanisms of UPEC can lead to the development of UTI treatments and prophylactics. The identification of virulence determinants, especially responsible for initial attachment and adhesion of bacterial cells to receptors can be the basis for the development of targeted therapy that prevents the development of UTI. New strategies of UTIs treatment and prevention include chemical compounds such as pilicides and mannosides that block UPEC adhesion or vaccines against siderophores, pili, and UPEC toxins. However, they are still at the preclinical stage of development. These novel antivirulence therapies for treatment of UTIs still require substantial effort associated with future clinical trials.

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