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REVIEW ARTICLE

Aptitude of Uropathogenic *Escherichia coli* in Renal Transplant Recipients: A Comprehensive Review on Characteristic Features, and Production of Extended Spectrum β-Lactamase

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Abstract
Urinary tract infection is the most common infection in almost half of the renal transplant patients. The development of UTI in these patients may progress to bacteremia, acute T cell-mediated rejection, impaired allograft function, or allograft loss, along with the increased risk of hospitalization and death. Among various pathogens implicated, Uropathogenic *E. coli* (UPEC), especially sequence type 131 (ST131), is the most virulent and multidrug-resistant pathogen. High antimicrobial resistance to most *β*-lactam antibiotics, mediated by extended spectrum *β*-lactamases (ESBLs) produced by UPEC, is a challenge in the clinical management of UTIs in kidney transplant recipients. Indeed, multidrug resistance to β-lactam antibiotics is a direct consequence of ESBL production. Resistance to other antibiotics such as aminoglycosides, fluoroquinolones, and trimethoprim-sulphamethoxazole has also been reported in ESBLs-producing UPEC, which reduces the therapeutic options, rising healthcare-associated costs and subsequently leads to renal failure or even graft loss. In this review, we aimed to discuss the post-transplant risk factors of UTI, UPEC virulence factors (VF), and the related factors including quorum sensing, and stress resistance genes. Furthermore, we searched for the current treatment strategies and some of the alternate approaches proposed as therapeutic options that may affirm the treatment of ESBL-producing UPEC.

Introduction

Renal transplantation is a promising therapeutic strategy for the treatment of patients with end-stage renal disease to build on the quality of life [1, 2]. Despite significant advances in organ transplantation, post-transplant urinary tract infections (UTIs), which may range from asymptomatic bacteriuria to acute cystitis and pyelonephritis, are still major cause of morbidity and mortality in these recipients [3]. There is considerable variation in the reported incidences of post-transplant UTI that might be due to local outbreaks, differing resistance rates, antibiotic strategies, and diagnostic criteria. UTIs occur more often in female than in male renal transplant recipients [4]. Most of the UTIs (74%) have been reported during the first year after kidney transplantation (81.9%), within the first 3 months after surgery [5]. Although the risk time for the development of UTI decreases as time passes, however, the recipients do face recurrent infections [6]. Transplantation of kidneys from living donors potentially leads to lower rates of UTI, probably due to shorter periods of cold ischemia, less severe ischemic-reperfusion injury, and a lower rate of delayed graft function while transplantation from deceased donors increases the incidence of postoperative UTI [4] which may be because of greater injury of the renal allograft or the routine cytotoxic agents used during cadaveric organ transplantation [3]. Uropathogenic *Escherichia coli* (UPEC) is a common etiology of UTIs among transplant recipients [3]. The UTI is managed and controlled with antibiotics

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nevertheless, and the emergence of multidrug resistance has become a continued and deep concern. As cephalosporins are prescribed for the treatment of UTI caused by Enterobacteriaceae, the organism should be considered for ESBL production as well as carbapenem resistance when evaluating renal transplant recipients with recurrent UTIs [7]. Longer duration of catheterization, immunosuppression, diabetes mellitus, and manipulation of the urinary tract are some of the other important risk factors for UTI after kidney transplantation. This review aimed to discuss the characterization of UPEC, the epidemiology of urinary tract infections developed in renal transplant recipients, its consequences, and the pathogenesis. As renal transplant patients are immunosuppressed, we also attempted to identify and appraise the issue of antibiotic resistance in UPEC especially, extended spectrum beta-lactamases (ESBLs) production, which is a major concern.

