International Journal of Current Research and Review
DOI: http://dx.doi.org/10.31782/IJCRR.2019.11232

Review Article

IJCRR
Section: Life Sciences
Sci. Journal Impact Factor: 6.1 (2018)
ICV: 90.90 (2018)

# The Survival Strategies of Uropathogenic *Escherichia coli*

**Flores-Encarnación M.[1*], Nava-Nolazco R.M.[1], Aguilar-Gutiérrez G.R.[2], Espino-Benítez A.S.[1], Morales-Baéz J.R.[1], Cabrera-Maldonado C.[3]**

[1]Laboratorio de Microbiología Molecular y Celular, Laboratorio 421 Edif. EMA1, Biomedicina, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, Puebla. México; [2]Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca Morelos, México; [3]Depto de Microbiología, Facultad de Ciencias Químicas. Benemérita Universidad Autónoma de Puebla. Puebla. México.

## ABSTRACT

The invasion of the healthy urinary system is restricted to a group of microorganisms known as "uropathogens". 80-90% of all urinary tract infections (UTI) are caused by uropathogenic *E. coli*. The development of UTI depends on several virulence factors of the infecting organisms. This work shows the most relevant aspects in relation to the strategies responsible for the survival of uropathogenic *E. coli* in various environments in the host.

**Key Words:** Virulence factor, *E. coli*, Uropathogenic, Urinary tract

## INTRODUCTION

UTI are an infectious condition α potentially severe complications (Mohajeri *et al.*, 2014). The invasion of the healthy urinary system is restricted to a group of microorganisms known as "uropathogens" (Flores-Mireles *et al.*, 2015). Various types of bacteria can cause UTI. For 80-90% of all UTI are caused by uropathogenic *E. Coli* (UPEC) (Mohajeri *et al.*, 2014). It has been reported that the UTI are produced by ethnic microorganisms of the fecal microbiota, which have reached there by drag or poor hygiene, or they can also be produced by microorganisms that are introduced into the urinary tract by manipulation (Minardi *et al.*, 2011). In general, the development of UTI depends on anatomical factors, the integrity of host defense mechanisms, and the virulence of the infecting organisms (Magistro and Stief, 2019). This work shows the virulence factors of greater importance present in UPEC.

### The virulence factors of uropathogenic *E. coli*

UPECcolonizes the bladder using a variety of virulence factors that play a critical role in the urinary tract pathogenesis. It can survive in the urinary tract and cause disease due to a diverse range of virulence factorsbelow described (Karam*et al.*, 2018; Terlizzi *et al.*, 2017).

### The polysaccharide capsule

The capsule (capsular antigen or K antigen) is a homogeneous layer of polysaccharides that provides protection against antiphagocytic effects and the serum resistance (Sarkar *et al.*, 2014). The capsule increase the virulence (Phanphak *et al.*, 2019).The capsule of *E. coli*is highly variable, with more than 80 different types described (Goh *et al.*, 2017). The capsules of group 2 are expressed by UPEC strains and are composed of different K antigens (K1, K2, K5, K100) (Goh*et al.*, 2017). The K1 and K2 capsules provide protection to killing mediated by complement (Sarkar *et al.*, 2014). It has been reported that K1 capsule is required for the development of intracellular bacterial communities contributing to host immune evasion (Anderson *et al.*, 2010). K1 capsule is also associated with strains that cause UTI, bacteriemia and meningitis (Goh *et al.*, 2017).

### The toxins of uropathogenic *E. coli*

The lipopolysaccharide (LPS) of UPEC plays an important role mediating the resistance to the bactericidal activity of

**Corresponding Author:**
**Flores-Encarnación M.,** Laboratorio 421 Edif. EMA1. Biomedicina. Facultad de Medicina. Benemérita Universidad Autónoma de Puebla. 13 sur 2702, Col. Volcanes, C.P. 72410. Puebla, Puebla, México; E-mail: mflores31@hotmail.com

