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A Review Article: Significance of virulence factors in pathogenicity of uropathogenic *Escherichia coli* (UPEC)

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ABSTRACT

Background: *Escherichia coli* are a versatile Gram-negative bacterium that is part of the normal intestinal flora of humans and animals. While most strains of *E. coli* are harmless and play a vital role in the gut microbiome, certain pathogenic strains can cause severe infections. Among these, uropathogenic *E. coli* (UPEC) is a prominent cause of urinary tract infections (UTIs), particularly in women. It is responsible for approximately 75–95% of uncomplicated UTIs and 40–50% of complicated UTIs worldwide, making it a significant public health concern. UPEC has evolved a range of virulence factors that enable it to colonize the urinary tract, evade the host immune system, and cause disease. These virulence factors include adhesins, such as type 1 and P fimbriae, which enable UPEC to attach to uroepithelial cells, and toxins like hemolysin and cytotoxic necrotizing factor 1, which damage host tissues. It also has mechanisms to acquire essential nutrients, such as iron, in the nutrient-limited environment of the urinary tract. Despite advances in understanding the pathogenesis of UPEC, UTIs remain a common and recurrent issue, partly due to the ability of UPEC to form biofilms and persist in the urinary tract. As antibiotic resistance among UPEC strains increases, there is a growing need for new therapeutic strategies to manage and prevent UTIs. **Conclusion:** Understanding the pathogenic mechanisms of UPEC is crucial for developing effective interventions against UTIs. Continued research into its virulence factors and resistance mechanisms is essential to address the challenges posed by recurrent and antibiotic-resistant infections.

Keywords: UPEC, Virulence factors, UTIs.
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INTRODUCTION

Escherichia coli, belonging to the Enterobacteriaceae family, is a rod-shaped bacterium that is facultatively anaerobic and does not form spores (1). *E. coli*, a bacterium usually present in the gut microbiota of warm-blooded organisms, is prevalent in the environment (2).

Uropathogenic *E. coli* (UPEC) are a subset of extraintestinal pathogenic *E. coli* that has developed from commensal *E. coli* through the acquisition of virulence factors via horizontal gene transfer. Urinary bladder invasion by the UPEC induces significant structural alterations in the bladder and triggers a robust immunological response. (3) Four primary UPEC phylogroups (A, B1, B2, and D) have been identified based on the presence of genomic Pathogenicity Islands (PAI) and the manifestation of virulence components, including adhesives, toxins, surface polysaccharides, flagella, and iron acquisition systems. Accounts for almost 80% of urinary tract infections. UPEC is widely recognized as the predominant bacterium responsible for both complex and simple urinary tract infections (4).

E. coli is a common commensal bacterium of the gastrointestinal tract (GIT); however, certain strains can act as opportunistic pathogens (5). *E. coli* has three types of antigens: the somatic O antigen, which is part of Lipopolysaccharide (LPS) located in the bacterial cell wall; the flagella H antigen, which is an antigenic protein found in motile species of *E. coli*; and the capsule K antigen, which is a polysaccharide found in encapsulated species that have flagella (6).

Virulence refers to an organism's ability to infect a host and produce sickness (3). *E. coli* possesses numerous virulence-associated components, such as adhesions, toxins, iron acquisition factors, lipopolysaccharides, polysaccharide capsules, and invasins (7). These factors are typically encoded on pathogenicity islands (PAIs), plasmids, and other mobile genetic elements. The components mentioned include flagella, outer-membrane vesicles, pili, curli, non-pilus adhesives, outer membrane proteins (OMPs), and secretion systems (8). UPEC relies on multiple virulence factors, including siderophores like aerobactin. Small molecules with a high affinity for iron are encoded by several members of the *iuc* gene family (9).

The proliferation and dissemination of bacteria resistant to antimicrobial agents, facilitated by multiple mechanisms and genes conferring resistance, pose a significant global public health risk(10). By 2050, it is projected that over 3 million individuals will perish as a result of MDR *E. coli* strains, specifically those that are resistant to carbapenem. The global spread of these strains is already underway, and the effectiveness of the only existing therapeutic option, colistin, is diminishing (11). Multi-drug resistance is now one of the most critical challenges facing the world. UPEC infections are typically treated with β-lactam antibiotics, fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole. However, the spread of third-generation cephalosporin resistance mediated by Ambler class A and C β-lactamases, and carbapenem resistance mediated by Ambler class A, B, and D β-lactamases has rendered many antibiotics ineffective (12).

