We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Uropathogenic *Escherichia coli*

Navneet Kaur, Ashwini Agarwal, Malika Grover
and Sanampreet Singh

Abstract

Urinary tract infections (UTIs) are among the most common infections encountered worldwide in clinical practice. *Escherichia coli* is by far the most frequent cause of infections responsible for nearly 80–90% of the infections. The strains of *E. coli* causing UTI are termed as uropathogenic *E. coli*. They vary from commensal strains as they have acquired virulence and resistant determinants through plasmids, bacteriophages, pathogenicity islands or DNA horizontal transfer of transposons which permits them to victoriously colonize the urinary tract and cause a broader spectrum of disease. For the fact, UPEC strains possess an abundance of both structural (as fimbriae, pili, flagella, capsule, lipopolysaccharide) and secreted (toxins, iron-acquisition systems, enzymes) virulence factors that play a crucial role in the pathogenesis. The pathogenesis of UPEC involves adherence, colonization, evading host defenses and damage to host tissue to achieve virulence. UTI is often treated empirically by broad-spectrum antibiotics in the absence of culture and susceptibility results. This over-use of antibiotics has resulted in the development of antibiotic resistance worldwide. Having a detailed understanding of the bacterium and its virulence factors can help us in developing new treatment options in presence of global antimicrobial resistance.

Keywords: UTI, UPEC, virulence factors, adhesins, toxins, antimicrobial resistance

1. Introduction

Urinary tract infections (UTIs) are among the most common infections encountered worldwide in clinical practice accounting for approximately 150 million cases annually causing heavy burden on health infrastructure [1]. Women, undoubtedly are at greatest risk as compared to males and it is been observed that almost 50% of all women have experienced UTI at least once in their lifetime. The infection may result either due to the pathogenicity of the offending microorganism, host susceptibility or a combination of both. While many different microorganisms are known to cause UTI which includes bacteria, viruses and fungi, bacteria remain the main cause responsible for over 95% of cases. Among bacteria, *Escherichia coli* (*E. coli*) is by far the most frequent cause responsible for nearly 80–90% of the infections [2]. The most common route of infection of *E. coli* is the bacterial colonization of the urethra followed by the ascension to the bladder. Normally, *E. coli* is present as a commensal flora in the lower gastrointestinal tract of

humans, nonetheless, there are a few highly adapted *E. coli* clones present that have acquired specific virulence attributes, which gives them an escalated ability to adapt to new niches and permits them to cause a broad spectrum of disease. Uropathogenic *Escherichia coli* (UPEC) is simply the pathotype of extraintestinal pathogenic *E. coli* which were first isolated from the urine of the patients having UTI. They differed from those cultured from the stool specimens of healthy individuals and those causing diarrhea, hence the term UPEC. UPEC strains possess an abundance of both structural (as fimbriae, pili, flagella) and secreted (toxins, iron-acquisition systems) virulence factors that play an important part in the pathogenesis, however its capability to adhere to host epithelial cells in the urinary tract serves as the most important determinant of pathogenicity [3].

2. What is uropathogenic *E. coli*? How it causes infection?

2.1 Uropathogenic *E. coli*

Escherichia coli, a Gram-negative bacilli belonging to the family Enterobacteriaceae resides in the gastrointestinal tract of humans as a part of their microbiota. It normally remains in harmony with its host and seldom causes disease except in an immunocompromised host. However, few strains of *E. coli* can split from their commensal cohort taking on a pathogenic form. That means these strains acquire specific virulence factors through plasmids, pathogenicity islands or DNA horizontal transfer of transposons that bestow them the ability to adjust to new niches and cause a broad spectrum of diseases [4]. Further, only the most successful combinations of virulence factors persist to become specific pathotypes of *E. coli* [4]. The strains of *E. coli* which are pathogenic are divided into diarrheagenic or enteric *E. coli* and extraintestinal *E. coli* (EXPEC) based on the body site they colonize. Diarrheagenic *E. coli* includes enterotoxigenic (ETEC), enteropathogenic (EPEC), shiga toxin-producing (STEC), enteroaggregative (EAEC), enteroinvasive (EIEC), and diffusely adherent *E. coli* (DAEC). While EXPEC is mainly uropathogenic *E. coli* (UPEC), neonatal meningitis *E. coli* (NMEC) and sepsis-associated *E. coli*. Based on phylogenetic analysis using multilocus enzyme electrophoresis, pathogenic *E. coli* pathotypes (from both intestinal and extra-intestinal *E. coli*) were divided into four phylogenetic groups A, B1, B2 and D. These phylogenetic groups are representative of their genetic origin [5].

Uropathogenic *E. coli* as described belongs to the extraintestinal pathogenic *E. coli* group and is associated with a subset of serogroups and serotypes (O1:H4, O1:H6, O1:H7, O1:H⁻, O2:H1, O2:H4, O4:H5, O6:H1, O7:H4, O7:H6, O7:H⁻, O18ac:H7, O18ac:H⁻, O22:H1, O25:H1, O75:H5 & O75:H7) and with the B2 or D phylogenetic groups [6]. UPEC possesses acquired virulence and resistant determinants which permits it to victoriously colonize the urinary tract and cause disease.

2.1.1 CFT073

CFT073 is a prototypical strain of UPEC that was recovered from a woman having severe pyelonephritis infection, it belongs to phylogenetic group B2. It was noted to have increased hemolytic activity in comparison to other UPEC strains. On sequencing, its virulence genes were found to be grouped into five pathogenicity islands [7, 8].

2.2 Route of infection

For UPEC to cause infection, the ultimate origin of it is the intestinal tract of the human host which finally acts as a fecal reservoir. Principally apparent in women, the first step is the bacterial colonization of the vaginal introitus and periurethral meatus. Notably, colonization takes place in parallel with the loss of protective vaginal *Lactobacillus* species. This follows ascension into the bladder and adherence to bladder epithelium (uroepithelium). This is followed by UPEC internalization by umbrella cells (it is the outermost layer of the uroepithelium). Inside the bladder cells, most of the bacteria are exocytosed while the minority of them will evade this mechanism gain entrance into the cytosol to form IBCs (intracellular bacterial communities). When these intracellular bacteria stop replicating, they enter another stage known as QIR (quiescent intracellular reservoir) and are behind recurrent UTI episodes.

