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Uropathogenic *Escherichia coli: A review*

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Abstract

The urinary tract is among the most common sites of bacterial infection, and *Escherichia coli* is by far the most common species infecting this site. Individuals at high risk for symptomatic urinary tract infection (UTI) include neonates, preschool girls, sexually active women, and elderly women and men. Subset of faecal *E. coli* that can enter, colonize urinary tract and cause infection are known as uropathogenic *E. coli* (UPEC). UPEC strains act as opportunistic pathogens taking advantage of host susceptibility using a diverse array of virulence factors. The presence of specific virulence associated genes on genomic/pathogenicity islands and involvement of horizontal gene transfer appears to account for evolution and diversity of UPEC. Antimicrobial resistance and its spread are the most important health problems nowadays. The increased antibiotic resistance of UPEC isolates was demonstrated and suggested a need for reassessment of empirical therapies in urinary tract infections treatment caused by this pathogen.

Keywords: *E. coli*, UPEC, UTI, bacterial infection, uropathogenic

Mini review article ***Corresponding Author:, e-mail:** ayman.soliman.oa55@gmail.com

1. Introduction

Urinary tract infections (UTIs) are the most prevalent pathogenic disorders in both community and healthcare-acquired infections. About 150 million individuals suffer UTIs every year globally. They occur in both females and males but increase in adult women that accounts for 50–60% with increasing prevalence with age **[1]**. UTIs associated with bacteremia are the major cause of secondary blood stream infections, which are associated with higher rates of morbidity and mortality. UTIs are caused by many uropathogens but the primary cause is uropathogenic *E. coli* (UPEC) which is a specific type of extraintestinal pathogenic *E. coli* (ExPEC) [2].

2. Epidemiology:

UPEC is the most prevalent ExPEC all over the world. It causes up to 80% of all cases. Their incidence in developing countries is higher than in developed countries. The percentage in developing countries is about 50%–85% but in developed countries is 3%–40% [3]. UPEC is the commonest cause of both community-acquired urinary tract infections (CA-UTI) and hospital-acquired UTIs (HA-UTI). Additionally, they account for considerable global medical expenses, morbidity, and mortality. About 70–95% of CA-UTIs are caused by UPEC which are present in feces and colonize the vagina and periurethral region [4]. Approximately 50% of HA-UTIs are caused by UPEC that are associated with urinary catheters and caused by multidrug resistant strains. The virulence potential of UPEC is important to develop the infection but patient immune status and general health are more important factors in developing an infection than the virulence potential of the pathogen alone [5]. UPEC can cause symptomatic and asymptomatic bacteriuria (ABU). ABU can continue for months or even years without causing harm to the mucosa of the host. It occurs in about 6% of healthy people, 20% of elderlies and increases in adult women to about 50–60% [6].

Symptomatic UTI caused by UPEC strains that colonize the urinary tract and may go up to the bladder to induce cystitis are typically accompanied by the familiar UTI symptoms of painful urination, frequency, and urgency. The main UPEC phylogroups that cause UTI are B2 and D. They are characterized by multiple virulence genes that help efficient colonization of the urinary tract [7]. There is a specific type of UPEC called invasive UPEC. It is characterized by a severe UTI and is considered as the major cause of pyelonephritis and a urinary source of bacteremia. It is the main origin of septicemia and sepsis [8].

3. Cell structure:

Outer membrane proteins (Omps), flagella, type I fimbriae, lipopolysaccharide (LPS), and phospholipids are all important structural features of *E. coli*, [6-9-10]. The outer membrane (OM) has significant effects on cell shape, division, phenotype, and stress responses. There are two different membranes in *E. coli*: the OM and the inner membrane (IM) which are the components of *E. coli* cell

envelope that determines the cellular shape and enables it to withstand heavy stresses like osmotic stress [6-9-10].

Many flagella and type I fimbriae are assembled on the envelope surface, especially uropathogenic *E. coli* (UPEC). Flagella provide motility of cells, while fimbriae mediate the bacterial adhesion to biotic and abiotic surfaces, resulting in colonization on infected hosts. In *E. coli*, the cost of flagellar synthesis is equal to about 2% of the cell's biosynthetic energy consumption [6-9-11]. LPS are negative charged molecules which are the major outer surface membrane components, and they are considered as the first line of defense against antimicrobial molecules and stress caused by changes in the environment surrounding the bacterium. LPS consists of lipid A, O-antigen and core oligosaccharide. Lipid A is the lipid component of endotoxins which are responsible for the toxicity of gram-negative bacteria and immune response stimulation. It is the innermost of the three regions of LPS [6-9-11]. O antigen consists of many repeats of an oligosaccharide unit. It appears to be a major target for both immune system and bacteriophages. It is one of the most variable cell constituents that contributes in the major antigenic variability of the cell surface. The variability of the O antigen provides the major basis for serotyping schemes.

The last component of LPS is the core oligosaccharide which is a short chain of branched and phosphorylated hetero-oligosaccharide contributing in the bacterial viability and stability of the outer membrane [6-9-11]. Phospholipids are found in the periplasmic space while LPS is found in the exterior leaflet. The two most significant OM porin proteins in *E. coli* are the Omp C and Omp F, which regulate the entry of small molecules into the interior of the cell. OmpA, another significant porin, contributes structurally to the stability of the bacterial cell surface [6-9-11].

