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The Pathogenesis of *Escherichia Coli* Urinary Tract Infection

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Abstract

Urinary tract infections (UTIs) are the commonest human bacterial infections and are responsible for substantial morbidity and mortality, resulting in increased healthcare costs. Most UTIs are caused by specialized *Escherichia coli* (*E. coli*) strains referred to as uropathogenic *E. coli* (UPEC). UPEC possess a variety of virulence factors (VFs), which the organism uses to attach, invade, and injure the host. These VFs include adhesins, toxins, iron acquisition factors, lipopolysaccharide capsules, and other invasins. Most studies on UTI pathogenesis have targeted VFs. The source of UPEC is the host's fecal flora. According to the pathogenicity theory, UPEC strains with special VFs move from the host's fecal flora to the urogenital tract and cause UTI. However, another theory states that the numerically abundant strain is responsible for UTI. Effective UTI management is hampered by the recent rise in antibiotic resistance, specifically, the recent emergence of multidrug-resistant *E. coli* sequence type 131. The distribution of VFs and other bacterial characteristics among different patient groups and UTI syndromes, is crucial understanding UTI pathogenesis, which would guide clinical decision making. For ST131 clonal group, further epidemiological studies are needed to clarify transmission pathways, risk factors for spread, and reservoirs, so that effective control measures can be devised.

Keywords: *Escherichia coli*, urinary tract infections, virulence factors, multidrug resistance

1. Introduction

Urinary tract infections (UTIs) are an important medical problem, being the second most common bacterial infection of humans after respiratory tract infection. They are often recurrent,

frequently difficult to treat, and can cause parenchymal damage to the kidney, leading to renal insufficiency and further complications [1–3]. UTIs impose a substantial burden on society and the health care system in relation to diagnosis, management, lost productivity, morbidity, and sometimes death [4–6]. Furthermore, increasing resistance to therapeutically important antimicrobial agents and the recent emergence of the virulent and multidrug-resistant ST131 clonal group have made UTI management progressively more costly and challenging [7, 8]. Several studies suggest that a greater array of VFs is generally needed to cause more invasive UTIs, although the extent appears to differ according to age and gender. Thus, further studies targeting VFs, which have been proposed as the best target for vaccine development, are needed. A better understanding of UTI pathogenesis, especially for the most common cause of UTI, namely *Escherichia coli*, is crucial for treatment and prevention of UTIs.

2. Etiology of UTI

UTIs are mainly caused by bacteria, although fungi and some viruses have also been implicated. Among bacteria, Gram-negative bacteria of the *Enterobacteriaceae* family, including *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus* species, *etc.*, are mostly involved. However, some Gram-positive organisms, principally *Staphylococcus aureus*, *Staphylococcus saprophyticus* and *Streptococcus agalactiae*, also play a role especially among young women. *E. coli* is the dominant causative agent in all patient groups, causing 80–90% of all UTIs [5]. Consequently, *E. coli* serves as a model pathogen for studying UTI pathogenesis.

Escherichia coli is a normal constituent of the intestinal microbiota of humans and animals [9, 10]. The distinctive *E. coli* strains that cause most UTIs have been designated uropathogenic *E. coli* (UPEC). They possess diverse virulence-associated factors (VFs) that assist them in attaching to, invading, and injuring the host, and include adhesins, toxins, siderophores, protective polysaccharide coatings, invasins, and serum resistance-associated proteins. The presence and numbers of such VFs predicts *in vivo* virulence [11].

3. Epidemiology and risk factors for *E. coli* UTI

Overall, UTI is more prevalent among females than males, attributable to the close proximity of the urogenital tract to the anus in females, the greater length of the male urethra, and the antibacterial activity of prostatic fluid in men [12, 13]. Functional, hormonal, and anatomical changes that occur during pregnancy predispose pregnant women to UTI [14]. UTI during pregnancy can result in devastating maternal and neonatal complications, including maternal sepsis, preterm labor, and premature delivery [14]. Thirty percent of patients with untreated asymptomatic bacteriuria (ASB) develop symptomatic cystitis and up to 50% develop pyelonephritis [13]. ASB is also associated with intrauterine growth retardation and low-birth-weight infants [13]. Up to 27% of preterm births have been associated with UTI in pregnancy [14].