In this manner, infection of the lower urinary tract has the power to advance to kidneys and enter the bloodstream to cause urosepsis (**Figures 1 and 2**) [3].

Figure 1.
Structure of the urinary bladder and urothelium. The urothelium (transitional epithelium) is believed to form vital and essential hurdle to infection that includes mucus glycosaminoglycans retarding adherence of UPEC, infection-resistant umbrella cells and glycoprotein plates known as uroplakins.

Figure 2. UPEC pathogenesis. UPEC expresses pili systems (Fim H) for adherence to the epithelial cells of the bladder. It follows invasion into the host cell which initiates replication to form IBCs and a subpopulation also undergoes cell elongation (filamentation). Ultimately the epithelial cell is overloaded and UPEC escapes, rupturing open the host cell releasing motile short and elongated cells which can infect neighboring host epithelia to continue the infective cycle.

3. Bladder defenses against UPEC

To cause infection, UPEC has to beat the natural urinary tract defenses that include physical and chemical defenses. Physical defenses include high urine flow, exfoliation of cells, high urine osmolality and low pH. Chemical defenses of the

Bacterial aim	Host barrier
Attachment to the host cell surface with the help of adhesins (P fimbriae, type 1 fimbriae)	Flow of urine, mucociliary blanket
Acquisition of nutrients by cellular lysis by hemolysin, iron acquisition by siderophores	Sequestration of nutrients (iron through intracellular storage)
Initial avoidance of bactericidal activity by the host—capsular polysaccharides and lipopolysaccharide	Phagocytic cells, complement, antimicrobial peptides
Late avoidance of bactericidal activity by the host—Antimicrobial resistance	Antimicrobial therapy, acquired immunity

Table 1. Interaction of UPEC with the human host.

urinary tract comprise secreted proteins such as THP (Tamm-Horsfall protein), IgA (immunoglobulin), antimicrobial peptides and immune system activation (innate and adaptive). **Table 1** summarizes the interaction of UPEC with the human host.

4. Virulence factors of UPEC

There are various virulence factors possessed by UPEC which enable its colonization and pathogenicity. These factors are inserted either in the genome (chromosome) by insertion elements or transposons or encoded on plasmids. The virulence factors are associated with the bacterial cell surface such as adhesins and factors that are secreted and carried to the site of action such as toxins [9].

4.1 Adhesins

For UPEC to colonize and cause infection, it needs to be equipped with some adhesive molecules which will promote attachment to the host cell surface. Adherence to host cell is regarded as the crucial step for colonization because in normal instances regular urinary flow does not permit colonization of the bacteria to the urinary tract. The adhesive factors found in UPEC are known to be adhesins which exists either in the form of filamentous surface organelles called pili or fimbriae or as non-filamentous proteins in the outer membrane.

4.1.1 *P fimbriae*

Edén and his colleagues discovered in the year 1976 when they identified that *E. coli* that was cultured from pyelonephritis cases attached in more numbers to exfoliated uroepithelial cells when compared to *E. coli* strains obtained from fecal samples [10]. This strong adherence was linked to the presence of 'fimbriae' which when isolated could also specifically adhere to the uroepithelial cell surface [11]. Those bacteria which were expressing this type of fimbria could agglutinate human O erythrocytes and the hemagglutination wasn't been able to be inhibited by mannose hence Mannose Resistant. This kind of agglutination made these new fimbriae distinct from type 1 fimbriae. Later work revealed the receptor to which these new fimbriae i.e., 'P fimbriae' binds is globoseries receptor which is a component of P blood group antigen found in human erythrocytes and uroepithelial cells. Furthermore, this antigen was identified to be a glycosphingolipid (synthesized by specific glycosyltransferases and constituent of glycocalyx surrounding the uroepithelial cells) with a lipid moiety anchored in the cell membrane and a chain of carbohydrates exposed on the erythrocyte surface. These globoseries glycosphingolipid receptors (Gal-Gal) are spread evenly all over the urinary tract especially in kidneys.

P fimbriae are said to increase UPEC virulence at various stages of infection. They help the bacteria to persist longer in the intestinal tract and expand more strongly in the urinary tract with the plan of colonization and going ahead with ascending infection [12, 13]. So, when they reach the urinary tract, *E. coli* strains having P fimbriae attach, persists and even in the presence of enhanced immune response (engaging toll-like receptors 4 and cytokine elaboration) invades kidneys and can cause bacteremia. For the reason, there is a correlation between P fimbriae and acute disease severity in more than 90% of cases. However, <20% asymptomatic carriers also express this P fimbriae. The adhesin complex is encoded by *pap* gene *EFG* sequences.

There exist 3 molecular variants of PapG adhesin encoded by *PapG* class I through IV alleles, these have different receptor binding preferences ultimately affecting clinical outcomes. For example, allele class II is predominant among strains causing pyelonephritis and bacteremia whereas class III is frequently encountered in women having cystitis and children [14].

4.1.2 Type I fimbriae

Type I fimbriae are considered as a crucial virulent factor in UTI but their exact individual role is challenging to understand as they are expressed by pathogenic as well as commensal strains of *E. coli* including other genera within family enterobacteriaceae. Additionally, it is found that there is an absence of any significant difference in the frequency of the *fim* gene (which encodes type I fimbriae) among more or less virulent strains [15]. These fimbriae are encoded by an operon that contains nine genes present on the chromosome of most of the UPEC in the order of: *fimB*, *fimE*, *fimA*, *fimI*, *fimC*, *fimD*, *fimF*, *fimG*, *fimH*; these encoding structural and regulatory proteins [3].