Classification of *E. coli*

E. coli strains are usually categorized according to which O (somatic), K (capsular polysaccharide), and H (flagellar) antigens are present. While the serogroup only relates to the type O antigen, the strain's stereotype encompasses all three antigens. The lipopolysaccharide component of the bacterial membranes outer core anchors around 180 different types of polysaccharides, which are found in the O antigen. A study revealed that three serogroups, O4, O6, and O75, accounted for 50% of UPEC. Antigens O1, O2, O4, O6, O7, O8, O16, O18, O25, and O75 are highly frequent among UPEC. Fewer patterns were found for specific antigens K and H (13). UPEC accounts for around 90% of urinary tract infections acquired in the community and up to 50% of those acquired in healthcare settings (14).

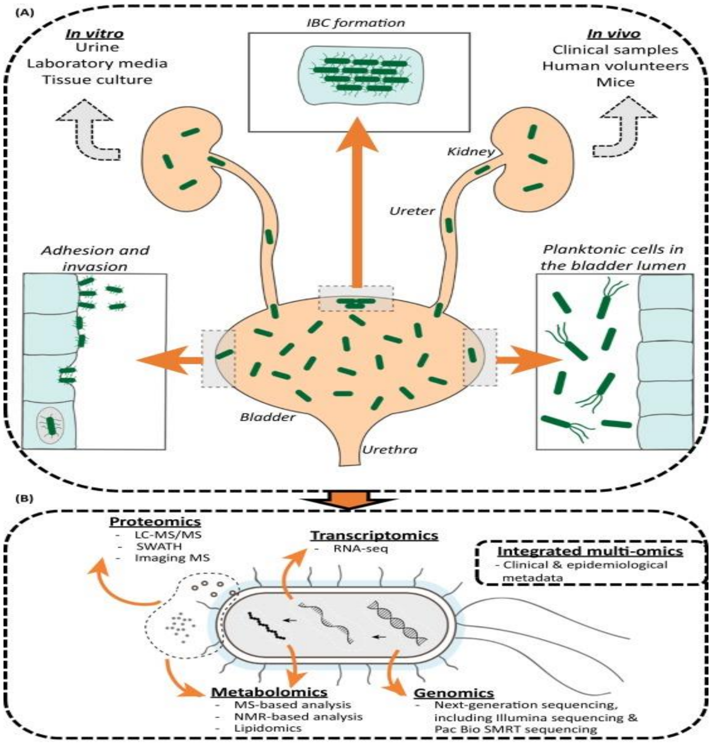
1. Uropathogenic *E. coli* (UPEC)

UPEC is a subtype of extraintestinal pathogenic *E. coli* that causes UTI. It possesses a diverse variety of genotypes. Through the acquisition of virulence factors through horizontal gene transfer, UPEC evolved from commensal *E. coli*. Urinary bladder invasion by UPEC induces significant structural alterations of the bladder and triggers a robust immunological response (15). Based on the presence of genetic Pathogenicity Islands (PAIs) and the expression of virulence components such as adhesives, toxins, surface polysaccharides, flagella, and iron acquisition systems, four primary UPEC phylogroups (A, B1, B2, and D) have been identified. Accounts for almost 80% of urinary tract infections. UPEC is widely recognized as the predominant bacterium responsible for both complex (40–50%) and simple (75–95%) urinary tract infections (16). Annually, around 150 million individuals worldwide receive a diagnosis of urinary tract infection. UPEC establishes itself in the bladder by employing Virulence factors, such as toxins, that alter and harm the host in order to facilitate infection (17) .

UPEC that causes UTIs goes through several steps. Firstly, UPEC colonizes the periurethral and vaginal areas, as well as the urethra. Secondly, it enters the bladder and grows as individual cells in the urine. Thirdly, the bacteria adhere to the bladder surface and interact with the bladder epithelium’s defense system, forming a biofilm. Fourthly, UPEC can invade the bladder cells and multiply, forming intracellular bacterial communities (IBCs) that act as dormant reservoirs within the urothelium. Finally, in severe cases, UPEC can also colonize the kidneys and cause damage to the host tissues, potentially leading to bacteremia/septicemia. The clinical manifestations of (UTI) vary, ranging from different forms of ascending infections, such as acute pyelonephritis and acute urosepsis, to asymptomatic bacteriuria (18, 19).