Among bacterial infections in children, UTI ranks highly, even outnumbering bacterial meningitis, pneumonia, and bacteremia [15]. About 1% of infants < 3 months old develop UTI, with more males affected than females. Proper and urgent UTI management is crucial in children as an estimated 10–15% of children with UTI will develop permanent kidney damage, leading to other chronic diseases such as hypertension and renal insufficiency [16, 17].

The propensity of UTIs to recur, often within a few weeks or months after an initial acute infection, is a problem in UTI management. Approximately 20–30% of women will have a recurrent bladder infection within 6 months after an initial episode, and an additional 3% will experience a third infection [18, 19].

4. *E. coli* UTI pathogenesis

UTI pathogenesis is a complex process that is influenced by various host biological and behavioral factors, and by properties of the infecting pathogen, including VFs. This presents a challenge in epidemiological studies regarding the role of specific VFs in UTI pathogenesis because of the confounding effect of host factors.

In most noncompromised individuals, the urinary tract is normally sterile, and the entry of exogenous microorganisms is prevented by urine flow, secreted and tissue-associated antibacterial factors, and the bactericidal activities of effector immune cells. In most cases, the host fecal flora is the source of the infecting *E. coli* strain, and spreads via the perineal, vaginal, and periurethral areas to the lower urinary tract (i.e., urethra and bladder) where they may establish colonization [20]. Two hypotheses have been proposed to explain the movement of the organism from the fecal flora to the urinary tract. The prevalence hypothesis holds that the numerically most prevalent *E. coli* clones in the feces will be involved, whilst the pathogenicity theory holds that *E. coli* strains with enhanced virulence potential will be selected [20]. These two mechanisms may not be mutually exclusive, but instead may jointly contribute to UTI pathogenesis [21].

Although the host's fecal flora is the major source of the *E. coli* infecting strain, other proximal external reservoirs of the organism have been described. Community outbreaks of UTI have been reported [22–24], but without any evidence of person-to-person transmission. Foods and water have been proposed as possible vehicles of such outbreaks [22–24]. Specifically, extensive molecular similarities between *E. coli* from retail meat products and healthy or infected humans have been described [22]. Within-household spread of *E. coli* among co-habitating humans and their pets, including between sexual partners, have been confirmed [4, 10, 11]. The VFs of the invading bacteria and the host's defense mechanisms determine the outcome of the infection [25]. A variety of host factors, such as age, gender, pregnancy, or immunological status, may predispose to UTI and allow less virulent pathogens to cause the disease [20]. If the infection is confined to the lower urinary tract, with symptoms such as dysuria and frequency of urination, the infection is referred to as acute cystitis. If the infection spreads to the upper urinary tract with symptoms such as flank pain, fever, and malaise, the infection is defined as an acute pyelonephritis.

5. Uropathogenic *E. coli* (UPEC) and virulence factors (VFs)

Virulence refers to the ability of an organism to cause disease, and is a function of the presence of distinct accessory traits, referred to as virulence factors (VFs). VFs are specific properties that enable organisms to overcome host defenses and cause disease [26]. However, although several VFs have been identified in UPEC, experimental and epidemiological data have shown that none uniquely defines these pathogens.

UPEC VFs are grouped by functional categories as adhesins, toxins, iron acquisition systems, and protectins. VFs are encoded by genes located on chromosomes or plasmids, with some being exclusively chromosomal (e.g., *pap* and *hly*), others exclusively or principally plasmid-associated, e.g., *iss* and *traT*, and some either chromosomal or plasmid-associated (*afa*). Consequently, VFs may be vertically or horizontally transmitted, further contributing to the complexity of understanding the role played by specific VF genes in UTI pathogenesis.

6. Structure of adhesins

Adhesins, which appear as hair-like fibers called fimbriae (or pili), facilitate the colonization with *E. coli* in the urinary tract by attaching to host epithelial cells. This attachment promotes the persistence of the organism in the bladder, and serves as a reservoir for ascending infection in the urinary tract [27].

Various adhesins have been identified and are classified mainly according to receptor specificity, with some being mannose resistant and others sensitive. P fimbriae (or pili), the best-described group of mannose-resistant adhesins of UPEC, are so named because they specifically bind to the Gal(α1–4) Gal disaccharide galabiose, which is an antigen within the human P blood group system [26]. Different components of the P fimbriae have been described, including four different units that are at the tip of the fibrillum, including PapG, PapE, PapF, and PapK [28–30]. These fimbrial proteins and other accessory proteins are encoded by a chromosomal multicistronic gene cluster termed *pap* (pilus associated with pyelonephritis), which can be carried on large chromosomal insertions called pathogenicity associated islands (PAIs) [31].