Type I fimbriae bind to uroplakin Ia and IIIa (urothelial mannosylated glycoprotein) through the *FimH* subunit [4]. *FimH* is a tip protein of type I fimbriae. In addition, it may also bind to other cell-surface proteins such as integrins, fibronectin, Tamm-Horsfall protein (THP), etc. This binding or interaction results in molecular phosphorylation events that are necessary for the stimulation of signaling pathways involved in invasion and apoptosis.

Besides, playing a role in attachment to bladder epithelium, it is also found to directly trigger invasion by UPEC into epithelial cells of the bladder (BECs) where they induce formation of IBCs and remain as reservoirs to act as a source of clinical relapse [16, 17]. Some studies have given an insight to the fact that type I fimbriae enhance the infectious potential of UPEC [18, 19] but the accurate timing of expression of fimbria during urinary tract infection remains blurred. It was also seen that UPEC isolates obtained from clinical samples (urine) during infection expressed little to no type I fimbriae [20]. In addition, fimbrial expression was more or less absent in UPEC strains from the urine of women with cystitis [21].

The expression of these fimbriae is finely regulated attending to environmental signals and is under the control of phase variation that determines the percentage of fimbriated cells in the population.

Hultgren and colleagues, in the experimental murine model of UTI, found out that *E. coli* which was obtained from bladder lumen did not express type I fimbriae, however, bacteria that were adhered to the bladder wall did express them. Therefore, their contribution in adherence and colonization cannot be effectively determined by measuring the expression of fimbriae in the bladder lumen [22]. There is also an observation that type I fimbriae are not especially prevalent in pyelonephritogenic strains and adherence of bacteria to urinary catheters is also type I fimbriae dependent.

4.1.3 Dr adhesins

The Dr adhesin family consists of both fimbrial and afimbrial adhesins on *E. coli* surface. There are four genes i.e., *dra A*, *B*, *C*, *D* which encode for adhesins and structural proteins. These adhesins can bind to Dr blood group antigen (a component of decay-accelerating factor which prevents lysis by complement). Inside the urinary

tract, they attach to the epithelium of the bladder and type IV collagen present on the basement membranes. Although, these adhesins are present in less number in UTI-causing strains, however collective data from various sources shows that the genes encoding for Dr adhesin family are widespread among cystitis and pyelonephritis strains when compared to control strains (fecal isolates). In the experiments involving mouse models, Dr adhesins exhibit tropism for the basement membrane of the renal interstitium, hence integral for chronic pyelonephritis development. Their presence has been linked to epithelial invasion. Some studies in rat models also point out that their interaction with the host cell receptors in kidneys is very much persistent. In addition, it also has a role in the pathogenesis of UPEC as evident in a mouse model study where Dr-positive strain leads to a disease pathologically similar to chronic tubulointerstitial nephritis and a Dr-negative isogenic mutant causes no disease. Type I fimbriae and Dr adhesin together are associated with invasion of epithelial cells of bladder along with intracellular persistence by UPEC [23, 24].

4.1.4 *S and F1C fimbriae*

S and F1C fimbriae are also involved in the urinary tract infection process. Both fimbriae are shown to have very related biogenesis genes however they have different adhesin alleles. They exhibit binding to epithelial and endothelial cells from the lower urinary tract and kidneys in humans [25, 26]. S fimbriae binds to sialic acid epitopes which are present in renal sialylated lipoproteins. Also, they particularly are also responsible for other extraintestinal infections such as sepsis, meningitis apart from UTI because they may promote the dissemination of bacteria within the host tissues. As per various pooled studies, F1C fimbriae are more usually seen in strains from pyelonephritis and cystitis patients than fecal strains used as controls [27]. Furthermore, experiments conducted in a try to know their exact role in UTI have not been reported clearly but in strain CFT073, in which type 1 and P fimbriae encoding genes have been inactivated, F1C fimbriae were expressed at elevated levels demonstrating a synchronize fimbrial expression in UPEC [28].

4.1.5 *Other adhesins*

Adhesins belonging to the Afa family are also involved in urinary tract infections. The UPEC strains expressing them have distinctive renal tissue tropism. Further findings suggest that these adhesins have properties that support the development of chronic or/and recurrent infections [4]. Other adhesins identified in vivo among UPEC strains are type 1c, G, M, X adhesins which vary in molecular binding specificities and serologic properties. **Table 2** summarizes various UPEC adhesins contributing to virulence.

4.2 **Toxins**

There are three main types of toxins that are secreted by UPEC. These are:

- A. Hemolysin
- B. Cytotoxic necrotizing factor 1 (CNF)
- C. Autotransporters

Type of adhesin	Corresponding receptor	Encoding genes	Special points
Type 1 fimbriae	PMNs and epithelial cells with mannose proteins	<i>fim B, fim E, fim H</i> and <i>Pil</i>	—
Type 1c fimbriae	Unknown	<i>Foc</i>	—
Type 3 fimbriae	M blood group	<i>mrkABCDF</i>	Mediate formation of biofilm
P fimbriae	P blood group antigen: Gal- α 1–4	<i>PapG, papGAP</i>	Associated with bacteremia, cystitis and pyelonephritis
S/F1C fimbriae	Sialyl- α -2-3 galactoside	<i>Sfa/fac</i>	THP inhibits the adherence
G fimbriae	Terminal N-acety-D-glucosamine	—	—
M fimbriae	Galactose-N-acetylglactosamine	—	—
Dr family	Type 4 collagen & Dr blood group antigen	<i>AfaE1–5, AfaF, Drb</i> operon	—

Table 2.
Summary of various adhesins of UPEC.

Apart from these, there are other toxins identified which are secreted by UPEC strains and have cytotoxic activity. Toxins production by UPEC leads to inflammatory response causing UTI symptoms.