**ISSN:** 2231-2196 (Print) **ISSN:** 0975-5241 (Online)
**Received:** 21.09.2019 **Revised:** 02.11.2019 **Accepted:** 24.11.2019

human serum (Sarkar *et al*., 2014). The O antigen types such as O1, O2, O4, O6, O7, O8, O16, O18, O25, O75, are the most common among UPEC strains. The glycosyl transferase enzymes seem to be responsible for the observed variations (Totsika*et al*., 2012).It has been reported that LPS promotes the synthesis of cytosines (IL-1, TNFα) enhancing the inflammatory response; it induces also the synthesis of specific antibodies to the O antigen (Sarkar *et al*., 2014; Totsika *et al*., 2012). The α-haemolysin (HlyA) is a lipoprotein and it is the most important virulence factor exported from UPEC. The production of toxins by colonizing *E. coli* may cause an inflammatory response, a possible pathway for urinary tract infection symptoms. The α-haemolysin is associated with upper UTI such as pyelonephritis (Dhakal*et al*., 2012). It is a family of toxins forming pores, which induces cell lysis producing the release of nutrients and other growth factors. At high concentrations, the α-haemolysin is able to lyse erythrocytes and nucleated host cells, which favors that UPEC crosses mucosal barriers, damage effect or immune cells, and gain enhanced access to host nutrients and iron stores. At low concentrations, α-haemolysin can induce eryptosis and the apoptosis of target host cells, including neutrophils, T lymphocytes, and renal cells, and promote the exfoliation of bladder epithelial cells. It has also been described that the α-haemolysin of *E. coli* triggers proteolysis of host proteins to disrupt cell adhesion, inflammatory and survival pathways (Carrizo-Velásquez *et al*., 2015;Dhakal and Mulvey, 2012; Ristow and Welch, 2016).The secreted autotransporter toxin (Sat) is a virulence factor of pyelonephritis *E. coli* strains, which has a toxic activity against cell lines of bladder or kidney; it may be important for pathogenesis of urinary tract infections. Sat has been found predominantly in UPEC (Maroncle *et al*., 2006). It has been described that Sat induces morphological alterations in the actin cytoskeleton in bladder cells, rounding them and in the kidney elongating them; it also produces the folding of the membrane of the cells (Moal *et al*., 2011). Sat causes vacuolization and glomerular damage; it is a vacuolating cytotoxin for bladder and kidney epithelial cells.The vacuolatin gautotransporter toxin (Vat) contributes to UPEC fitness during systemic infection. Vat-specific antibodies were detected in plasma samples from urosepsis patients infected by *vat*-containing UPEC strains, demonstrating that Vat is expressed during infection. It has been reported also that Vat has cytotoxic effects similar to those caused by the VacA toxin of *Helicobacter pylori* and induces the formation of intracellular vacuoles. The *vat* gene has been shown to be most prevalent in *E. coli* strains from the B2 phylogenetic group, with similar distributions observed among cystitis, pyelonephritis, prostatitis, and bloodstream isolates (Nichols *et al*., (2016). The cytotoxic necrotizing factor-1 (CNF1) is a 115-kDa toxin that is expressed by 40% of UPEC strains. CNF1 constitutively activates small Rho-family GTPases contributing to urothelial cell invasión and it has citotoxic effects on urotehlium (Michaud e*t al*., 2017). *In vitro*, changes include cell multinucleation, actin cytoskeletal rearrangement, apoptosis of urothelial cells, formation of lamellipodia and filopodia, decreased polymorphonuclear phagocytic capacity, activation of nuclear factor-B (NF-B)(Garcia *et al*., 2013). The cytolethal distending toxin (CDT) was discovered in an *E. coli* strain isolated from diarrheal patient in 1987. In more recent years, the *E. coli* producing CDT has been isolated from patients with gastrointestinal or UTI and sepsis. Apparently, healthy cattle and swine could be the reservoir of CDT, and they could be a potential source of human infections. When tested in HeLa cells, CDT produced giant mononucleated cells caused by an irreversible block in the cell cycle at the G2/M stage (Hinenoya *et al*., 2014).