Actual attachment of the organism to host epithelial cells is effected through PapG by recognition of glycolipid receptors expressed on host kidney cells and red blood cells [32]. Three variants of PapG, encoded by distinct alleles of the corresponding gene, *pap*, have been identified, namely PapGI, PapGII, and PapGIII [32–34]. Most studies indicate that allele II is the main PapG variant in *E. coli* bacteremia (regardless of primary source), acute pyelonephritis, and acute prostatitis, whilst allele III predominates in acute cystitis [33, 9]. Other studies found statistically significant associations between allele III and several compromising host conditions, such as urinary anatomical abnormalities, diabetes [33, 35].

Type 1 fimbriae are the commonest adhesive organelles of *E. coli*. They mediate adhesion of the organism to secreted and cell-bound mannosylated glycoproteins and exhibit mannose

sensitive hemagglutination of guinea pig erythrocytes [36]. The ubiquitous distribution of these fimbriae in *E. coli* makes it difficult to show an association with UTI outside an experimental setting. However, type 1 fimbriae exhibit several different phenotypes due to allelic variation of the gene for the lectin subunit, fimH, and these phenotypes have been shown to be distributed differentially among fecal and UTI isolates [37–39]. Type 1 fimbriae are encoded by a chromosomal fim gene cluster that contains genes for a structural subunit, an adhesin, several accessory proteins, and regulatory proteins (fimACDFGH) [30, 39].

Phase variation controls the expression of type 1 fimbriae by site specific recombination. A 314-bp phase-variable invertible element, that contains the promoter, controls the transcription of the fimbrial genes fimACDFGH. The promoter drives the expression of type 1 fimbriae when the switch is in the ON orientation but not when it is in the OFF orientation [40]. It has been shown that the expression of type 1 fimbriae coordinately affects the expression of P fimbriae in an inverse manner, providing evidence of a direct communication between genes related to pathogenesis [41, 42].

Although most studies have confirmed that type 1 fimbriae are particularly important in bladder colonization [43, 44], the proportions of UPEC strains from urine and feces expressing type 1 fimbriae appear to be similar [26], ranging from a high of 71% among isolates from cystitis patients to a low of 58% among those from patients with ASB, with fecal strains in the mid-range at 60% [26]. However, in contrast, the level of expression of type 1 fimbriae among UPEC blood isolates (81%) is significantly different from that of fecal strains [45, 46].

Another adhesin family is the Afa/Dr family, which consists of adhesins that include the uropathogen-associated fimbrial adhesin Dr, along with other nonfimbrial adhesins, including Afa-1, Afa-2, Afa-3, Afa 4, NFu1, and Dr-11. These adhesins have a different structure from other *E. coli* fimbrial adhesins in that they appear as fine mesh, a coil-like structure or as a filamentous capsule coating on the cell surface [45, 47, 48]. Epidemiological studies show that *E. coli* strains that express adhesins of the Afa/Dr family are involved in 25–50% of cases of cystitis in children, and 30% of cases of pyelonephritis in pregnant women [49]. Moreover, *E. coli* strains expressing Dr adhesins have been associated with a two-fold increase in the risk of a second UTI. It has also been shown that UPEC encoding the Dr adhesin could survive for more than 1 year within renal tissue [49, 50]. These findings suggest a possible role for Dr/Afa adhesins in recurrent or chronic UTI.

Finally, the closely-related S fimbriae and F1C (fimbriae of serotype 1C), so named because of their binding specificity for terminal sialyl-galactoside residues, mediate X-type mannose resistant hemagglutination of human erythrocytes [51–53]. They agglutinate human and bovine red cells [54, 55]. S fimbriae have a similar, but less well defined, structure to both type 1 and P fimbriae. Just like type 1 and P fimbriae, expression of S fimbriae exhibits phase variation [51]. Binding sites for S fimbriae are located on epithelial cells of the proximal and distal tubules, collecting ducts and glomerulus [55]. In humans, S-fimbriated *E. coli* strains are more closely associated with meningitis and bacteremia than with UTI [56]. They could therefore be important in the movement of the organism from the urinary tract to the blood stream. Few studies have been carried out on the role played by these two types of fimbriae in UTI pathogenesis. FIC fimbriae are expressed by about 14% of UPEC and 7% of *E. coli* fecal isolates [53].

