Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.324518.3603 Volume 31, Issue 1, January. 2025
Manuscript id: ZUMJ-2409-3603
Doi: 10.21608/zumj.2024.324518.3603
REVIEW ARTICLE

Invasiveness and Virulence factors of Uropathogenic Escherichia coli

Mohamed Hossam Al-Din Abd Alaziz[1], Said Hamed Al Abbadi[2], Nada Ayman Mohammed Abd Al Rahman[2*], Hanaa I. Abd El-Hady[1]
[1]Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Medical Microbiology and Immunology Department, Faculty of Medicine, Suez University, Ismailia, Egypt

***Corresponding author:**

Nada Ayman Mohammed Abd Al Rahman

Email:
ayman.soliman.oa55@gmail.com

Submit Date:29-09-2024
Revised Date:09-10-2024
Accepted Date:14-10-2024

ABSTRACT

Background: One of the most prevalent infectious diseases in the world is urinary tract infections (UTIs). Escherichia coli (E. coli) is the pathogen most often isolated from simple UTIs. E. coli must get beyond the host's defense mechanisms, such as urine flow, uroepithelial cell exfoliation, endogenous antimicrobial agents, and invading neutrophils, in order to establish infection in the urinary tract. Therefore, the bacterium known as uropathogenic E. coli (UPEC) possesses several virulence and fitness characteristics that allow it to withstand and surpass these various defense mechanisms. Furthermore, a large number of putative virulence or fitness variables have considerable redundancy. Fimbriae are required for adhesion to and invasion of the host cells; type 1 pilus is a well-known virulence factor in UPEC and is essential for a urinary tract infection to be successful. Toxins and flagella encourage the spread of germs, yet several iron-acquisition mechanisms enable bacterial survival in the iron-deficient urinary tract environment. The immunological reaction to UPEC is principally facilitated by toll-like receptors that identify flagella, lipopolysaccharide, and additional bacterial surface features. Urosepsis is a type of sepsis which originates from the urogenital tract infections. UPEC is the most common cause of urosepsis. It is responsible for 50% of urosepsis cases. So, we aimed to discuss the role of virulence factors in uropathogenic Escherichia coli.
Conclusion: Identification of virulence factors and mechanisms may facilitate the application of more precise approaches in phenotypic or molecular diagnosis and epidemiology. Urosepsis can be a serious condition, especially in patients with low immunity and those without treatment.

Keywords: Urinary tract infection, Uropathogenic E.coli, Virulence factors, urosepsis

INTRODUCTION

One of the most prevalent infectious diseases in the world is urinary tract infections (UTIs). Uropathogenic *Escherichia coli* (UPEC) strains account for around 80% of community-acquired UTIs (CA-UTIs) that are not too difficult, and this same species is often isolated from hospital-acquired infections as well. Acute pyelonephritis is a type of UTI that affects the kidney, while cystitis is restricted to the lower urinary tract. Bacteria may eventually enter the bloodstream and result in septicemia, a potentially fatal condition. The majority of patients are female, and among those over 32, half of all women have had a UTI at least once; otherwise, healthy women may experience a recurrence of cystitis within six months, and many will experience three or more bouts per year (recurrent UTI). Even though emerging antimicrobial resistances make treatments more challenging, acute UTIs of the lower and upper urinary tract in otherwise healthy, premenopausal, and non-pregnant women without any urinary tract anatomical abnormalities are considered uncomplicated and easily treatable with antibiotics **[1, 2]**.

Upper urinary tract infections are less common than lower urinary tract infections, but infection can still spread and result in kidney infection (acute pyelonephritis) **[3].**

Asymptomatic bacteriuria (ABU) is the term for the presence of large amounts of *E. coli* in the urine without any symptoms. These infections are usually left untreated in healthy, non-pregnant women, and they may even shield against infections from strains that produce symptoms of illness **[4].**

Many virulence factors found in UPEC strains contribute significantly to the pathogenicity associated with symptomatic UTIs. Two categories of virulence factors exist: The first category consists of structural virulence factors such as flagella, adhesins, lipopolysaccharides, and polysaccharide capsules. The second category consists of virulence factors that are secreted, such as hemolysins, autotransporter toxins, cytotoxic necrotizing factor 1(CNF1), and proteases **[5, 6].**

So, we aimed to discuss the role of virulence factors in uropathogenic *Escherichia coli*.