4.2.1 Hemolysin

In 1921, Dudgeon *et al.*, documented that 50% of *E. coli* isolates which caused UTI were causing hemolysis on blood agar plates in comparison with 13% of fecal isolates. This action was credited to the hemolysin protein secreted by *E. coli* (belonging to the family of RTX toxins (repeats-in-toxin)) [29]. α -hemolysin (Hly A) is the most vital virulence factor secreted by UPEC that is associated with pyelonephritis. The *hly* genes encode for proteins that are needed to synthesize and secrete hemolysin. This toxin shows dual activity dependent on concentration i.e., low and high concentration:

- At low concentrations, it can cause apoptosis of target host cells which involves neutrophils, T-lymphocytes and renal cells and also stimulate the exfoliation of epithelial cells of the bladder [30].
- At high concentrations, HlyA can lyse erythrocytes and nucleated host cells including uroepithelial cells. This may enable UPEC to cross mucosal barriers effectively, destroy effector immune cells and gain advanced access to nutrients and iron stores of the host.

α -Hemolysin can also result in the elevated elaboration of IL-6 and IL-8 by inducing Ca^{2+} oscillations in renal epithelial cells. In addition, this toxin is associated with renal complications in 50% of cases of pyelonephritis and also causes endothelial damage and renal vasoconstriction. To add up permanent renal scarring is a usual complication that follows infection by HlyA *E. coli* [31].

4.2.2 CNF-1

CNF-1 is frequently detected in *E. coli* strains causing UTI and almost always in association with hemolysin with which it is linked genetically. This protein is secreted by

E. coli in vitro and prompts actin stress fibers formation and membrane ruffle formation in a Rho GTPase dependant manner. Various studies describe its potential role in UPEC pathogenesis. CNF-1 appears to increase the attachment of PMNs (polymorphonuclear leukocytes) to T84 monolayers (epithelial cells) thereby decreasing their phagocytic effect. Besides, it leads to apoptosis in the 5637-bladder cell line, an event that might be elucidate the exfoliation of bladder epithelial cells after UPEC infection [32].

4.2.3 Autotransporters

Autotransporters toxins also named as type V secretion toxins consists of SAT (secreted autotransporter toxin) and VAT (vacuolating autotransporter toxin) encoded by UPEC [33]. SAT is demonstrated more commonly among *E. coli* strains (55% strains) associated with pyelonephritis relative to fecal strains (22%). SAT which was first isolated from *E. coli* CFT073 have highest similarity to SPATES (serine protease autotransporters of Enterobacteriaceae) proteins made by diarrheagenic *E. coli* and *Shigella species*. Experiment shows SAT possess toxic activity against bladder and kidney cell lines and thereby may have an important role in the pathogenesis of UTI.

VAT was originally discovered in avian pathogenic *E. coli*. In addition, there are Pic and Tsh autotransporters recognized. Pic is known to have serine protease activity while Tsh lacks. These both are seen to be more prevalent in pyelonephritis strains than fecal strains.

Moreover, recent studies have identified other proteins which are secreted by UPEC and known to have cytotoxic activity. These are NRPS (nonribosomal peptide synthases) and PKS (polyketide synthases) which are produced by B2 *E. coli* strains and are involved in arresting cell cycle [3].

4.3 Iron acquisition by UPEC

Iron, a necessary cofactor for enzymes found in all organisms, remains concealed by iron-binding proteins in humans. Iron is very crucial for the growth of the bacteria. Therefore, bacteria colonizing and causing infections in humans should have some systems to obtain it. Iron is present at a very low concentration at the infection site of the urinary tract and UPEC is known to have multiple systems for iron scavenging. One such potent way to hunt iron is the possession of siderophores by bacteria as it has got a very high affinity for Fe^{3+} that enables *E. coli* to escort iron back to the cell. It is documented that siderophores are usual in *E. coli* strains causing UTI as compared to fecal strains [34]. UPEC encodes a siderophore called enterobactin (which is also present in commensal bacterium) in addition it contains multiple other iron acquisition systems such as yersiniabactin, salmochelin and aerobactin [35]. The gene that encodes aerobactin has been identified to be *iutA*. Furthermore, there is fact that UPEC does not use siderophores alone for scavenging iron, it also employs other iron receptors that are found in the outer membrane which binds iron and takes it back inside the bacterial cell. CFT073 (prototypical UPEC strain) encodes for 14 such outer membrane iron receptors [36].

4.4 Extracellular polysaccharides

There are a variety of extracellular polysaccharides produced by *E. coli* such as O antigen, core polysaccharides of LPS (lipopolysaccharide), colonic acid or capsule, etc. Their role in the pathogenesis of UTI is not well understood. LPS of UPEC is

regarded important in stimulating proinflammatory response in cases of uncomplicated UTI. Also, it is also noted in animal models that acute renal failure due to LPS is not dependant on the presence of functional LPS receptors TLR4 in the kidney but systemic response to LPS.

The capsule is known to provide protection against phagocytosis and complement-mediated bactericidal effect in the host. In addition, it has been found that the K2 capsule and not the K54 capsule acts to be confirmed urovirulence factor [3, 37].

4.5 Proteases

Proteases are enzymes that leads to the cleavage of peptide bonds. They are generally found in mobile genetic elements like transposons, plasmids or prophages [38]. Although, they are not needed for the survival and replication of bacteria, they may be vital for virulence.

OmpTins are considered outer-membrane proteases seen in various members of the Enterobacteriaceae family. *E. coli* can encode upto 3 ompTins such as *ompT*, *ompP* and *arlC* [39]. OmpT have been recognized as a significant virulence factor in UPEC strains causing cystitis, pyelonephritis, urosepsis as opposed to asymptomatic strains [39].

4.6 Flagella

Flagella is an organelle that accounts for the motility in bacteria and flagellated UPEC is responsible for nearly about 70–90% of all UTIs. Genes for synthesis of flagella form a well-regulated and directed cascade of three 3 classes. The benefits of having flagella mediated motility by *E. coli* during colonization of the urinary tract include the capability of dissemination to new sites of the urinary tract to obtain nutrients and in addition to escape from immune responses of the host [4].