UTI in Renal Transplant Recipients

Renal transplant recipients are at risk of developing UTIs [8] which if not treated or partially treated may progress to bacteremia, sepsis, and pyelonephritis [9]. UTIs in such patients are important since they present a potential risk for poorer graft and recipient outcomes [10]. Other subsequent complications of UTIs in transplant recipients consist of chronic functional impairment, potential drug interactions, and bacterial resistance that may influence long-term graft survival leading to death [11]. Indeed, in renal transplant recipients, infections are the second most prevalent cause of death, though UTIs have not been directly associated with increasing mortality [3]. UTIs are the most common cause of acute kidney allograft injury [8]. The prevalence of renal disorders caused by infections is more than acute rejection and calcineurin inhibitor (CNI) toxicity [8]. CNI especially cyclosporin A (CsA) and tacrolimus are widely used in solid organ transplants to prevent graft rejection and to treat immune-mediated glomerular diseases [12]. On the other hand, CNIs lead to the excretion of Mg^{2+} from the kidneys by reducing the regulation of transport proteins in the renal tubules, and as a result, hypomagnesemia occurs in kidney transplant recipients [13]. Due to the important role of Mg^{2+} in the human body, including the control of the immune system, studies have shown that Mg^{2+} deficiency is independently associated with urinary tract infections and viral infections in the early stages after kidney transplant [13].

Asymptomatic UTIs account for 17–51% of infections in kidney transplant patients (KTP), and it is a threat to subsequent urinary tract infection [14]. while UTIs happen in the first 3 months after the transplant and are frequently associated with pyelonephritis and bacteremia, compared to less severe infections that happen later [15].

UTI accounts for 30% of all hospitalizations in renal transplant patients in the world [16]. As a general anatomical rule, women who undergo renal transplants are more prone to attain UTI [14]. Old age, especially higher than 65 years of age, is also a risk factor for developing UTIs in pre-transplant patients due to sedentary life, poor hygiene, increased urinary retention in the bladder, prostate, and/or bladder atrophy, and a decrease in immunity [3]. Table 1 reveals other risk factors for urinary tract infections in renal transplant patients.

Pathogenesis of Uropathogenic *Escherichia coli* (UPEC)

UPEC strains display a notable proficiency in hosting a wide range of virulence components (Table 2) thereby increasing their aptitude to adapt to new niches, invade host tissues, and colonize them, escape the host immune response, uptake the nutrients from the host, and eventually result into the disease [17].

The bacterium utilizes multinuclear superficial facet cells that encompass integral membrane proteins called uroplakins to its advantage [18]. These uroplakins act as a barrier to uroepithelium, in addition to acting as receptors (Ia and IIIa receptors) for protein Fim H, the tip adhesion of UPEC type 1 fimbriae [19]. This binding induces actin rearrangement and bacterial internalization via unknown signaling pathways. Some of these strains utilize uroplakin-independent invasion pathways by binding protein Fim H to mannosylated α3β integrins. Moreover, intracellular bacterial communities (IBCs) or pods form into superficial facet cells through the binding of type 1 pili to α3β1 integrins which are shown in Fig. 1 [20].

Pore-forming hemolysin A (HlyA) toxin inhibits the activation of Protein kinase B or Akt protein ultimately triggering host cell apoptosis and exfoliation, lysis of host cell through pore formation, facilitation of iron release, and nutrient uptake [20]. Exfoliation exposes the underlying transition cells to promote the UPEC invasion, thereby expediting the inhabitation of these cells by bacteria and forming quiescent intracellular reservoirs (QIRs) that be the cause of recurrent infection (Fig. 1) [20].

Pathogenicity islands (PAI) markers are widespread among commensal *E. coli* and UPEC isolates, and it is said that these commensal isolates may be reservoirs for transmission of these markers [21]. Indeed, major virulence factors of UPEC and their regulators usually are encoded by PAIs, and the difference in the type of PAIs is postulated to affect the antibiotic susceptibility pattern of the bacteria [22]. In a study aimed at investigating the relationship between the phylogenetic groups, virulence factors, and PAIs among UPEC in Iran, significant association between