2. Pathogenesis pathway of UTIs

E. coli normally colonizes infants within hours after birth and forms an important part of the normal human gut flora (20). Certain *E. coli* isolates can cause extraintestinal disease and are therefore termed ExPEC (21). Organs targeted are diverse, for example, the urinary tract, the central nervous system, and the lungs. The mechanisms by which *E. coli* gain access to the urinary tract reflect an exceptional ability to adapt to an environment very different from the gut. They need to alter their metabolism (22), ascend against the flow of urine, and adhere to the epithelial layer. The *E. coli* that successfully invade the urinary tract harbor specific factors that enable them to survive. These strains of *E. coli* are commonly referred to as UPEC. The virulence of UPEC, compared to non-pathogenic *E. coli*, results from specific virulence genes in the bacterial chromosome. These vary considerably among different isolates, and no single gene has been implicated solely in uropathogenesis (23). Hence, UPEC is not a homogeneous group but rather a collection of *E. coli* isolates with different subsets of virulence factors that enable adherence, invasion, and survival in the urinary tract. In line with this, there are currently no tests that can determine whether an *E. coli* strain is uropathogenic or not, unless it has been appropriately isolated from the urine of a patient with symptoms of UTI. Many bacterial factors contribute to the complex pathogenesis of UTI. In fact, 131 UPEC-specific genes were reported, many of which may contribute to virulence (24). Flagella are thread-like structures that provide *E. coli* with the ability to move. It has been found to bind to TLR5 (25) and is of importance for the immune response to *E. coli* in UTI in mice (26).



Trends in Microbiology

Figure 1: UPEC attachment to urinary bladder cells and renal epithelial cells (26).

Virulence factors of UPEC

The ability of an organism to infect a host and cause illness is referred to as virulence (27). Many virulence-associated components are present in *E. coli*, including toxins, lipopolysaccharides, polysaccharide capsules, iron acquisition factors, and invasins. Usually, plasmids, pathogenicity islands (PAIs), and other mobile genetic elements encode these components. Flagella, outer-membrane vesicles, pili, curli, non-pilus adhesives, outer membrane proteins (OMPs), and secretion systems are among the components discussed (28). UPEC relies on many virulence factors, including siderophores like aerobactin, which are small molecules with a high affinity for iron encoded by several *iuc* genes (29).

Surface-associated and secreted/exported virulence factors are the two types of *E. coli* virulence factors that are anticipated to have a significant influence on the development of UTI, as shown in Figure 2.

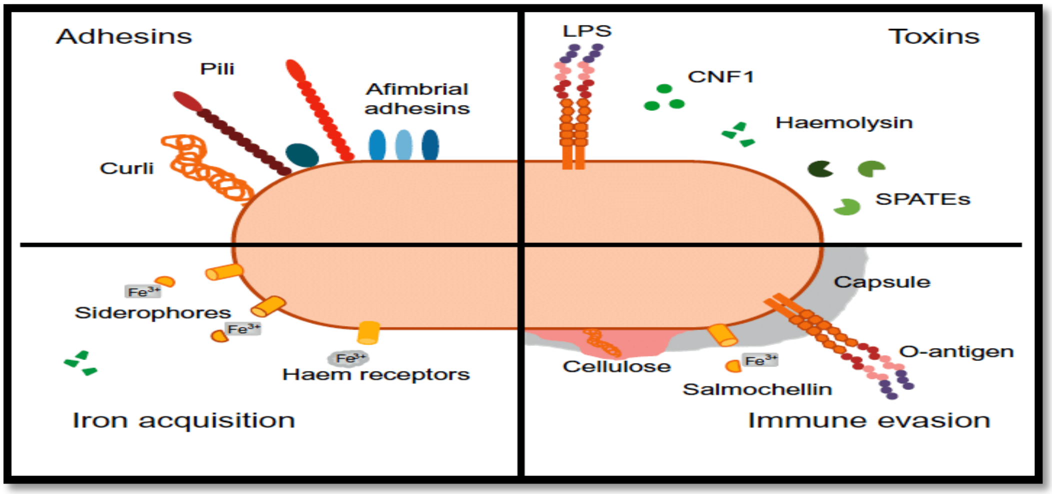


Figure 2: Virulence factors of UPEC (28).