I. Structural virulence factors:

1. Flagella*:*

Flagella are hair-like structures that are responsible for bacterial motility and facilitate UTI.

2. Adhesins:

Adhesins are virulence factors that are found on the surface of the bacterial membrane that allow bacteria to attach to host cells. They play a crucial role in the infection's earliest stage of adhesion to host tissues. Because they promote interactions between host cells and mucosa that aid in the colonization and infection of bacteria, they are regarded as important virulence factors. They are able to withstand minor environmental stressors such as pH, mechanical pressures, temperature changes, and osmolarity variations **[7]**.

Adhesins are classified into two important types: fimbrial (pilli) and afimbrial.

a. Fimbrial adhesins (Pilli): Fimbriae are different from flagella. They are far more common on the cell surface and have smaller diameters. They are also shorter, straighter, and lack the curled spiral structure of flagella.

They have many types, and each one has a different function. Type1 fimbria are the most prevalent forms of fimbriae, type 2, P fimbria and S fimbria (figure.1) **[7]**.

Type 1 fimbriae: Mannose-sensitive pili are known as type 1 fimbriae. They are roughly 1-2 μm in length and 6.9 nm in width, and they are frequently expressed in pathogenic strains of *Escherichia coli.* They are considered one of the most important structures for biofilm biosynthesis because they are attached to the mannose portion of uroplakin on the surface of transitional uroepithelial cells that line the bladder **[9].**

They are encoded by an operon that contains the chromosomal genes of most of the UPEC, such as fimA, *fimC, fimD, fimF, fimG,* and *fimH.* Adhesin *fim H* is very important because it recognizes mannosylated uroplakins and $\alpha_1\beta_3$ integrins that help in bacterial adhesion on the surface and penetration of uroepithelial cells. Thus, *fimH* adhesin enhances renal infection **[6]**.

Type 2, P fimbriae: P fimbriae (pyelonephritis associated pilli) or *pap* are a large linear type of pilli that protrudes from the surface of bacteria attaching to the major glycolipid receptor present on the renal cell membrane. P fimbriae are considered the main cause of pyelonephritis, cystitis, and bacteremia **[10].**

S fimbria: S fimbriae are a type of fimbriae encoded by many genes. The most important one is *the SfaH* gene, which codes for a protein that binds to sialic acid molecules in uroepithelial cells and endothelial *tissues of the bladder and kidney **[6].***

b. Dr adhesins:

They are formed from fimbrial and fimbiral structures on the surface of *E. coli* give rise to the Dr adhesin family, which binds to the Dr blood group antigen, which is part of the decay-acceleration factor that stops complement from lysing cells. *DraE* is the most important gene of Dr adhesin, which binds with uroepithelial cells in the kidney and Bowman capsules **[11].**

c. Afimbrial adhesins:

Type one secretion A (TosA) is an afimbrial adhesin that helps bind to kidney epithelial cells and promote bacterial invasion **[12].**

3. Lipopolysaccharides (LPS):

Lipopolysaccharides (LPS) are structural virulence factors that are of many different serotypes, comprising an intact lipid A Variable O antigen region and a core region **[13].**

4. Capsules:

Capsules are cell surface structures consisting of multiple polysaccharides and provide protection against phagocytosis and complement. K1 and K2, the most significant capsules, are involved in the early phases of acute UTI and aid in host immune evasion, which involves phagocytosis **[14]**.

II. Secretory virulence factors:

1. Hemolysins:

Hemolysins are the most important virulence factors secreted by UPEC, especially the α hemolysin (Hly A) toxin, which is associated with pyelonephritis and is encoded by the genes. The

level of concentration affects the toxin's activity. It can exfoliate urinary bladder epithelial cells and induce T-lymphocytes, neutrophils, and renal cells to undergo apoptosis at low concentrations. At high concentrations, however, it can lyse erythrocytes and nucleated host cells, including uroepithelial cells. This could enable UPEC to pass mucosal barriers and eliminate effector immune cells **[6]**.