Table 1 Risk factors for urinary tract infection at various transplant levels

Transplant level risk associated with UTI development		References
Pre-transplant	Advanced age	[3]
	Female gender	[3]
	Diabetes mellitus	[80]
	Prolonged dialysis	[80]
	Polycystic kidney disease	[80]
	Pre-transplant urinary infection	[80]
Transplant procedure	Deceased donor	[80]
	Allograft trauma	[80]
	Microbial contamination of cadaver kidney	[80]
	Technical complications with anastomosis	[80]
	Postoperative bladder catheterization	[80]
	Ureteral stent	[80]
Post-transplant	Urinary tract obstruction	[3]
	Uremia/poor graft function	[15]
	Bladder dysfunction	[15]
	Increased urinary aluminum secretion	[15]
	Immunosuppressive therapy [especially azathioprine (imuran)]	[3]
	Vesicoureteral reflux	[80]
	Reimplantation	[80]
	Acute rejection episodes (ARE)	[80]
	Cytomegalovirus (CMV) infections	[8]
	Malnutrition	[81]
	Percutaneous nephrostomy (PNC) placement < 3 months after KT (kidney transplantation)	[82]
	Surgical re-intervention < 3 months after KT	[82]

the phylogenetic group B2 and all the studied virulence genes and PAI markers was found [21]. Another investigating study on the UPEC isolates showed that Fim-like recombinase gene *fimX* is the only family member that has a significant association with UPEC compared to commensal isolates and PAI-X genes are highly prevalent among UPEC isolates and have a strong positive correlation with genomic virulence factors, suggesting a potential role for PAI-X in the extraintestinal pathogenic *E. coli* lifestyle [23].

UPEC Biofilm and the Associated Factors

UPEC forms multicellular communities known as biofilms on urinary catheters, as well as on and within bladder epithelial cells [24]. Indeed biofilm is a major contributing factor in the development of UTIs by UPEC [25]. Bacterial biofilms are damaged by the destruction of natural barriers like the urethral sphincter and, thus, provide a nidus for infection [26].

Different adhesion factor genes (AFGs) are involved in the attachment of bacterial cells to the urinary tract and biofilm development [27]. Integration host factor (IHF) protein of DNABII present in the bacterial biofilm not only affects biofilm formation in vitro but also the community architecture of UPEC in vivo along with regulation of expression of several genes associated with virulence such as Type I pilus, P pilus, and capsule [28]. UPEC uses pilus-mediated adherence to initiate biofilm formation in the urinary tract. Oxygen gradients within *E. coli* biofilms regulate the expression and localization of adhesive type 1 pilus. A transposon mutant screen for strains defective in biofilm formation identified the *ubiI* (formerly visC), the aerobic ubiquinone synthase as a critical gene for UPEC biofilm formation [29]. People with chronic kidney diseases are at higher risk for biofilm formation due to the existence of kidney stones, peritoneal catheters, and hemodialysis interventions [30]. Similar to biofilm formed by other bacteria, in the UPEC biofilm formation process, initial attachment is the main step because the survival of any microorganism is determined by its ability to bind complex environment [31]. Type 1 fimbriae or pili encoded by the *fim* gene are among the most important virulence factors attached to abiotic surfaces [32].

Attachment to the surface causes the adhered UPEC cells as initially as sessile and flagella repress reconversion from a sessile state with the help of several small molecules such

Table 2 UPEC allied virulence factors, associated genes, and their respective functions