7. Iron acquisition systems for UPEC

Bacteria and the host compete for available iron, which is needed for oxygen transport and storage, DNA synthesis, electron transport, and metabolism of peroxides [57, 58]. Pathogenic bacteria, including UPEC, have devised ways of accessing iron by producing siderophore-mediated iron transport systems. UPEC exhibit multiple mechanisms for extracting iron from the host, mainly siderophore-siderophore receptor systems, but also heme uptake [59–62]. Siderophores, which are secreted low molecular weight molecules, have a high affinity for ferric (Fe^{3+}) iron, which is insoluble as a free cation. UPEC retrieve iron-bound siderophores through receptors that facilitate the transportation of siderophore-iron complexes through the bacterial membrane and into the cytosol where the iron is concentrated and utilized. While all *E. coli* can produce the siderophore enterobactin, production of alternative siderophores has been shown to increase virulence of strains causing bacteremia [10].

Several enterobacteria contain a gene cluster called the high pathogenicity island (HPI), which encodes proteins for biosynthesis of the yersiniabactin siderophore and its uptake system [63, 64]. The HPI is widespread among members of the *Enterobacteriaceae* family, and is essential for virulence in *Yersinia* and certain pathotypes of *E. coli* [63]. One of the important genes residing on the HPI is *fyuA* encoding the 71 kDa outer membrane protein *FyuA* (ferric siderophore uptake), which act as a receptor for Fe-yersiniabactin uptake [65]. FyuA, which was first described in *Yersinia species*, is associated with virulence in many members of the *Enterobacteriaceae* family [65]. Studies by Hancock and Klemm have confirmed that the ferric yersiniabactin receptor (FyuA) is required by UPEC for efficient biofilm formation [66].

Aerobactin is another important hydroxamate siderophore synthesized from the condensation of two lysine and one citrate molecules. In UPEC, the aerobactin system is encoded by a five-gene operon with four genes encoding the enzymes needed for aerobactin synthesis and a fifth encoding the outer membrane receptor protein [67, 68]. The synthesis genes are designated *iuc*, for iron uptake and chelation and the receptor gene is *iut*, for iron uptake and transport [69]. Successive steps in the biosynthesis of aerobactin are catalyzed by the iuc genes and involve hydroxylation of lysine and acetylation of the hydroxyl group to form hydroxamic acid molecules which react with citrate to form aerobactin [69].

Previous studies have shown that the aerobactin system and P fimbriae are commonly found together in UPEC isolates from patients with UTI and urosepsis [70, 71]. However, among urosepsis patient isolates, this association is only true for chromosomally encoded aerobactin [71]. An association of chromosomally encoded aerobactin with hemolysin among urosepsis or UTI patient isolates has also been confirmed [71]. These observations suggest that the association of aerobactin with other VFs differs between plasmid and chromosomal aerobactin. Plasmids carrying the aerobactin region sometimes also carry antimicrobial resistance genes [71–73]. The aerobactin system is found more commonly among UPEC strains from patients with pyelonephritis (73%), cystitis (49%), or bacteremia (58%) than among ASB patient isolates (38%) or fecal strains (41%), which suggest that aerobactin contributes to virulence both within and outside of the urinary tract. The association of aerobactin with more serious forms of UTI is seen specifically in infants, girls, and women [26, 9].

Finally, UPEC produce salmochelins in order to access iron during invasion of the host. The salmochelin siderophore system, so named because it was first shown to be characteristic of *Salmonella* strains [74], is also present in UPEC. This siderophore system is encoded by *iroA* gene cluster, which is made up of five genes, *iroB*, *iroC*, *iroD*, *iroE*, and *iroN*. *iroN* gene encodes an outer membrane siderophore receptor which transports different catechol siderophores, including N-(2,3-dihydroxybenzoy)-L-serine and enterochelin. *iroB* encodes a glucosyltransferase that glucosylates enterobactin, *iroC* encodes an ABC transporter required for transport of salmochelins, whilst *iroD* and *iroE* encode a cytoplasmic esterase, and a periplasmic hydrolase, respectively [75]. The salmochelin receptor iroN may play a dual role as an iron uptake receptor as well as an internalization factor [10]. Using a neonatal rat model, it was shown that *iroN* plays a major role during the bacteremic step of the disease [76]. These findings suggest that *iroN* is associated with increased virulence. Studies by Bauer et al. showed that *iroN* occurred 2.1–4 times more frequently in UTI isolates than in rectal isolates [77].