2. Autotransporters toxins:

Vacuolating autotransporter toxin (VAT) and secreted autotransporter toxin (SAT) make up autotransporter toxins (type V secretion toxins). SAT has cytopathic action, so the host tissue may be damaged, and it can also enhance UPEC spreading. This toxin facilitates entry to the circulation by damaging the proximal tubules and glomeruli. **[6]**.

3. Cytotoxic necrotizing factor 1:

Numerous UPEC strains release cytotoxic necrotizing factor 1 (CNF1), which aids in UPEC invasion of renal cells. Additionally, it promotes polymorphonuclear leukocytes and phagocytes apoptosis and bladder epithelium scarring **[15]**.

4. Proteases:

Enzymes called proteases aid in the breakage of peptide bonds. Their genes can be found in transposons, plasmids, and prophages, among other mobile genetic elements. They are not necessary for the survival and reproduction of bacteria, but they might be essential for virulence. The *ompT*, *ompP*, and *arlC* genes encode proteases known as outer-membrane proteases (omptins), which are found in the outer membrane of *E. coli*. The most crucial one is *OmpT*, which is known to be a major virulence factor in UPEC strains that cause urosepsis, pyelonephritis, and cystitis **[6]**.

Pathogenicity associated islands:

Pathogens with distinct genetic components that encode varying virulence traits are referred to as "pathogenicity islands" (PAIs). Phages, transposons, and plasmids are the means by which these genes are horizontally transported across bacterial strains. PAIs are commonly found in pathogenic strains but are absent in nonpathogenic strains. They play a role in the mutation of commensal *E. coli* strains to be UPEC because genetic components on it encode the virulence factor that may contribute to bacterial pathogenesis and play roles in the disease by this large horizontal transferring of genetic elements **[16]**.

Invasive uropathogenic *E.coli*:

One of the most significant adhesins in invasive UPEC is P fimbria, which is made up of many subunits called *PapA-G* and is expressed by the pap operon, a functional DNA unit that is found on pathogenicity islands and has a cluster of genes regulated by a single promoter **[17].**

The pap operon's genes encode five structural proteins (*papA, papK, papE, papF, and papG*), four transport and assembly-related proteins (*papC, papD, papH, and papJ*), and two operon expression-regulating proteins (*papB, papI*). There is pap G near the tip of P fimbriae, which aids with the P fimbriae's binding to epithelial cells (Figure 2) **[18]**.

PapG has four alleles; (*papGI, papGII, papGIII and papGIV)* which differ in their binding specificity because each of them has unique glycan receptor and special binding specificities.

PapGI allele binds to the globotriaosylceramide-3 (GbO_3) of human uroepithelial cells It is rarely found in *E. coli* causing UTIs in human **[8].**

PapG II allele binds to GbO_4 of uroepithelial cells. It is the major gene that is associated with pyelonephritis, urinary-source bacteremia, and urosepsis **[18, 19].**

PapG III allele binds to GbO5 of uroepithelial cells. It is associated with asymptomatic bacteriuria, cystitis, pyelonephritis, and acute prostatitis **[17]**.

Role of *PapGII* in invasiveness:

PapGII gene is the most common type of *papG* gene. It is the major cause of severe pyelonephritis, urosepsis and bacteremia. Invasive UPEC carry *papGII*-containing PAIs that emerges through repeated horizontal transfer of genetic elements **[21]**.

PapGII at the tip of *PapG* adhesins binds with digalactoside receptor in the renal epithelium leading to the release of sphingolipid ceramide. Sphingolipid ceramide regulates immunological responses, including proinflammatory cytokines and chemokines (IL-6 and IL-8), via activating the toll like receptor-4 (TLR-4) signaling pathway. Inflammation can aid in the removal of UPEC cells, but it can also damage kidney tissue, which can result in the formation of UTI **[10]**.