Virulence factors	Virulence genes	Functions	References
Type 1 fimbriae	*fim*	UPEC adhesion, binds to uroplakin and $\alpha_3\beta_1$ integrins, form intracellular bacterial communities (IBCs) and bacterial survival, promote invasion, colonize in extraintestinal infections, biofilm formation, induce mucosal inflammation	[83–85]
P fimbriae	*Pap*	Adhesion and colonization in extraintestinal infections on the tubular epithelium, stimulate cytokine expression by T lymphocytes	[83–85]
S fimbriae	*sfa*	Adhesion to intestinal epithelial cells, kidney, and lower urinary tract cells; facilitate the penetration of bacteria into the tissues	[83, 84]
F1C fimbriae	*foc*	Adhesion to renal epithelial and endothelial cells of the bladder and kidneys	[83, 84]
Dr fimbriae	*dra*	Binding to the decay-accelerating factor (DAF) receptor on the surface epithelial cells, internalize bacteria to the host cells, activates PI-3-kinase	[83, 84]
Afimbrial adhesion	*afa*	The non-fibrous adhesion, binding to the DAF receptor on the cell surface epithelium, hemagglutination capacity	[83, 84]
Capsule	*kps*	Protect the bacterium against phagocytic and host immune system, engulfment and bactericidal effect	[85]
lipopolysaccharide (LPS)	*rf*	Inducing cytokine expression through nitric oxide and activation of proinflammatory response in uncomplicated UTIs	[85]
Flagella protein H antigen	*flic*	Invasion, responsible for bacterial motility, the interaction of various pathogenic *E. coli* strains with epithelial cells, facilitated dissemination, chemotaxis	[85]
Iha	*iha*	Iron-regulated-gene-homologue adhesion	[83]
Curli fimbriae	*crl, csg*	Adhesin, binding to fibronectin, biofilm formation, and promote pathogenicity	[83]
Secreted Hemolysin A	*hlyA*	Pore-forming toxin, cell lysis, hemolysis, inflammation of human's urothelial cells	[83]
Cytotoxic necrotizing factor1	*cnf*	Invasion, malfunction, apoptosis in human's urothelial cells, engaging in cell necrosis	[83]
Vacuolating autotransporter toxin	*Vat*	The proteolytic toxin, Inducing host cell vacuolization	[83]
Secreted autotransporter toxin	*sat*	The proteolytic toxin, cytotoxic effect on cell vacuolization	[83]
Serin protease autotransporter	*pic*	Destroy mucins, facilitating colonization on the epithelium and injury of the cell membrane	[83]
UpaH	*upaH*	Contributing to bacterial adherence, colonization, and biofilm formation	[85]
SitABC	*sitA, B, C*	Transportation of Fe, Mn	[83]
ChuA, Hma	*chu, hma*	Iron acquisition from hemoglobin, heme transport	[83]
Salmochelin	*iroN*	Siderophore receptor, iron acquisition	[83]
Aerobactin	*iuc,aer*	Siderophore, iron acquisition ($Fe^{2+}/^{3+}$)	[83]
Antigen43	*flu*	Autotransporter family protein, adhesion, and biofilm development	[83]

as cyclic diguanylic acid (c-di-GMP), the concentration of which later rises during biofilm formation comparative to the planktonic state of bacteria. Type 1 fimbriae or pili encoded by the *fim* gene and curli fimbriae are important in the irreversible adhesion of UPEC to the surface [32] and autotransporters, extracellular polymeric substances, quorum sensing, and stress resistance genes are important for biofilm maturation [32].

Autotransporters

Antigen 43 (Ag43) is the key autotransporter protein that promotes cell-to-cell adhesion, auto-aggregation, and three-dimensional development of biofilm structure [33]. Some transporter proteins (AidA and TibA) also promote biofilm formation and aggregation [33]. In most *E. coli* pathotypes, including UPEC, Ag43 causes strong aggregation and biofilm formation. Published literature shows that in UPEC strain UTI89, the autotransporter is associated with intracellular bacterial community formation similar to biofilms and contributes to chronic urinary tract infection [34].