8. Toxins produced by UPEC

Most hemolytic UPEC strains secrete a heat-labile cytolytic protein toxin known as alpha hemolysin [78], which is encoded by a polycistronic operon, consisting of four genes arranged in the order of hly-CADB [79]. The product of hlyC is important in the activation of the hemolytic toxin, which is the product of the *hlyA* gene. The gene products of *hlyB* and *hlyD* together with TolC are involved in secretion of the hemolysin through the bacterial cell wall [80]. The hemolysin determinants are located on the bacterial chromosome in human isolates of *E. coli*, in contrast to the plasmid location among animal strains [32].

Alpha hemolysin lyses red cells of all mammals and even of fish [81], and is toxic to host cells resulting in inflammation, tissue injury, and impaired host defenses. Hemolysin stimulates super-oxide anion and hydrogen peroxide release from and oxygen consumption by renal tubular cells, including histamine release from mast cells and basophils [82, 83]. Hemolytic uropathogenic strains almost always also express P fimbriae [84]. Hemolysin production is found most commonly in UPEC strains from patients with pyelonephritis (49%), followed by cystitis isolates and ASB [85]. These data demonstrate an association of hemolysin production with invasive uropathogenic strains. UPEC strains that produce increased amounts of alpha hemolysin are also more resistant to the complement action of human serum when compared to strains that are nonhemolytic or produce reduced amounts of hemolysin [81].

UPEC also produce a toxin referred to as cytotoxic necrotising factor type 1 (CNF-1). CNF-1 is a chromosomally encoded UPEC toxin that catalyzes the glutamine deamination of the small GTPases RhoA, Rac, and Cdc 42 [86], leading to the disturbance of numerous eukaryotic cellular functions including formation of actin stress fibers, lamellipodia, filopodia, and modulation of inflammatory signaling pathways [87, 88].

Yamamoto et al. showed that 61% of UTI isolates and 38% of bacteremia isolates produced CNF-1 as opposed to only 10% of commensal fecal isolates [89]. Of these isolates, approximately 98% that produced CNF-1 also produced hemolysin. Studies by Mitsumori et al. showed a

CNF-1 prevalence of 64% among UPEC isolates from prostatitis and 36% from pyelonephritis. These results suggest that CNF-1 is associated with increased virulence in UTI pathogenesis. CNF-1 production may also increase the inflammatory response of the host [90]. Specifically, Elliott et al. reported that CNF-1 evokes edema and necrosis and is associated with inflammation in the intestines of rabbits in a diarrhea model of infection [90]. Human neutrophils have been observed to be less effective at killing CNF-1 positive, than CNF-1 negative bacteria.

9. Protectins

UPEC also express outer membrane proteins, such as traT and Iss, which may enhance serum resistance through avoidance of complement killing [26]. Bacteria are killed by normal human serum through the lytic activity of the complement system [91]. The alternative pathway is activated by bacteria in the absence of specific antibody and plays a more important role in serum killing than the classic pathway [92]. Resistance of *E. coli* to killing by serum results from the individual or combined effects of capsular polysaccharide, O-polysaccharide side chains, and surface proteins [93].

Although the K1 capsule is important in certain strains, other mechanisms appear to be more significant determinants of serum resistance in some populations of *E. coli* isolates. On the whole, smooth strains are more serum resistant than rough strains [94] and the degree of serum resistance is proportional to the amount of lipopolysaccharide (O antigen) the strain contains [95]. Serum-resistant strains are usually more nephropathogenic than comparable serum-sensitive strains in a variety of models of UTI [96, 97] even though these resistant strains may not be associated with increased lethality [96].