4.7 Chemotaxis

Chemotaxis is generally a behavior that is used by the bacteria to sense and then respond to external chemical signals. There are mainly four chemotaxis protein receptors that are necessary for chemotaxis in *Escherichia coli* such as Tar and Tsr (amino acids), Trg (saccharides) and Tap (dipeptides) [40]. There is an observation of *tar* and *tsr* being present in 100% and 98% of all motile UPEC isolates respectively. While *trg* and *tap* were found significantly less among UPEC in comparison to fecal isolates [41].

5. Antimicrobial resistance in UPEC

Antimicrobial therapy is generally recommended for all symptomatic UTI cases including uncomplicated and complicated cases. The choice of an antibiotic should be led by spectrum and susceptibility patterns of the causative agent, its efficacy for the particular indication, tolerability and adverse events, costs and availability, etc. The most commonly used antimicrobials for treating uncomplicated cases include nitrofurantoin, cotrimoxazole (first line), fosfomycin and pivmecillinam (alternative), fluoroquinolones (second line). Ceftriaxone, cefepime, piperacillin-tazobactam, aminoglycosides and carbapenams are used for complicated cases [42]. The international guidelines recommend the use of nitrofurantoin, fosfomycin trometamol and trimethoprim-sulfamethoxazole for the treatment of uncomplicated UTI. Fluoroquinolones

in such situations should be kept in reserved as they are used to treat complicated UTI and mild to moderate pyelonephritis [42].

UTIs and especially recurrent UTIs are associated with significant use of antibiotics that promotes resistance. Antimicrobial resistance in UPEC and the spreading of multidrug resistant (MDR) UPEC is a concerning clinical problem, particularly in women with recurrent UTIs. Increasing ineffectiveness of the antimicrobials has led to the emergence of MDR UPEC (resistance to at least one antibiotic in three or more classes) and XDR UPEC (resistance to at least one in all but at least two or fewer classes) [43].

The various mechanisms responsible for resistance include:

1. Bacterial mechanisms

- Target site inactivation
- Presence of β -lactamases enzyme
- Efflux pumps mechanism
- Through mobile genetic elements such as transposons, gene cassettes, insertions sequences, integrons, etc.

2. Antibiotic consumption without bacterial characterization of the UTI pathogen.

3. Over the counter availability of antimicrobials, thus leading to its overuse.

5.1 Drug resistance mechanisms in different classes of antibiotics

5.1.1 Beta lactam drugs

They are cell wall synthesis inhibitors. One of the main mechanisms of resistance in UPEC is the production of the β -lactamase enzyme which is encoded by the *bla* genes, located on the plasmids. ESBL (extended-spectrum β -lactamase) is one of the types of β -lactamases and is responsible for conferring resistance to penicillin, cephalosporins and monobactams. ESBLs are susceptible to cephamycins, carbapenems and beta lactamase inhibitors; thus making carbapenems drug of choice in such cases. CTX-M, TEM and SHV are most common ESBLs observed among UPEC.

5.1.2 Fluoroquinolones

They are bactericidal drugs. It functions by inhibiting the enzymes topoisomerase II (DNA gyrase, which is encoded by *gyr A* and *gyr B* genes) and topoisomerase IV (*parC* and *parE*) involved in winding—unwinding of the DNA. It is one of the most widely prescribed drugs due to easily available oral formulations. Fluoroquinolone resistance may be due to chromosomal mutations, plasmid mutations, alteration of outer membrane proteins causing decreased antibiotic uptake and presence of efflux pump systems.

Chromosomal mutation in DNA sequences of *gyr A* QRDRs i.e., quinolone resistance determining region is predominantly responsible for fluoroquinolone resistance. Resistance is also mediated via PMQR (plasmid-mediated quinolone resistance) genes which include *qnr* genes such as *qnrA*, *qnr B* and *qnr C*.

5.1.3 Fosfomycin

It is also a bactericidal drug that blocks cell wall synthesis at early stages. It's a widely used drug as a single dose of 3 g is used for the treatment of uncomplicated UTI, and also because of its activity against ESBL and MBL (metallo- β -lactamases). Resistance to fosfomycin is not widespread till date, however, if present may be conferred by:

- Presence of efflux pumps
- Enzymatic cleavage by Fos A, Fos X
- Point mutations

5.1.4 Trimethoprim-sulfamethoxazole

It works by inhibiting the folate synthesis pathway thus inhibiting the DNA synthesis in the susceptible organism. Though widely used as a first-line therapy for uncomplicated cystitis, the use of trimethoprim-sulfamethoxazole has been stopped for empirical use because of its resistance. Over 20% of the UPEC isolates are resistant to trimethoprim-sulfamethoxazole. Resistance to the drug is mediated by

- Efflux pump mechanism
- Target enzyme modification
- Mutational changes in target enzymes

5.1.5 Nitrofurantoin

Reactive intermediates are formed from nitrofurantoin by the action of flavoproteins as a result of which the bacterial ribosomal proteins are inactivated. Resistance to nitrofurantoin till date is much lesser in comparison to the other drugs available, this is attributed to the fact that it acts on multiple targets in the bacterial cell. Resistance may develop due to gene mutations such as nsfA and nfsB genes [44].