Extracellular Polymeric Substance (EPS)

EPS similar to other biofilms is responsible for providing cell-to-cell and cell-to-surface interactions, and three-dimensional architecture, thereby supporting the biofilm cells [33]. There are three major exopolysaccharides including polymeric β-1, 6-*N*-acetyl-D-glucosamine (PGA) (mediating cell-to-cell adhesion, attachment to surfaces, and stabilizing the biofilm), cellulose (for rigid biofilm formation), and colanic acid (for protection of biofilm cells from environmental

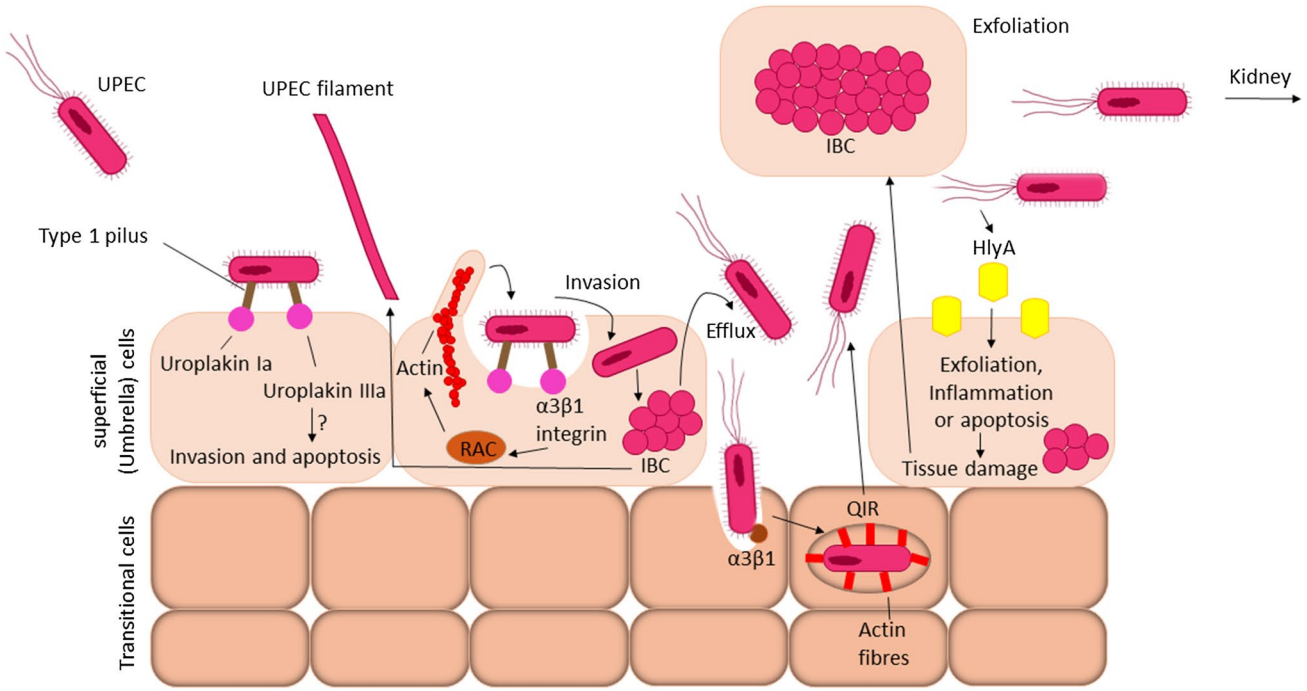

Fig. 1 Pathogenesis of uropathogenic *Escherichia coli* (UPEC). UPEC adheres to uroepithelium cells through type 1 pili, which bind to uroplakin Ia and IIIa receptors. This binding mediates invasion and apoptosis through stimulation of unknown signaling pathways. Binding of type 1 pili to $\alpha_3\beta_1$ integrins induces actin rearrangement through activation of RAC proteins (RHO-family GTPases), resulting in the invasion of bacteria. Binding of type 1 pili to $\alpha_3\beta_1$ integrins also induces bacteria internalization into superficial facet cells to form intracellular bacterial communities (IBCs) or pods. Pore-forming hemolysin A (HlyA) toxin can inhibit the activation of Protein kinase B or Akt protein and lead to host cell inflammation, apoptosis and exfoliation. Exfoliation of the uroepithelium promotes the spread of UPEC to other hosts following urine excretion or to expose deeper layers of the uroepithelium for QIRs [20]