PapGII, which controls host gene expression in kidney cells and causes the expression of interferon regulatory factor-7(IRF-7), is the cause of acute pyelonephritis **[6].**

Acute pyelonephritis is caused by *PapGII*, which helps to move UPEC up to the ureter to the kidney, especially renal tubules **[6]**

After reaching renal tubules, extremely near to the circulatory system, invasive UPEC passes through capillary endothelial cells to access blood stream causing bacteremia and systemic transmission through the blood circulation **[18].**

Urosepsis:

One kind of sepsis that results from urogenital tract infections is called urosepsis. UPEC is the most frequent cause of urosepsis. Fifty percent of cases of urosepsis are caused by it. **[22]**.

Diagnosis:

After examining a patient's medical history, the diagnosis of urosepsis entails assessing the following symptoms, signs, and test results:

1- Clinical picture:

The symptoms and indicators of sepsis and UTI are part of the clinical picture of urosepsis. Tachypnea, fast breathing, chills, persistent fever, altered sensorium, hypotension, and gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea) are some of the signs and symptoms of sepsis. **[23].**

The clinical picture of a UTI comprises the following conditions: pyelonephritis, which manifests as fever, chills, flank pain, costovertebral angle discomfort, and vomiting; cystitis, which presents as dysuria, frequency, urgency, suprapubic pain, and hematuria with fever, chills, rigors, and malaise. **[22]**.

2- Laboratory diagnosis:

A-Serum or plasma biomarkers:

Numerous inflammatory biomarkers aid in the diagnosis of sepsis. White blood cell (WBC) count, erythrocyte sedimentation rate, and C-reactive protein are a few examples. Increased monocytes, polymorph nuclear leucocytes, or white blood cells suggest a potential infection. **[24].**

The most helpful biomarker for sepsis and severe bacterial infections is procalcitonin (PCT), which aids in diagnosis and subsequent treatment. When there is organ dysfunction along with additional signs of "severe sepsis" or "septic shock," high plasma PCT levels are seen. It rises in the first three hours of sepsis and stays in the bloodstream for up to 48 hours before falling off swiftly with appropriate treatment for bloodstream infections. **[25]**.

B-Blood culture:

Since blood cultures are the gold standard for identifying bloodstream infections, they play a crucial function in microbiological laboratories. Blood cultures come in a variety of forms, including automated blood culture systems like BACTEC and BACT/ALERT, as well as traditional blood cultures, non-conventional blood cultures like the septic-check system, and biphasic blood culture system. **[26].**

C- Molecular diagnosis:

Molecular methods are becoming helpful in cutting down on lab time. PCR tests, which focus on a conserved area of the 23S ribosomal DNA gene and are ideal for the detection and quantification of pathogenic bacteria in human blood, enable the direct detection of bacteria in blood without the need for culture. **[27].**

Complications:

Serious complications can arise from urosepsis, particularly in individuals with weakened immune systems and those who are untreated. It can lead to other infections in the body, such as cellulitis, endocarditis, meningitis, osteomyelitis, peritonitis, and pneumonia. Delayed management can lead to severe consequences such as disseminated intravascular coagulation (DIC), septic shock, organ failure, and death [28].

CONCLUSION

Accumulation of theoretical knowledge through virulence studies allows practical applications. Identification of virulence factors and mechanisms may facilitate the application of more precise approaches in phenotypic or molecular diagnosis and epidemiology. As a result, new targets will be recognized for antimicrobial intervention. Finally, the perspectives of prevention may improve by the utilization of receptor analogs or vaccine-candidate monovalent/polyvalent antigens.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

REFERENCES

1. Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo C. Urinary tract infections: the current scenario and future prospects. Pathog. 2023, 12(4), 623.
2. Glover M, Moreira CG, Sperandio V, Zimmern P. Recurrent urinary tract infections in healthy and non-pregnant women. Urol. Sci., 2014, 25(1), 1-8.
3. Czajkowski K, Broś-Konopielko M, Teliga-Czajkowska J. Urinary tract infection in women. MENOPAUSE REV., 2021, 20(1), 40-7.
4. Ipe DS, Sundac L, Benjamin WH, Moore KH, Ulett GC. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. FEMS Microbiol. Lett., 2013, 346(1), 1-10.
5. Terlizzi ME, Gribaudo G, Maffei ME. UroPathogenic *Escherichia coli* (UPEC) Infections: Virulence factors, bladder responses,