6. New therapeutic options, what is in pipeline?

Emerging drug resistance has led to decreased therapeutic options. Therefore, it is imperative to find alternative treatment options. The options are in pipeline for

Newer therapeutic and disease target	Target in UPEC	Available evidence
Anti-adhesives		
Mannosides for acute cystitis	Type 1 pili (FimH)	In a mouse model, the reduced bacterial burden was observed following treatment and also as a prophylactic agent in mouse models [46, 47]
Galactosides for chronic cystitis and/or pyelonephritis	Fim-like (Fml) pili	In experimental mouse model infected with chronic UTI, reduced bacterial burden in the bladder and kidney [48]

Newer therapeutic and disease target	Target in UPEC	Available evidence
Vaccine		
FimCH against acute and chronic cystitis	UPEC expressing type 1 pili	Phase 1 clinical trial showing no safety concerns and a reduction in total UTI recurrence in treatment cohort; approved for compassionate use as an investigational intervention
Uro-vaxom	Contains a lyophilized mix of membrane proteins from 18 different strains of <i>E. coli</i>	Licensed in 30 countries, represents a safe and effective treatment option for prophylaxis of recurrent UTIs [49]
Urovac		Recurrent UTI [49]
Others		
Non-steroidal anti-inflammatory drugs (NSAIDS)—chronic and recurrent cystitis	UPEC	<i>In vivo</i> mouse models. It demonstrates reduced bladder remodeling, and in human clinical studies demonstrate effective resolution of symptoms with a reduction in overall antibiotic used when used in place of antibiotics [50]
HIF-1 α inhibition (AKB-4924)	UPEC	Decreased adherence and invasion of UPEC of cultured human uroepithelial cells, decreased inflammation and bacterial load in mouse models of infection [51]
Probiotics—recurrent UTI	UPEC	Reduced frequency of infection in various patient populations having rUTI [52]
Lactoferrin—cystitis	UPEC	Reduced adherence to human bladder epithelial cell lines and reduced mouse bladder bacterial burdens following treatment with exogenous lactoferrin [53]
Antibiotic—recarbrio (Imipenem, cilastatin and relebactam)		Approved by FDA (U.S. Food and Drug Administration) for the treatment of complicated UTI

Table 3.
Newer therapeutics options in pipeline for the treatment of urinary tract infections caused by UPEC [45].

preventing and treating infections caused by UPEC includes antibiotic recarbrio (FDA approved), vaccines, anti-adhesives etc. **Table 3** highlights newer therapeutics options in the pipeline for the treatment of urinary tract infections caused by UPEC [54].

7. Conclusion

Urinary tract infections, community and hospital-associated affects millions of people especially women worldwide each year. As UPEC is the most common microorganism behind these infections, so adequate knowledge and understanding of UPEC, its virulence factors and antimicrobial resistance pattern is vital for adequate treatment and prevent recurrences. In addition, this can help in developing new therapeutics options in the era of widespread antimicrobial resistance.

Conflict of interest

None.

Author details

Navneet Kaur¹, Ashwini Agarwal^{1*}, Malika Grover² and Sanampreet Singh³

1 Department of Microbiology, All India Institute of Medical Sciences, Rajkot, Gujarat, India

2 Department of Microbiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

3 Independent Researcher, Newport Beach, California, United States of America

*Address all correspondence to: ash.afmc@gmail.com

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Kucheria R, Dasgupta P, Sacks S, Khan M, Sheerin N. Urinary tract infections: New insights into a common problem. *Postgraduate Medical Journal*. 2005;**952**:83. DOI: 10.1136/pgmj.2004.023036
- [2] Loh KY, Sivalingam N. Urinary tract infections in pregnancy. *Malaysian Family Physician*. 2007;**2**:54-57
- [3] Mobley HL, Donnenberg MS, Hagan EC. Uropathogenic *Escherichia coli*. *EcoSal Plus*. 2009;**3**(2):1-27. DOI: 10.1128/ecosalplus.8.6.1.3
- [4] Bien J, Sokolova O, Bozko P. Role of uropathogenic *Escherichia coli* virulence factors in development of urinary tract infection and kidney damage. *International Journal of Nephrology*. 2012;**2012**:1-9. DOI: 10.1155/2012/681473
- [5] Johnson JR, Kuskowski MA, Gajewski A, Soto S, Horcajada JP, De Anta MT, et al. Extended virulence genotypes and phylogenetic background of *Escherichia coli* isolates from patients with cystitis, pyelonephritis, or prostatitis. *The Journal of Infectious Diseases*. 2005;**191**:46-50. DOI: 10.1086/426450
- [6] Ballesteros-Monrreal MG, Arenas-Hernández MM, Enciso-Martínez Y, Martínez-de la Peña CF, Rocha-Gracia RDC, Lozano-Zaraín P, et al. Virulence and resistance determinants of uropathogenic *Escherichia coli* strains isolated from pregnant and non-pregnant women from two states in Mexico. *Infection and Drug Resistance*. 2020;**13**:295. DOI: 10.2147/IDR.S226215
- [7] Mobley HL, Green DM, Trifillis AL, Johnson DE, Chippendale GR, Lockatell CV, et al. Pyelonephritogenic *Escherichia coli* and killing of cultured human renal proximal tubular epithelial cells: Role of hemolysin in some strains. *Infection and Immunity*. 1990;**58**:1281-1289. DOI: 10.1128/iai.58.5.1281-1289.1990
- [8] Luo C, Hu GQ, Zhu H. Genome reannotation of *Escherichia coli* CFT073 with new insights into virulence. *BMC Genomics*. 2009;**10**:1. DOI: 10.1186/1471-2164-10-552
- [9] Emödy L, Kerényi M, Nagy G. Virulence factors of uropathogenic *Escherichia coli*. *International Journal of Antimicrobial Agents*. 2003;**22**:S29-S33. DOI: 10.1016/S0924-8579(03)00236-X
- [10] Edén CS, Jodal U, Hanson LA, Lindberg U, Åkerlund AS. Variable adherence to normal human urinary-tract epithelial cells of *Escherichia coli* strains associated with various forms of urinary-tract infection. *The Lancet*. 1976;**308**:490-492. DOI: 10.1016/S0140-6736(76)90788-1
- [11] Korhonen TK, Virkola R, Holthöfer H. Localization of binding sites for purified *Escherichia coli* P fimbriae in the human kidney. *Infection and Immunity*. 1986;**54**:328-332. DOI: 10.1128/iai.54.2.328-332.1986
- [12] Plos K, Connell H, Jodal U, Marklund BI, Mårild S, Wettergren B, et al. Intestinal carriage of P fimbriated *Escherichia coli* and the susceptibility to urinary tract infection in young children. *Journal of Infectious Diseases*. 1995;**171**:625-631. DOI: 10.1093/infdis/171.3.625
- [13] Wullt B, Bergsten G, Samuelsson M, Gebretsadik N, Hull R, Svanborg C. The role of P fimbriae for colonization and

host response induction in the human urinary tract. *The Journal of Infectious Diseases*. 2001;**183**:s43-s46