conditions), having an effect on biofilm formation by covering Antigen 43 and adhesin involved in diffuse adherence (AidA) proteins [33]. The *E. coli* AIDA-I or AidA autotransporter adhesin, as a prototype of the AIDA adhesin family, represents a tripartite antigen consisting of the functional adhesin AIDA-I (alpha-domain), which mediates the specific attachment of bacteria to target cells [35]. The AIDA-I protein is one of the few glycosylated proteins found in the organism. O-glycosylation is mediated by the product of the *aah* gene, which codes for a heptosyltransferase that uses ADP-glycero-manno-heptose precursors from the LPS biosynthesis pathway [36]. Little else is known about *aah* and the mechanisms involved in the modification of AIDA-I [36]. Lipopolysaccharides and capsules are also important factors in the biofilm formation of *E. coli* [37].

Quorum Sensing (QS)

QS, the ability of bacterial cell population to respond to the signaling response [38], occurs in UPEC, with the intervention of acyl-homoserine lactone (AHL) and autoinducer-2 (AI-2). The structure of AHLs consists of a core *N*-acyl-homoserine-lactone ring and a 4–18 carbon acyl chain that enables them to spread freely across the cell membrane [39]. AI-2 is a 4, 5-dihydroxy-2,3-pentandione (DPD)-derived molecule [40] and has been shown that its production is directly related to biofilm production in *E. coli* [41].

Stress Resistance Genes

During the formation of the UPEC biofilm, various stress resistance genes protect the biofilm in unfavorable environmental conditions such as low pH of the stomach, heat, peroxide, and cadmium [33]. Table 3 shows the stress resistance and the other genes involved in biofilm formation.

Bacterial biofilms show more resistance to antimicrobial stress in comparison to planktonic populations [30]. Poor penetration of antimicrobials or antiseptic solutions into and through biofilm due to anaerobiosis, deeper and dense biofilm layers, slow growth rate, altered metabolism, persister cells, oxygen gradients, and extracellular biofilm matrix, lead to antibiotic tolerance mechanisms in biofilms [30, 42].

Table 3 UPEC-related genes and proteins involved in biofilm formation and their respective function

Name of the gene	Protein synthesized	Function	References
fim	Type1 fimbriae or pili	Initial attachment to abiotic surfaces and initial development of biofilm	[85]
Chaperone-usher class fimbrial genes: c	F9 fimbriae	Adhesion and biofilm formation	[85]
csg	Curli fimbriae	Attachment to the extracellular matrix proteins of the, adhesion to abiotic surfaces by enhancing the cell-to-surface interaction, and facilitating the cell-to-cell communication	[85]
flu	Antigen 43 (Ag43)	Adhesion, facilitating auto-aggregation and three-dimensional development	[33]
pgaABCD	Pga C glycosyltransferase	Synthesis, export, and localization of the b-1, 6-*N*-acetyl-D-glucosamine polymer (PGA) polymer, biofilm formation, and stabilization	[33]
bcsABZC	Cellulose synthase protein BcsA	Rigid biofilm formation	[33]
sdiA	SdiA	Upregulating uvrY and csrA genes which enhance the biofilm formation, motility, and virulence of *E. coli*	[33]
sisA(c3557)	SisA	Suppression of the host immune system during UTIs by down-regulating the innate inflammatory response	[86]
sisB (c4492)	SisB		
hfq	Hfq	Biofilms formation in the harsh environment of the urinary tract	[33]
ycfR	YcfR/BhsA	Stimulation indole production by *BhsA* makes biofilm resistant to acid, heat, peroxide, and cadmium	[33]
ymgB	AriR	Causing acid resistance and survival in low pH	[33]
rpoS	RNA polymerase Sigma factor RpoS		
	Sigma S encoding factor, a stress-related gene regulator		[33]
rapA	RNA polymerase-associated protein RapA	Increase biofilm antibiotic resistance, alteration gene regulation in biofilm	[33]
yhcQ	*P*-hydroxybenzoic acid efflux pump subunit AaeA	Encoding a multidrug resistance pump	[33]
yafQ	mRNA interferase YafQ	Increase of *Escherichia coli* biofilms tolerance to specific antibiotics	[33]