## Adhesins

The ability to adhere to host epithelial cells in the urinary tract represents the most important factor of pathogenicity in UTI. Among the adhesins reported, P-pili have thought to be a major virulence factor in UPEC (Terlizzi *et al*., 2017). The pathogenic strains of *E. coli* express adherence factors which form pili or fimbriae of different types for their attachment in the sites where they usually do not live. These structural virulence factors include P fimbriae and type 1 fimbriae. The fimbrial adhesins such as PapG and CsgA are virulence factors that facilitate the attachment of *E. coli* (Luna-Pineda *et al*., 2018). UPEC can impair host immune system by a variety of ways: the toxins and iron acquisition systems causing an inflammatory response and with it the UTI symptoms (Olson and Hunstad, 2016). P fimbria is the most studied adhesin and the main virulence factor of strains that cause pyelonephritis and urosepsis. At the distal tip of pili P a specific adhesin protein, called PapG, which mediates bacterial adhesion to host cells is located. There are three types of PapG adhesion: PapG I, II, and III and they recognize globotriasylceramide variants on the surface of target cells. PapG I and PapG II adhesins bind preferentially to globotriaosylceramide(Gb3) and globoside (GbO4) (abundant in human uroepithelial cells). UPEC strains containing PapG I and PapG II adhesins have been associated with pyelonephritis and bacteremia. The PapGIII adhesins bind to the Forssman antigen or GbO5(Lane and Mobley, 2007). GbO5 is a heterophilic glycolipid with structural similarity to the antigen of blood group A. Mouse and dog were also classified as Forssman-positive, and human and other anthropoid apes as Forssman-negative. The Forssman antigen was also found in species other than mammals. For example, chicken, turtles, and carp express the antigen, whereas goose, pigeon, and frog lack the antigen (Yamamoto *et al*., 2012).

## Biofilm

Biofilms are complex ecosystems of microorganisms and their extracellular products adhered on a biotic or abiotic

surface, which are made up of approximately 15% cells and 85% extracellular matrix. It is believed that the extracellular matrix has a fundamentally protective mission, some components can sometimes serve as food for resident organisms and it confers resistance against disinfectants and antibiotics (Costerton *et al*., 1999; Flores-Encarnación *et al*., 2014). It has been observed that UPEC strains have the ability to invade the cells of the bladder and biofilm formation protect them to action of antibiotics. The ability to form biofilm by UPEC is mediated by pili type 1, which binds to mannose receptors in the bladder epithelial cells, favoring the bacterial adhesion and invasion (Lewis *et al*., 2016). Once inside the bladder cells, UPEC multiplies and forms morphologically distinct colonies called intracellular bacterial communities, which provide a safe haven against effectors of host immunity. These communities are collections of rod-shaped bacteria, that then mature into coccoid organisms with a different architecture and a non-replicative state or latent state (quiescent state). Later, they eventually adopt a filamentous phenotype separating themselves from the community and reestablishing infection in epithelial cells and eventually starting a new cycle of intracellular bacterial communities (Blango and Mulvey, 2010).

### Iron-acquisition systems

UPEC strains possess iron-acquisition systems (Terlizzi *et al*., 2017). As is known, iron is an essential factor for many cellular processes, both in eukaryotic and prokaryotic cells. It has been reported that the UPEC have developed multiple strategies to scavengiron from the host (Correnti and Strong, 2012). The role of iron as a critical nutrient in pathogenic bacteria is widely regarded as having driven selection for iron acquisition systems among UPEC isolates. The iron acquisition systems use siderophores to scavengiron from the environment. Bacteria capture iron bound to siderophores through receptors that facilitate the transport of iron-siderophore complexes through the bacterial membrane and into the cytosol where iron is released. The advantage that gives the bacteria is to colonize and survive in environments where the concentration of iron is very low, as is the case of the urinary tract (Robinson *et al*., 2018). To combat this, the host has developed mechanisms defense in the form of iron chelating proteins, such as transferrin. This protein is highly conserved among mammals, birds, fish and amphibians and it has a strong affinity for iron (Recalcati *et al*., 2010).

## CONCLUSION

The UPEC is a bacterium of great interest in the world due to its participation in UTI processes. UTI are a serious public health problem, so that knowledge of the virulence factors of UPEC allow better understanding of the pathogenesis of bacterium.

## ACKNOWLEDGEMENTS

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed. Thank also to PRODEP and Facultad de Medicina-BUAP for the facilities provided for the development of this work.

**Conflict of Interest**

Authors have no conflict of interest.

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