[14] Otto G, Magnusson M, Svensson M, Braconier J, Svanborg C. pap genotype and P fimbrial expression in *Escherichia coli* causing bacteremic and nonbacteremic febrile urinary tract infection. *Clinical Infectious Diseases*. 2001;**32**:1523-1531. DOI: 10.1086/320511

[15] Plos K, Lomberg H, Hull S, Johansson I, Svanborg C. *Escherichia coli* in patients with renal scarring: Genotype and phenotype of Gal α 1-4Gal β -, Forssman- and mannose-specific adhesins. *Pediatric Infectious Disease Journal*. 1991;**10**:15-19

[16] Zhang L, Foxman B. Molecular epidemiology of *Escherichia coli* mediated urinary tract infections. *Frontiers in Bioscience*. 2003;**8**:e235-e244

[17] Oelschlaeger TA, Dobrindt U, Hacker J. Virulence factors of uropathogens. *Current Opinion in Urology*. 2002;**12**:33-38. DOI: 10.1097/00042307-200201000-00007

[18] Johnson JR. Microbial virulence determinants and the pathogenesis of urinary tract infection. *Infectious Disease Clinics*. 2003;**17**:261-278. DOI: 10.1016/S0891-5520(03)00027-8

[19] Marrs CF, Zhang L, Tallman P, Manning SD, Somsel P, Raz P, et al. Variations in 10 putative uropathogen virulence genes among urinary, faecal and peri-urethral *Escherichia coli*. *Journal of Medical Microbiology*. 2002;**51**:138-142

[20] Marrs CF, Zhang L, Foxman B. *Escherichia coli* mediated urinary tract infections: Are there distinct uropathogenic *E. coli* (UPEC) pathotypes? *FEMS Microbiology Letters*.

2005;**252**:183-190. DOI: 10.1016/j.femsle.2005.08.028

[21] O'Brien GJ, Chambers ST, Peddie B, Mahanty KH. The association between colicinogenicity and pathogenesis among uropathogenic isolates of *Escherichia coli*. *Microbial Pathogenesis*. 1996;**20**(3):185-190. DOI: 10.1006/mpat.1996.0017

[22] Kostakioti M, Hultgren SJ, Hadjifrangiskou M. Molecular blueprint of uropathogenic *Escherichia coli* virulence provides clues toward the development of anti-virulence therapeutics. *Virulence*. 2012;**3**(7):592-593

[23] Nowicki B, Labigne A, Moseley S, Hull R, Hull S, Moulds J. The Dr hemagglutinin, afimbrial adhesins AFA-I and AFA-III, and F1845 fimbriae of uropathogenic and diarrhea-associated *Escherichia coli* belong to a family of hemagglutinins with Dr receptor recognition. *Infection and Immunity*. 1990;**58**(1):279-281. DOI: 10.1128/iai.58.1.279-281.1990

[24] Das M, Hart-Van Tassell A, Urvil PT, Lea S, Pettigrew D, Anderson KL, et al. Hydrophilic domain II of *Escherichia coli* Dr fimbriae facilitates cell invasion. *Infection and Immunity*. 2005;**73**:6119-6126. DOI: 10.1128/IAI.73.9.6119-6126.2005

[25] Hacker JS, Morschhäuser J. In: Klemm P, editor. *Fimbriae, Adhesion, Genetics, Biogenesis, and Vaccines*. Boca Raton, Fla, USA: CRC Press; 1994. pp. 27-36

[26] Marre R, Kreft B, Hacker J. Genetically engineered S and F1C fimbriae differ in their contribution to adherence of *Escherichia coli* to cultured renal tubular cells. *Infection and Immunity*. 1990;**58**:3434-3437. DOI: 10.1128/iai.58.10.3434-3437.1990

- [27] Donnenberg MS, Welch RA. In: Mobley HLT, Warren JW, editors. Virulence Determinants of Uropathogenic *Escherichia coli* Urinary Tract Infections: Molecular Pathogenesis and Clinical Management. Washington, D.C: American Society for Microbiology; 1996. pp. 135-174
- [28] Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: Self-reported incidence and associated costs. *Annals of Epidemiology*. 2000;**10**:509-515. DOI: 10.1016/S1047-2797(00)00072-7
- [29] Dudgeon L, Worldley E, Bawtree F. On *Bacillus coli* infections of the urinary tract, especially in relation to hemolytic organisms. *Journal of Hygiene*. 1921;**10**:137-164. DOI: 10.1017/S002217240003391X
- [30] Chen M, Tofighi R, Bao W, et al. Carbon monoxide prevents apoptosis induced by uropathogenic *Escherichia coli* toxins. *Pediatric Nephrology*. 2006;**21**:382-389. DOI: 10.1007/s00467-005-2140-1
- [31] Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Archives of Disease in Childhood*. 1994;**70**:111-115. DOI: 10.1136/adc.70.2.111
- [32] Mills M, Meysick KC, O'Brien AD. Cytotoxic necrotizing factor type 1 of uropathogenic *Escherichia coli* kills cultured human uroepithelial 5637 cells by an apoptotic mechanism. *Infection and Immunity*. 2000;**68**:5869-5880. DOI: 10.1128/IAI.68.10.5869-5880.2000
- [33] Parham NJ, Pollard SJ, Desvaux M, Scott-Tucker A, Liu C, Fivian A, Henderson IR. Distribution of the serine protease autotransporters of the Enterobacteriaceae among extraintestinal clinical isolates of *Escherichia coli*. *Journal of Clinical Microbiology*. 2005;**43**(8):4076-4082. DOI: 10.1128/JCM.43.8.4076-4082.2005
- [34] Johnson JR, Moseley SL, Roberts PL, Stamm WE. Aerobactin and other virulence factor genes among strains of *Escherichia coli* causing urosepsis: Association with patient characteristics. *Infection and Immunity*. 1988;**56**:405-412. DOI: 10.1128/iai.56.2.405-412.1988
- [35] Garcia EC, Brumbaugh AR, Mobley HL. Redundancy and specificity of *Escherichia coli* iron acquisition systems during urinary tract infection. *Infection and Immunity*. 2011;**79**(3):1225-1235. DOI: 10.1128/IAI.01222-10
- [36] Welch RA, Burland V, Plunkett GI, Redford P, Roesch P, Rasko D, et al. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic *Escherichia coli*. *Proceedings of the National Academy of Sciences*. 2002;**99**:17020-17024. DOI: 10.1073/pnas.252529799
- [37] Cunningham PN, Wang Y, Guo R, He G, Quigg RJ. Role of Toll-like receptor 4 in endotoxin-induced acute renal failure. *Journal of Immunology*. 2004;**172**:2629-2635. DOI: 10.4049/jimmunol.172.4.2629
- [38] Potempa J, Pike RN. Bacterial peptidases. *Contributions to Microbiology*. 2005;**12**:132-180. DOI: 10.1080/14756366.2021.1937619
- [39] Lundrigan MD, Webb RM. Prevalence of ompT among *Escherichia coli* isolates of human origin. *FEMS Microbiology Letters*. 1992;**97**:51-56. DOI: 10.1111/j.1574-6968.1992.tb05438.x
- [40] Hedblom ML, Adler J. Genetic and biochemical properties of *Escherichia coli* mutants with defects in serine