Antibiotic Resistance

In general, antibiotic resistance means an increase in the minimum inhibitory concentration (MIC) of an antibiotic on account of many phenotypic and genetic factors associated with antimicrobial resistance in the bacteria [42]. Routine peri-transplant antimicrobial prophylaxis or excessive and inappropriate use of antibiotics may all promote the development of multi-drug-resistant (MDR) and ESBL-producing UPEC strains [6, 43]. The current therapeutic view shows that the phenomenon of MDR is on the rise in urinary pathogens worldwide [44]. It is not only a threat for immunocompromised patients but also a challenge for clinicians [44]. A previous study showed that in kidney transplant recipients, 69.1% of MDR isolates accounted for symptomatic UTIs [45]. Few antibiotics are available to treat infections caused by these pathogens, and those that can be prescribed are mostly for parenteral administration and carry a higher risk of adverse effects. Moreover, infections caused by MDR organisms are often associated with severe outcomes [44]. These organisms have many risk factors including prior use of antimicrobials without the antibiotic susceptibility testing being performed, hospitalization, genitourinary disorders, age, and recurrent UTIs [46].

Extended Spectrum β-Lactamases (ESBLs) in UPEC

In kidney transplant patients (KTPs), UTIs and high antimicrobial resistance of extended spectrum β-lactamases (ESBL)-producing UPEC are one of the most important therapeutic and epidemiological challenges. Alevizakos et al. [47] reported that 1 in 10 renal transplant recipients

get infected with a UTI from an ESBL-producing Enterobacteriaceae. ESBL-producing UPEC strains have a significant disadvantageous effect on the clinical management of UTIs in these patients. ESBL-producing *E. coli* reduces therapeutic options and is associated with rising healthcare-associated costs, morbidity, and mortality rates [48, 49]. The infection can cause subsequent renal failure or even transplant loss [50]. ESBL-producing bacteria are difficult to eradicate, requiring prolonged intravenous, broad-spectrum antibiotic therapy [51]. KTP recipients display many risk factors for UTI and are considered a particularly vulnerable population to such infections. Published literature evaluated risk factors for UTI in community infections and healthcare settings [52–54]. The high incidence of ESBL-positive infections among KTPs recipients with diabetes mellitus and those who received previous antimicrobial therapy were reported by others [55].