1. Surface virulence factors

A. Type 1 fimbriae (Mannose- sensitive adhesions)

The filamentous reference sections are mostly seen on the bacterial surface. They are mostly composed of proteins and play a crucial role in binding to receptors on eukaryotic host cells, including urine glycocalyx, erythrocytes, and uroepithelial cells. Furthermore, these segments can form biofilms on inanimate objects like plastic catheters (30).

Type 1 fimbriae mediate attachment to both biotic and abiotic surfaces and are involved in the early stages of biofilm formation (31). In *E. coli*, type 1 fimbriae play a crucial role during UTI by mediating adhesion to mannose-containing receptors on the uroepithelium and promoting the formation of intracellular bacterial communities. Those adhesins are encoded by the *fim* determinant composed of two independent transcription units coding for the recombinases FimE and FimB, and a polycistronic operon encoding the structural components (FimA , FimF, FimG, and FimH) and a pilus assembly system (FimC and FimD); *fimA* encodes for the major structural subunit; *fimF* encodes for the minor structural subunit; *fimG* encodes for the connector protein; *fimH* encodes for the adhesin that binds mannose (32). Phase variable expression of the *fim* operon is associated with the inversion of a 314-bp chromosomal region, flanked by two 9-bp inverted repeats, that contains the *fimA* promoter. When the invertible element is in the so-called ON orientation, the promoter is directed towards the structural *Fim* genes, thus allowing transcription, whereas transcription is abolished in the inverted OFF orientation. The inversion process is catalyzed by FimB and FimE, two members of the tyrosine site-specific recombinase family (33). Several regulators are involved in the fine modulation of the expression of type 1 fimbriae by environmental conditions. The proper supercoiling state of the DNA and the presence of accessory proteins, such as the DNA-binding proteins Lrp and IHF, are essential features that affect the recombination process and determine whether the cell is fimbriated or not . Other regulators such as RpoS, ppGpp, NanR, and NagC modulate type 1 fimbriation mostly by altering the expression of the recombinases that catalyze the recombination event (34).

B. P-fimbria (Mannose- resistant adhesions)

The *pap* genes encode P-fimbriae, which bind receptors other than mannose, playing a major role in the development of acute kidney infections (Pyelonephritis) and ascending UTIs in humans (17). Therefore, the presence of mannose cannot prevent this specific form of fimbria (35).

The P-fimbriae are responsible for agglutinating human red blood cells and for their adhesion to the mucosa. P fimbriae are composed of diverse fibers comprising distinct protein components. The distribution frequency of host cell receptors plays a critical role in determining vulnerability to recurrent urinary tract infections caused by *E. coli* (36). Individuals who lack these receptors seldom encounter mild *E. coli* urinary tract infections. Binding of the receptor to P fimbriae induces the liberation of ceramide, which functions as a stimulant for Toll-like receptor 4 (TLR4). TLR4 plays a role in triggering immune cell responses that can lead to inflammation, contributing to pain in UTI patients(37).

The biofilm-forming bacteria usually express the *papC* gene significantly higher than non-forming bacteria. However, in a previous study, the percentage of adhesion factors in patients with cystitis was reported as follows: *fimH* around (79.5%), *papC* around (32.7%) (38).

C. Curli fimbriae

Salmonella typhimurium and *E. coli* are two examples of the Enterobacteriaceae family that form curli, a sort of thin, aggregative fimbria (39). Curli is the main protein component of the extracellular matrix and is associated with biofilm formation (40).

Curli biogenesis is mediated by two operons, *csgBAC*, and *csgDEFG*. The *csgA* gene encodes the main structural component of curli fibers, while *csgB* encodes a nucleator protein that triggers CsgA polymerization on the cell surface, and proteins encoded by the *csgDEFG* regulate curli expression and assembly (41).

D. Capsule

The bacterium is enveloped and protected from the host's immune system by the polysaccharide structure that makes up the capsule. It offers defense against complement activation and phagocytic engulfment, two host defense mechanisms (42). Capsular antigens, or K antigens, are associated with upper urinary tract infections and contribute to the development of *E. coli* UTIs by promoting the bacterial communities known as biofilms within the host. By reducing antibody adhesion and enhancing bacterial surface properties, thereby increasing bacterial pathogenicity (43,44).