9.1. Outer membrane protease T

Outer membrane protease T (OmpT) of *E. coli* is a surface membrane serine protease and is the prototypical member of the omptin family of Gram-negative bacteria [98]. OmpT is an enzyme that catalyzes the activation of plasminogen to plasmin [99, 100], a function that is physiologically relevant for the virulence of *Yersinia pestis* and for clinical *E. coli* isolates [101, 102]. OmpT also plays a role in virulence by cleavage of protamine and other cation peptides with antibiotic activity [103, 104]. Studies by Hui et al. indicated that OmpT promotes *E. coli* persistence in the urinary tract by interfering with the antimicrobial activity of urinary cationic peptides [100].

9.2. Uropathogenic specific protein

Uropathogenic specific protein (Usp) in *E. coli*, which was discovered by chance, is encoded by *usp* located on PAIs [105]. Usp, which is homologous to the *Vibrio cholerae* zonula occludens toxin gene [106], is significantly more prevalent among UPEC isolates than fecal *E. coli* isolates from healthy individuals. Several studies have shown various roles for Usp in UTI pathogenesis in different UTI syndromes and patient groups. Studies by Rijavec et al. showed

a strong association between Usp and bacteremia of urinary tract origin, suggesting that Usp is important in the migration of UPEC from the urogenital tract to the blood stream [107]. Other studies have shown comparable prevalences of Usp in cystitis, pyelonephritis, and prostatitis isolates [108]. Furthermore, Usp has (frequently) been associated with all common serotypes of UPEC [109].

10. Biofilm production by UPEC

Biofilm production by *E. coli* is an important VF which may also protect bacteria from antibiotic action and so contribute to resistance [110–113]. Recent studies have shown that biofilm production in *E. coli*, mediated by co-expression of curli and cellulose, supports long-term survival of UPEC in the urinary tract by surrounding the organism with an inert, hydrophobic extracellular matrix [110, 113, 114]. Most studies of biofilm formation in UTI have addressed its role in recurrences.

Curli belong to a class of fibers known as amyloids and are involved in adhesion to surfaces, cell aggregation and, finally, biofilm development. Curli fibers are encoded in the curling subunit gene (*csg*) gene cluster, made up of two differently transcribed operons. One operon codes for *csgB*, *csgA*, and *csgC*, and the other one for *csgD*, *csgE*, and *csgG* [115]. Expression of both curli operons is important for curli fiber assembly. Curli fibers are also essential for internalization of bacteria during an infection [30].

Co-expression of curli and cellulose tends to decrease in prevalence from more severe to less severe UTI, then to commensal isolates, suggesting that biofilm may facilitate progression from the lower to upper urinary tract [110]. Furthermore, co-expression of both biofilm components is associated with a high prevalence of individual VF genes, high VF scores, and phylogenetic group B2, consistent with heightened urovirulence of such strains. Notably, there may be an interaction between classic VFs and biofilm formation. For example, in one study, all isolates that co-expressed both biofilm components also harbored fyuA, implying that iron uptake via the yersiniabactin system may play a significant role in biofilm growth [64]. Additionally, recent studies have shown that the biofilm components, curli fimbriae and cellulose, also play important roles in adhesion, invasion, and long-term survival of UPEC within the host urinary tract [110, 111].

11. Phylogenetic group and VF distribution among patient groups and clinical syndromes

E. coli is commonly classified into four main phylogenetic groups namely A, B1, B2, and D [116] as defined by multilocus enzyme electrophoresis and multilocus sequence typing [117]. Several studies have shown that *E. coli* pathogenic strains from extraintestinal infections mostly derive from group B2, and to a less extent group D [21, 118, 119]. Most studies quote prevalence rates around 63–65% for group B2 in pathogenic strains, and 10–15% for group D [21]. Commensal

E. coli are mainly associated with phylogenetic groups A or B1, and are mainly devoid of virulence determinants [118, 120, 121]. The overlapping associations of VFs and phylogeny with clinical virulence makes it difficult to understand which directly determines virulence. However, some studies in children showed that pyelonephritis isolates more often belonged to group B2, contained on average higher prevalences of individual VF genes, and consequently had higher VF scores than did cystitis or fecal isolates, suggesting that both VF repertoire and phylogenetic background play important roles in UTI pathogenesis.