chemotaxis. Journal of Bacteriology. 1980;**144**:1048-1060. DOI: 10.1128/jb.144.3.1048-1060.1980

[41] Lane MC, Lloyd AL, Markyvech TA, Hagan EC, Mobley HL. Uropathogenic *Escherichia coli* strains generally lack functional Trg and Tap chemoreceptors found in the majority of *E. coli* strains strictly residing in the gut. Journal of Bacteriology. 2006;**188**:5618-5625. DOI: 10.1128/JB.00449-06

[42] European Association of Urology. Urological infections. Netherlands: EAU; 2020

[43] Ochoa SA, Cruz-Córdova A, Luna-Pineda VM, Reyes-Grajeda JP, Cázares-Domínguez V, Escalona G, et al. Multidrug-and extensively drug-resistant uropathogenic *Escherichia coli* clinical strains: Phylogenetic groups widely associated with integrons maintain high genetic diversity. Frontiers in Microbiology. 2016;**7**:2042. DOI: 10.3389/fmicb.2016.02042

[44] Kot B. Antibiotic resistance among uropathogenic *Escherichia coli*. Polish Journal of Microbiology. 2019;**68**:403. DOI: 10.33073/pjm-2019-048

[45] Klein RD, Hultgren SJ. Urinary tract infections: Microbial pathogenesis, host-pathogen interactions and new treatment strategies. Nature Reviews Microbiology. 2020;**18**:211-226. DOI: 10.1038/s41579-020-0324-0

[46] Jarvis C et al. Antivirulence isoquinolone mannosides: Optimization of the biaryl aglycone for FimH lectin binding affinity and efficacy in the treatment of chronic UTI. ChemMedChem. 2016;**11**:367-373. DOI: 10.1002/cmdc.201600006

[47] Mydock-McGrane L et al. Antivirulence C-mannosides as

antibiotic-sparing, oral therapeutics for urinary tract infections. Journal of Medicinal Chemistry. 2016;**59**:9390-9408. DOI: 10.1021/acs.jmedchem.6b00948

[48] Kalas V, Hibbing ME, Maddirala AR, Chugani R, Pinkner JS, Mydock-McGrane LK, et al. Structure-based discovery of glycomimetic FmlH ligands as inhibitors of bacterial adhesion during urinary tract infection. Proceedings of the National Academy of Sciences. 2018;**115**:E2819-E2828. DOI: 10.1073/pnas.1720140115

[49] Aziminia N, Hadjipavlou M, Philippou Y, Pandian SS, Malde S, Hammadeh MY. Vaccines for the prevention of recurrent urinary tract infections: A systematic review. BJU International. 2019;**123**:753-768. DOI: 10.1111/bju.14606

[50] Bleidorn J, Gágyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?-results of a randomized controlled pilot trial. BMC Medicine. 2010;**8**:1-8. DOI: 10.1186/1741-7015-8-3

[51] Lin AE, Beasley FC, Olson J, Keller N, Shalwitz RA, Hannan TJ, et al. Role of hypoxia inducible factor-1 α (HIF-1 α) in innate defense against uropathogenic *Escherichia coli* infection. PLoS Pathogens. 2015;**11**:e1004818. DOI: 10.1371/journal.ppat.1004818

[52] Darouiche RO, Green BG, Donovan WH, Chen D, Schwartz M, Merritt J, et al. Multicenter randomized controlled trial of bacterial interference for prevention of urinary tract infection in patients with neurogenic bladder. Urology. 2011;**78**:341-346. DOI: 10.1016/j.urology.2011.03.062

[53] Patras KA, Ha AD, Rooholfada E, Olson J, Rao SP, Lin AE, et al. Augmentation of urinary lactoferrin enhances host innate immune clearance of uropathogenic *Escherichia coli*. *Journal of Innate Immunity*. 2019;**11**(6):481-495. DOI: 10.1159/000499342

[54] Terlizzi ME, Gribaudo G, Maffei ME. UroPathogenic *Escherichia coli* (UPEC) infections: Virulence factors, bladder responses, antibiotic, and non-antibiotic antimicrobial strategies. *Frontiers in Microbiology*. 2017;**8**:1566. DOI: 10.3389/fmicb.2017.01566