E. Lipopolysaccharides (LPS)

Lipopolysaccharides are found in the outer membrane of Gram-negative bacteria. Three covalently linked components make up lipoprotein synthetic liposaccharide (LPS): an interior disaccharide with multiple fatty acids called lipid A, which is responsible for the toxicity of Gram-negative bacteria; an outer carbohydrate chain with 1–50 oligosaccharide units known as the O antigen or O-specific side-chain; and a core oligosaccharide. (45).

F. Flagella

The flagellum, an organelle that facilitates bacterial motility, is involved in the communication between several pathogenic *E. coli* strains and epithelial cells. UPEC with flagellated forms, responsible for 70–90% of UTIs (46)

2. Secreted virulence factors

A. Toxins

Proteins or other compounds produced by specific UPEC *E. coli* strains are known as toxins, and they play a critical role in the progression of UTIs. These toxins have the power to modulate the host's inflammatory response and alter the channels through which cells communicate (47,48).

These poisons can alter the routes by which cells communicate and regulate the host's inflammatory response. In 1987, the discovery of cyclomodulin toxin (CDT) marked its identification as a potent toxin in UPEC *E. coli.* Subsequently, other toxins were also identified, including cytotoxic necrotizing factor 1 encoded by the *cnf1* gene, secreted autotransporter toxin (SAT), cytolysin A, plasmid-encoded toxin (PET), vacuolating autotransporter toxin (VAT), Shigella enterotoxin-1 (SHET-1), and α-hemolysin (*hlyA*), which is considered the most significant toxin (49). Hemolysins are lipoproteins that induce the formation of holes on the surfaces of cells to which they adhere, resulting in the release of ATP and subsequent cell death. When it binds to red blood cells, this leads to the release of hemoglobin into the surrounding environment. The liberated hemoglobin is subsequently digested by the bacteria (50).

B. Siderophores

For a number of vital processes, including metabolism, electron transport, DNA replication, and bacterial growth, iron is necessary. Nonetheless, transferrin is the primary form of iron found in human bodies. To overcome this obstacle, bacteria produce substances called siderophores, which attach to iron and then cling to certain receptors on the bacteria's surface. The use of iron obtained by this method is crucial for the colonization process in UPEC-caused urinary tract infections (51).

Formation of biofilm

E. coli develops a biofilm in response to an unfavorable environment, food deficiency, or a large concentration of cells in a particular area. The biofilm consists of polysaccharides and chemicals derived from the bacterium's environment. The study by (52) identified various essential components, including nutrients, minerals, amino acids, and cell wall components. Henrici first observed in 1933 that dense bacterial colonies form on submerged slides in various water sources (53).

Biofilm development is regulated by a combination of bacterial genetic elements and environmental signals. The factors that can affect early attachment are osmolality, pH, nutritional circumstances, iron availability, oxygen tension, and temperature (54).

Biofilm formation is carried out in five steps.

i. Reversible attachment: Initially, planktonic cells are transported from bulk liquid to the surface either by physical forces and chemotaxis or by bacterial appendages such as flagella. Factors such as nutrient levels, surface functionality, bacterial orientation, iron, temperature, and oxygen contribute to bacterial reversible adhesion (55).

ii. In the case of *E. coli*, irreversible attachment is mediated by type 1 pili, curli fibers, and antigen, which also promotes interbacterial contacts. (56).

iii. Creation of polysaccharides contributes to the external matrix's formation by facilitating adhesion, aggregation, and improved surface colonization. Colic acid, polyglucosamine, and cellulose make up the *E. coli* matrix. The matrix can also contain proteins, lipids, and ions like calcium, surfactants, nucleic acids, and membrane vesicles. Known by another name, slime, this matrix makes up around 90% of biomass (57).

iv. Biofilm maturation: involves the development of three-dimensional structures with macrocolony morphology, which is facilitated by interactions between bacteria. This process results in the creation of a diverse physicochemical environment that sets biofilms apart from their planktonic counterparts (58). Within the biofilm, microcolonies are separated by water channels that serve to supply nutrients and remove waste products. These water channels are present throughout various regions of the biofilm (59).

v. Biofilm detachment: is the process by which cells transition from a biofilm state to a planktonic state, enabling them to form biofilms in different environments. It is believed that bacterial detachment can occur through active mechanisms, such as enzymatic degradation, as well as passive mechanisms, which are influenced by external forces such as shear forces and erosion. Dispersal of biofilms is a crucial step for many bacterial species, as it allows them to be transmitted from the environment to human hosts, as well as between different environments and hosts, and even within a single host, thereby spreading the infection (60).