UTI syndrome-specific differences among *E. coli* clinical and fecal isolates from men are consistent with findings from women, which have shown a gradient of virulence from *E. coli* strains causing more invasive UTI syndromes, such as pyelonephritis and febrile UTI, through those causing cystitis, to fecal strains [9, 122]. However, men are less likely than women or girls, to develop cystitis due to low-virulence strains, which is consistent with a previous observation that isolates from men with febrile UTI appeared relatively virulent, even in the presence of host compromise [122].

In most patient groups, pyelonephritis isolates tend to exhibit the highest prevalences of many individual VFs, have the highest VF scores, and are the most likely to belong to phylogenetic group B2, ST131, and a UTI-associated O type. The reported higher prevalence of pap operon genes (encoding P fimbriae) in pyelonephritis than cystitis isolates correlates with increased tropism for the kidney of P fimbriated strains [121, 123]. papGII has been shown, experi-mentally, to contribute to pathogenesis of pyelonephritis [124, 125], and OmpT is strongly associated with febrile UTI in men [122, 126]. However, it is not clear whether these VFs act individually or in concert with other known or unknown VFs in causing pyelonephritis.

In men and women, although cystitis and pyelonephritis isolates differ in inferred molecular virulence, phylogenetic group distribution is similar between the two clinical syndromes. However, within each phylogenetic group, VF scores exhibit a gradient across source groups (fecal < cystitis < pyelonephritis), suggesting the presence of different virulence strata within each phylogenetic group, with more virulent strains selectively causing pyelonephritis and less virulent strains being associated with cystitis and fecal isolates in that order. This suggests that VF repertoire is as, or more, important than phylogenetic background for predicting pathogenic behavior in UPEC [122, 127].

Although cystitis and pyelonephritis isolates differ significantly in inferred virulence in vari-ous patient groups, no single VF profile is unique to any clinical syndrome or patient group, implying that UTI pathogenesis is multiply determined, as suggested by several previous studies [122, 128]. Thus, intervention strategies based on VF genes might have to involve multiple targets, which would offer the extra advantage of protection against a wide range of UTI syndromes.

12. Transmission of VFs

The genes encoding specific UPEC VFs can be exclusively chromosomal (e.g., *pap* and *hly*); exclusively or principally plasmid-associated (e.g., *iss* and *traT*); or can occur in either location

(e.g., the aerobactin operon and afa/drab). Plasmid-borne VFs have an obvious vehicle for horizontal transmission among *E. coli* lineages. Such VFs tend to be distributed more broadly but more sporadically within the species than are chromosomal VFs [129]. Studies have demonstrated that certain VFs commonly occur together, in a way that suggests co-selection or direct genetic linkage [130, 131]. Direct genetic linkage of VFs has been shown on PAIs and plasmids [132–134].

13. Antimicrobial drugs and uropathogenic *Escherichia coli*

Managing UTI caused by UPEC has become challenging over the years due to increasing resistance to the commonly used antibiotics [135–139], which poses a great threat to future capacity to treat UTI caused by UPEC. Although TMP-SMX has traditionally been used as a first-line treatment for UTI [140], there are reports of increased resistance to this antibiotic, which in some countries is in the range 15–20% [137]. Many UPEC strains resistant to TMP-SMZ are also resistant to amoxicillin and cephalexin. Nitrofurantoin remains highly effective against UPEC, but is mainly used for cystitis treatment due to its inability to attain sufficient serum levels to treat invasive or systemic infections [137], and all have excellent bioavailability and achieve high urinary concentrations. However, increased FQ use has resulted in a rise in the prevalence of resistance, and FQ-resistant *E. coli* has become a major problem in several countries [141].

14. Relationship between antibiotic resistance and virulence or phylogenetic background in UPEC

Previous studies show that in *E. coli* isolates from patients with urosepsis, resistance to antimicrobial agents such as ampicillin, sulfonamides, tetracycline, chloramphenicol, and streptomycin is negatively associated with virulence and a phylogenetic group B2, but positively associated with host compromise (immune deficiency, diabetes, and other urinary anatomical abnormalities) [26]. There is a similar negative association between FQ resistance and VFs and group B2 [142–144]. This suggests that, resistance may provide a greater fitness advantage to *E. coli* than traditional VFs or a group B2 background, allowing them to cause infections in compromised hosts with weakened defenses who are frequently exposed to antibiotics.