antibiotic, and non-antibiotic antimicrobial strategies. *Front. microbiol*, 2017; *8*, 1566.
6. Kaur N, Agarwal A, Grover M, Singh S. Uropathogenic *Escherichia coli*. In *Enterobacteria*. IntechOpen. 2022.
7. Bessaiah H, Anamalé C, Sung J, Dozois CM. What Flips the Switch? Signals and Stress Regulating Extraintestinal Pathogenic *Escherichia coli* Type 1 Fimbriae (Pili). *Microorganisms*, 2021; *10*(1), 5.
8. Govindarajan DK, Kandaswamy K. Virulence factors of uropathogens and their role in host-pathogen interactions. *Cell surface (Amsterdam, Netherlands)*, 2022; *8*, 100075.
9. Gunther IV NW, Snyder JA, Lockatell V, Blomfield I, Johnson DE, Mobley HL. Assessment of virulence of uropathogenic *Escherichia coli* type 1 fimbrial mutants in which the invertible element is phase-locked on or off. *Infect Immun*, 2002; *70*(7), 3344-54.
10. Yang W, Liu P, Chen Y, Lv Q, Wang Z, Huang W, et al. Dictamnine inhibits the adhesion to and invasion of uropathogenic *Escherichia Coli* (UPEC) to urothelial cells. Mol. 2022; *27*(1), 272.
11. Bahrani-Mougeot FK, Buckles EL, Lockatell CV, Hebel JR, Johnson DE, Tang CM, et al. Type 1 fimbriae and extracellular polysaccharides are preeminent uropathogenic *Escherichia coli* virulence determinants in the murine urinary tract. Mol. Microbiol., 2002, 45(4), 1079-93
12. Luterbach CL, Forsyth VS, Engstrom MD, Mobley HL. TosR-mediated regulation of adhesins and biofilm formation in uropathogenic *Escherichia coli*. *Msphere*, 2018; *3*(3), e00222-18.
13. Sarkar S, Ulett GC, Totsika M, Phan MD, Schembri MA. Role of capsule and O antigen in the virulence of uropathogenic *Escherichia coli*. *PloS one*, 2014; *9*(4), e94786.
14. Goh KG, Phan MD, Forde BM, Chong TM, Yin WF, Chan KG, et al. Genome-wide discovery of genes required for capsule production by uropathogenic *Escherichia coli*. *MBio*, 2017; *8*(5), 1128-39.
15. Etefia E. Virulence Factors of Uropathogenic *Escherichia coli*. Intech Open, 2023.
16. Zakaria AS, Edward EA, Mohamed NM. Pathogenicity islands in uropathogenic *Escherichia coli* clinical isolate of the globally disseminated O25: H4-ST131 pandemic clonal lineage: first report from Egypt. *Antibiotics*, 2022; *11*(11), 1620.
17. Kudinha T, Kong F. Distribution of papG alleles among uropathogenic *Escherichia coli* from reproductive age women. *J. Biomed. Sci.*, 2022; *29*(1), 66.
18. Zhou Y, Zhou Z, Zheng L, Gong Z, Li Y, Jin Y, et al. Urinary tract infections caused by Uropathogenic *Escherichia coli*: mechanisms of infection and treatment options. *Int. J. Mol. Sci.*, 2023; *24*(13), 10537.
19. Laverty G, Gorman SP, Gilmore BF. Biomolecular mechanisms of Pseudomonas aeruginosa and *Escherichia coli* biofilm formation. *Pathog.* 2014; *3*(3), 596–632.
20. Biggel M, Xavier BB, Johnson JR, Nielsen KL, Frimodt-Møller N, Matheeussen V, et al. Horizontally acquired papGII-containing pathogenicity islands underlie the emergence of invasive uropathogenic *Escherichia coli* lineages. *Nat. Commun.*, 2020; *11*(1), 5968.
21. Kuruoglu T, Sensoy L, Atilla A, Temocin F, Gur D, Tanyel E. Evaluation of risk factors for the development of bacteremia and complications in patients with brucellosis: Is it possible to predict the clinical course?. *J Infect Dev Ctries*, 2023; *17*(09), 1277-84.
22. Porat A, Bhutta BS, Kesler S. Urosepsis. In StatPearls [Internet]. StatPearls Publishing. 2023.
23. Smith DA, Nehring SM. Bacteremia. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2023. PMID: 28723008.
24. Samraj RS, Zingarelli B, Wong HR. Role of biomarkers in sepsis care. Shock, 2013; 40(5), 358–65.
25. Gregoriano C, Heilmann E, Molitor A, Schuetz P. Role of procalcitonin use in the management of sepsis. J Thorac Dis, 2020; 12(Suppl 1), S5–S15.
26. Van der Poll, T., Shankar-Hari, M., & Wiersinga, W. J. The immunology of sepsis. Immunity, 2021, 54(11), 2450-64.
27. Abd Elsamiea SAE, Ismail YM, Assar EH, Nassar NM. Direct molecular diagnosis of bacterial etiology of sepsis in children in whole blood samples. Benha Med. J., 2023; 40(2), 528-41.
28. Kuruoglu, T., Sensoy, L., Atilla, A., Temocin, F., Gur, D., & Tanyel, E. Evaluation of risk factors for the development of bacteremia and complications in patients with brucellosis: Is it possible to predict the clinical course?. The Journal of Infection in Developing Countries, 2023, 17(09), 1277-84