UPEC *E. coli* that exist within cells can undergo maturation into biofilm, a process linked to the occurrence of persistent and recurring urine infections. This is especially accurate for an *E. coli* strain that has type 1 P, and S/F1C fimbriae, together with K1 capsule genes. These genes demonstrate the pivotal role of adhesion structures in the process of biofilm formation. When bacteria attach to the uroepithelium and create a biofilm, they have the ability to infiltrate the renal tissue, resulting in pyelonephritis and potentially giving rise to persistent bacterial infections (61).

Biofilms can lead to economic losses through multiple adverse impacts, including product deterioration, decreased production efficiency, corrosion, pipe obstructions, and equipment failure (62). Nevertheless, it is important to acknowledge that biofilms also have valuable applications in bioremediation and biofuel production (63,64). Biofilm has a significantly higher resistance, up to 1000 times, to antimicrobial drugs, including antibiotics, and immunological responses from the host, resulting in the failure of medical treatments (65,66,67).

CONCLUSION

E. coli, a common gut bacterium, can be beneficial or harmful. Most strains are harmless, but some can cause diarrhea, urinary tract infections, and other illnesses. *E. coli's* composition and antigens influence its impact on human health.

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أهمية عوامل الضراوة في إمراضية بكتيريا الإشريكية القولونية الممرضة للجهاز البولي

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الخلاصة:

الخلفية: تُعد بكتيريا إشريشيا القولون (*Escherichia coli*) من البكتيريا سالبة الجرام المتعددة الوظائف والتي تشكل جزءاً من الفلورا المعوية الطبيعية لدى البشر والحيوانات. وعلى الرغم من أن معظم سلالات الإشريكية القولونية غير ضارة وتؤدي دورًا حيويًا في ميكروبيوم الأمعاء، إلا أن بعض السلالات الممرضة يمكن أن تسبب التهابات خطيرة. من بين هذه السلالات، تُعد إشريشيا القولون المسببة لعدوى الجهاز البولي (UPEC) سبباً رئيسياً لالتهابات المسالك البولية(UTIs) ، وخاصة لدى النساء. فهي مسؤولة عن حوالي 75-95٪ من حالات التهاب المسالك البولية غير المعقدة و40-50٪ من حالات التهاب المسالك البولية المعقدة في جميع أنحاء العالم، مما يجعلها مصدر قلق كبير للصحة العامة. تطورت إشريشيا القولون المسببة لعدوى الجهاز البولي لتكتسب مجموعة من عوامل الضراوة التي تمكنها من استعمار الجهاز البولي، والتهرب من الجهاز المناعي للمضيف، والتسبب في المرض. تشمل هذه العوامل عوامل الالتصاق، مثل الشعيرات من النوع 1 وشعيراتP ، التي تسمح للبكتيريا بالالتصاق بخلايا الظهارة البولية، والسموم مثل الهيموليسين والعامل السام الخلوي النخر 1، التي تلحق الضرر بأنسجة المضيف. كما تحتوي على آليات للحصول على العناصر الغذائية الأساسية مثل الحديد في البيئة المحدودة بالمواد المغذية للجهاز البولي. وعلى الرغم من التقدم في فهم آليات الإمراض للبكتيريا، إلا أن التهابات المسالك البولية لا تزال مشكلة شائعة ومتكررة، ويرجع ذلك جزئيًا إلى قدرة البكتيريا على تشكيل الأغشية الحيوية والبقاء في الجهاز البولي. ومع تزايد مقاومة إشريشيا القولون للمضادات الحيوية، تتزايد الحاجة إلى استراتيجيات علاجية جديدة لإدارة ومنع التهابات المسالك البولية. **الاستنتاج:** يُعد فهم الآليات المرضية لإشريشيا القولون المسببة لعدوى الجهاز البولي أمرًا بالغ الأهمية لتطوير تدخلات فعالة ضد التهابات المسالك البولية. يُعد استمرار البحث في عوامل الضراوة وآليات المقاومة أمرًا ضروريًا لمواجهة التحديات التي تفرضها الالتهابات المتكررة والمقاومة للمضادات الحيوية.

الكلمات المفتاحية: إشريشيا القولون الممرضة للجهاز البولي، عوامل الضراوة، التهابات المسالك البولية.