15. *E. coli* sequence type 131 (ST131)

Determining the clonal types of UPEC is crucial for understanding the role of clonal spread to emerging antimicrobial resistance, which is important for defining and interrupting transmission pathways. Multidrug-resistant *E. coli* sequence type 131 (ST131) has emerged over the past decade as a globally disseminated cause of extraintestinal infections in humans and animals [145–147]. The recent emergence of this clone has coincided with an increase in antibiotic resistance among *E. coli* generally, suggesting a contributing role for ST131 in resistance.

In contrast to traditional antimicrobial resistant *E. coli*, which mostly derive from low virulence phylogenetic groups A and B1, ST131 derives exclusively from phylogenetic group B2, which is traditionally known to be enriched for VF genes. This, plus limited experimental evidence of virulence and several case reports of unusually severe or fatal extraintestinal infections due to ST131, suggests that the emergence of ST131 may be due to a high virulence potential (in addition to antibiotic resistance) compared with other *E. coli* types. However, despite this, some studies have reported absence of traits commonly associated with B2 phylogeny, particularly adhesins (e.g., P, S, and FIC fimbriae) and toxins (e.g., hemolysin and cnf1).

Most ST131 clinical isolates are FQ resistant, and many are also co-resistant to aminoglycosides and/or trimethoprim-sulfamethoxazole (TMP-SMZ). A minority produces extended-spectrum beta-lactamases (ESBLs) that confer resistance to extended-spectrum cephalosporins. *E. coli* clonal group ST131 may be associated with other beta-lactamases but some isolates are cephalosporin susceptible [148, 149].

Despite limited epidemiological evidence of increased virulence of ST131, a recent study revealed that ST131 exhibits a marked prevalence gradient across source groups, from pyelonephritis to cystitis isolates, and finally to fecal isolates [126]. This is consistent with increased urovirulence, and provides epidemiological evidence of increased virulence for ST131, which has been presumed but without evidence from experimental animal models [8, 150]. The antibiotic resistance advantage, in combination with the possible presence of enhanced virulence, could explain the recent worldwide emergence of ST131. The increasing prevalence of ESBL-producing *E. coli* has been associated with the emergence of CTX-M-ST131 pandemic clonal group [151]. Available evidence supports that ST131 is an important contributor to the spread of ESBLs among reproductive-age women in some regions, albeit limited research in many parts worldwide [141, 152].

Four VF genes (*iutA*, *ompT*, *usp*, and *traT*) are associated with ST131 isolates, and so could represent potential targets for vaccines or other interventions, particularly if a functional role in virulence or dissemination can be demonstrated for them. Most of the ST131 isolates (85%) are of the O25b variant, and the remainder are type O16 [153, 154].

Resistance of ST131 to extended-spectrum cephalosporins is often due to production of ESBLs. The initial descriptions of ST131 emphasized its association with CTX-M-15, but subsequent studies have shown that it is more commonly ESBL-negative but FQ-resistant [154–156]. Previous studies in Australia and Japan showed that ST131-O25b, ST131-O16, and group D-ST405 clonal groups contribute to the spread of ESBL-producing *E. coli* [151, 152]. The dominant ESBL, in *E. coli*, globally and in Australia [157] is CTX-M-15, which is frequently encoded on plasmids carried by the ST131 pandemic clonal group.

16. Conclusions

A wide range of UPEC VFs have been established epidemiologically or experimentally (*in vivo*) as being important in UTI pathogenesis. No single VF profile has been proven to be important in causing any particular UTI syndrome. Indeed, studies have suggested that

UTI pathogenesis is multiply determined. Thus, intervention strategies based on VF genes might have to involve multiple targets, which would offer the extra advantage of protection against a wide range of UTI syndromes. This observation, which is in agreement with previous studies, provides evidence that VF repertoire is as, or more, important than phylogenetic background for predicting pathogenic behavior in UPEC.

The prevalence of antibiotic resistance among human urine *E. coli* isolates has risen substantially in recent years, especially to first line agents such as fluoroquinolones and trimethoprim-sulphamethoxazole. Furthermore, multidrug-resistant *E. coli* ST131 has shown rapid global dissemination among humans and animals, which has coincided with the general increase in resistance among *E. coli* clinical isolates. A better understanding of the microbiological basis for the emergence of UPEC antibiotic resistance is necessary for guiding efforts aimed at interrupting this process. Further studies on ST131 are clearly needed to explain its impressive emergence so that control measures can be devised and implemented.

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