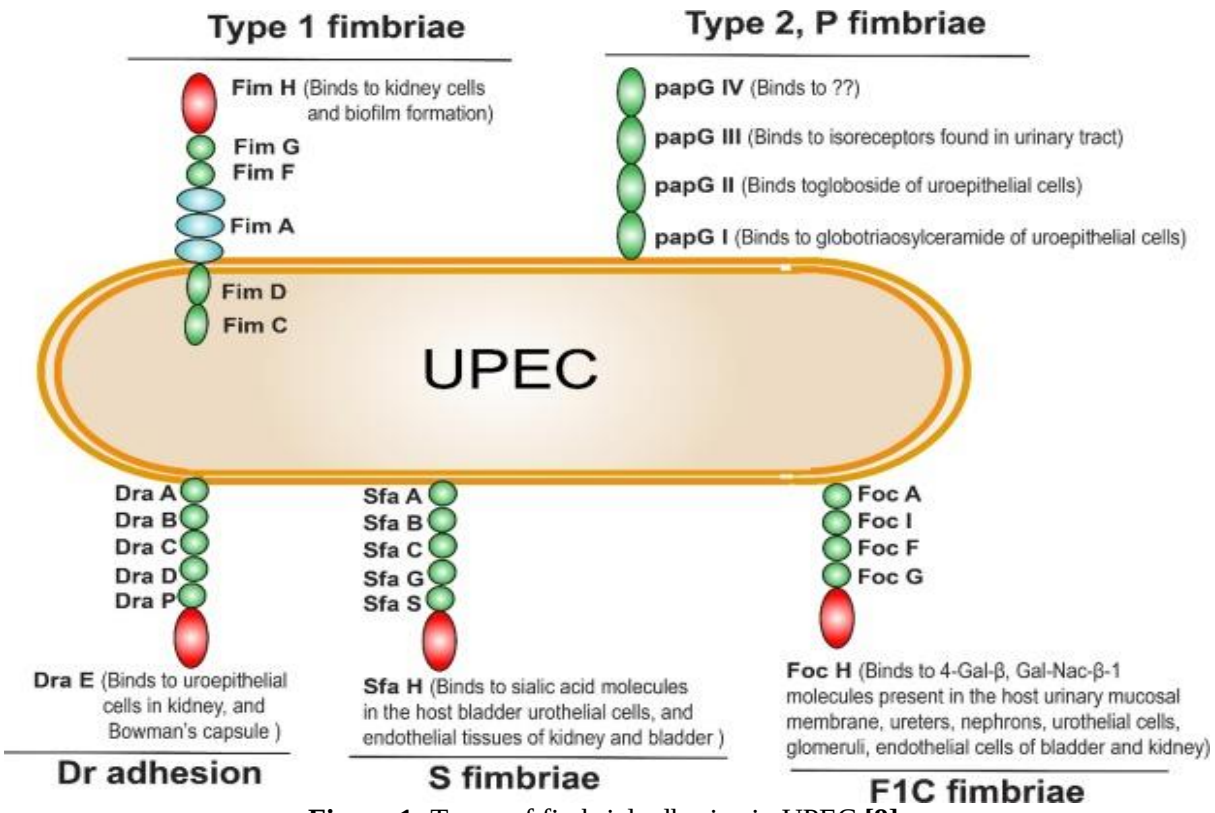

Figure 1: Types of fimbrial adhesins in UPEC **[8].**

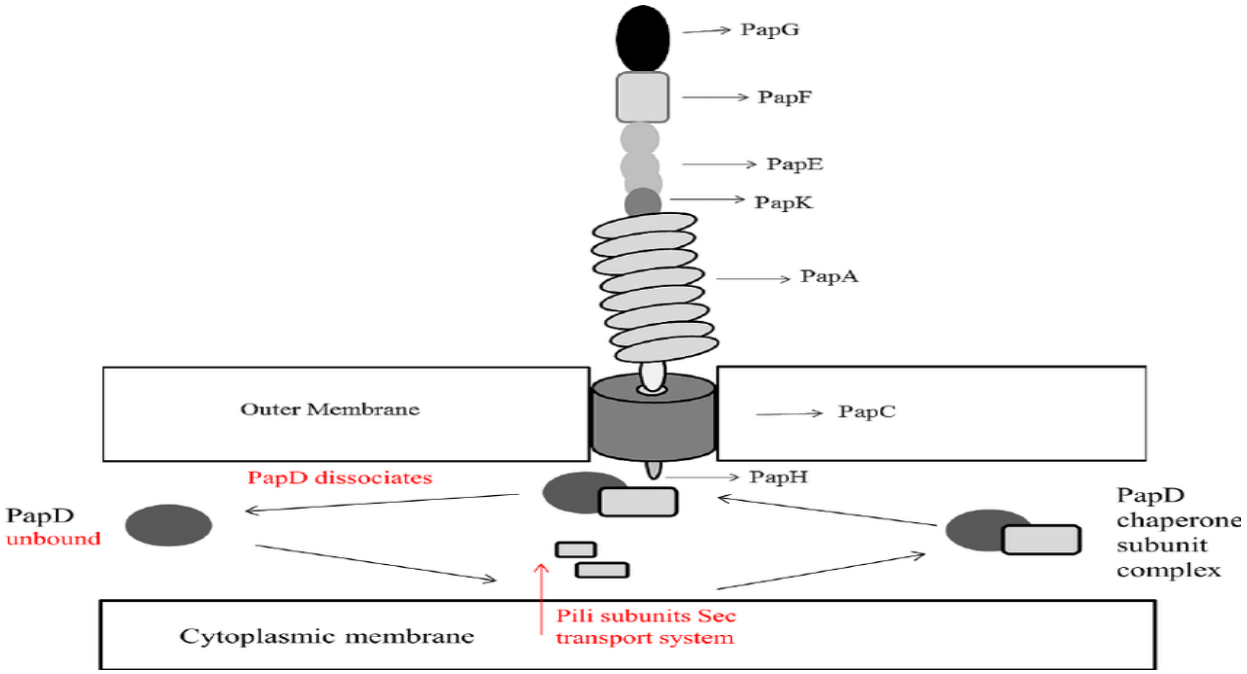

Figure 2: P fimbrial structure of *E.coli* **[20].**

Citation

Abd Alaziz, M., Al Abbadi, S., Abd Al Rahman, N., Abd El-Hady, H. Invasiveness and Virulence factors of Uropathogenic Escherichia coli. Zagazig University Medical Journal, 2024; (288-293): -. doi: 10.21608/zumj.2024.324518.3603