4. Chromosomal structure:

E. coli has only one circular chromosome which contains double stranded DNA molecules that encode the genetic material in haploid form. It's chromosome helps in replication by the origin of replication (oriC) which is the starting point of replication and a terminus of replication (ter), which is located opposite to oriC that pauses the replication fork to avoid over-replication in the leading strand because it interacts with the terminator protein called terminus utilization substance (Tus), which binds to the termination sites This circular DNA chromosome contains protein-coding genes organized into operons. It is about 4,600 kilo base (kb), about 4,300 kb are potential coding sequences [6-9-11]. The *E. coli* genome contains accessory genes acquired by horizontal gene transfer in around 50% of the population. The ability of E. coli to adapt to environment is increased by combining these genes in various combinations. Additionally, several of them help in the colonization and infection processes of their hosts. Transposable genetic elements, repetitive elements, bacteriophage, and plasmids help in horizontal gene transfer and diversity of this species[6-9-11].

5. Antigenic structure:

There are three antigens: the somatic (O), capsular (K), and flagellar (H) antigens which are used to divide *E. coli* into 150–200 serotypes or serogroups. There are 173 kinds of O somatic antigens, 75 types of H flagellar antigens and 103 different varieties of the K capsular antigen [6-9-11].

6. UTI pathogenesis:

UPEC are present in feces and can cause contamination around vagina and periurethral meatus. It is mostly in females because the urethra is short and close to the anus. All of these predisposing factors help in migration and colonization around the vagina which are associated with decrease of protecting vaginal lactobacillus species and bacterial colonization around the urethra which is the first stage of UTI pathogenesis [6-9-11]. UPEC ascends into the bladder and adheres to the bladder epithelium (uroepithelial cell) via type 1 fimbriae, which connect to urothelial cell integrins α3, β1 and uroplakins receptors and also enters by umbrella cells (outermost layer of the uroepithelium) to the urinary bladder cells. It starts to invade the cell and replicates with rupture of bladder cell. After invading the bladder, UPEC migrates up the ureter via the P fimbriae's function and results in acute pyelonephritis[6-9-11].

7. Antimicrobial resistance:

A wide range of antimicrobial agents effectively inhibit the growth of *E.coli*. The β- lactams, fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole are often used to treat community and hospital infections [6-9-11]. UTIs especially recurrent UTIs are associated with repeated and frequent use of antibiotics that promote resistance especially multidrug resistant (MDR) and extensive drug resistant (XDR) strains due to increase ineffectiveness of the antimicrobials. Prevalence of recurrent UTIs are mostly in women with repeated sexual intercourse and reinfection with the same organism [6-9-11]. There are various mechanisms responsible for resistance. It may be an inherent trait of the organism that renders it naturally resistant or may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source [6-9-11].

I. <u>Inherent (natural) resistance:</u>

Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of gram negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic [6-9-11].

II. <u>Acquired resistance:</u>

a) Vertical gene transfer:

The spontaneous mutation frequency for antibiotic resistance is in the order of about 10^8-10^9. Once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication [6-9-11].

b) Horizontal gene transfer:

Lateral or horizontal gene transfer (HGT) is a process where genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species [6-9-11].

There are at least three possible mechanisms of HGT:

I) Conjugation:

It occurs when there is direct cell-cell contact between *E. coli* and another bacterium (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place.

II) Transformation:

It is a process where parts of DNA are taken up by *E. coli* from the external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium.

III) Transduction:

Transduction occurs when bacteria specific viruses (bacteriophages) transfer DNA between two closely related bacteria**[6-9-11]**.

8. Beta- lactamase enzymes:

Beta lactamase**s** are a group of plasmid encoded or chromosomally encoded bacterial enzymes that can hydrolyze the cyclic amid bond in the beta- lactam ring of bet lactams making them inactive. Synthesis of β lactamase enzyme**s** encoded by the *bla* genes found on the plasmids, is one of the primary mechanisms of resistance in UPEC. One form of β lactamase**s** called extended-spectrum β lactamase (ESBL) is in charge of causing resistance to antibiotics like penicillins, cephalosporins, and monobactams but most of ESBLs are sensitive to carbapenems and cephamycins [6-9-11].

9. Conclusions

When weighing the contributions of various virulence determinants to construct a model for UPEC pathogenesis, it is important to consider that UTI is not a mechanism of spread. That is, it is unlikely that *E. coli* successfully infecting the urinary tract are transmitted to new hosts directly via urine. Thus, it is also unlikely that the urinary tract represents an essential step in the lifecycle of these strains. More probable is the model that certain *E. coli* strains, by virtue of their unique genetic composition, are able to take advantage of the distinct urinary tract niche, possibly avoiding competition with the intestinal microbiota. These considerations, along with analysis of the *E. coli* genomes and efforts to identify novel virulence genes should advance the field significantly and allow for the development of a comprehensive model of pathogenesis for uropathogenic *E. coli*.

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