When ESBL-producing UPEC among Iranian KTP recipients were characterized, it was found that most UPEC isolates were significantly more frequent in KTP recipients compared with the non-KTPs group (43.5% vs 23.1%, $P=0.021$), and the molecular results revealed that among ESBL coding genes, $bla_{CTX\text{-}M}$ and bla_{TEM} were significantly higher among KTP recipients than the non-KTPs group [6]. The same group of researchers when performing the phylogenetic characterization and virulence traits of UPEC isolated from KTPs as well as non-KTPs and analyzed the clonal distribution of ESBLs-producing UPEC containing $bla_{\text{CTX-M}}$ gene by MLST technique found ST131 as the most common clone followed by ST1193. Moreover, they observed relatively high diversity in UPEC isolates obtained from KTPs in relation to non-KTPs. In terms of virulence traits, KTP isolates significantly differed from non-KTP isolates only in terms of the prevalence of pap GI elements. In addition, the most frequent UPEC isolates were in phylogenetic group B2, followed by group D and group A [56]. Another research conducted in Nigeria furnished that ESBL production was significantly associated with the degree of biofilm formation but the level of resistance to ceftazidime does not differ among strong and moderate biofilm producers [57]. A decade back risk factors were studied for ESBL-producing UPEC isolates in KTP vs. non-KTPs, and it was noticed that age, gender, HLA mismatches, etiology of chronic kidney disease, diabetes mellitus, acute rejection, induction treatment, and type/level of immunosuppression did not differ between the groups with or without ESBL-related UTI; however, high increased incidence of ESBL-related UTI was observed among KTP recipients, particularly patients with recurrent UTI [51]. These researchers emphasized that prevention of the first episode is of great importance among KTP recipients as they found that the risk of ESBL-related UTI increased linearly with the number of UTI treatments, illustrated by an increased incidence among second and third UTI episodes and by the recurrence rate. Espinar et al. [55] concluded in their study that delayed graft function, diabetes mellitus, previous antibiotic exposure, antibiotic prophylaxis, and relapsing UTI are independent risk factors for acquiring infections by ESBL-producing *E. coli* and *Klebsiella pneumoniae*. Molecular epidemiology results of them showed that $bla_{CTX\text{-}M}$ were the most common ESBL-encoding gene, either alone or in association with other genes. Low eGFR (estimated glomerular filtration rate) and high blood creatinine are risk factors for UTI recurrence [55]. The high co-resistance to other antibiotics (non-β-lactams) found in the ESBL-producing bacteria in UTI among KTP recipients, remains a serious clinical challenge. Although the level of recurrence in this study found for both groups was similar, the relapsing percentage was significantly higher in non-KTPs [55]. Explaining why ESBL infections increase with an increasing number of days patients are required to have a ureteral stent in place, Singh et al. [7] stated that ureteral stricture is one of the most common complications of a post-renal transplant. Transplant recipients routinely have percutaneous stents placed to relieve the stricture. The length of stent placement varies among patients. These stents may serve as a focal point for biofilm production. Biofilm provides the perfect environment for bacterial growth and higher survival rates due to poor antibiotic penetration. Additionally, the proximity of various microbial genes allows for the exchange of antibiotic resistance plasmids [7]. Furthermore, they suggested as the presence of plasmid-mediated beta-lactamase is capable of hydrolyzing carbapenems, carbapenem-resistant Enterobacteriaceae must be considered when evaluating renal transplant recipients with recurrent UTIs caused by ESBL-producing organisms [7]. Among Iranian renal transplant patients, plasmid-mediated quinolone resistance (PMQR) has been increasingly identified in UPEC [58].

Due to the high rate of urinary tract infection in renal transplantation and the results of ESBL phenotype, control of the spread of ESBLs-producing isolates among KTPs is essential [6] and is an important problem in healthcare settings [48].

Phylogenetic Groups in ESBL-Producing UPEC

In 2013, an additional gene target, *arpA*, was added to the three candidate markers (*chuA*, *yjaA,* and *TspE4.C2*) by Clermont et al. [59], and a quadruplex PCR assay was developed later to classify *E. coli* isolates into eight phylogroups including A, B1, B2, C, D, E, F, and clade I/II. The use of this method has been found to correctly assign 95% of all *E. coli* strains.

A relationship between different *E. coli* phylogenetic groups, antimicrobial resistance, and virulence features has been illustrated by phylogenetic analysis. According to the literature, the most virulent and antimicrobial-resistant extraintestinal *E. coli* strains mainly belong to group B2 and, to a less extent to group D [60]. *Escherichia coli* sequence type 131 (ST131), belonging to group B2, is an important emerging pathogen among renal transplant recipients, with resistance to most *β*-lactam antibiotics and multiple resistance, and possessing virulence factors, resistance to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole (co-resistance) and even to last-line carbapenems. Based on the epidemiological studies, the genomic phylogeny of ST131 is delineated into three clades including clade A (the most divergent), clade B, and clade C (or H30). Clade C is the largest clade of ST131 and is divided into two sublineages including C1 (H30R) and C2 (H30Rx). C2 sub-lineage is responsible for the high prevalence of CTX-M-15 production among T131 isolates, but both of them are resistant to fluoroquinolones and have limited treatment options [61]. Most ST131 strains, with the specific O25b type, belong to the O25:H4 serotype. However, O16:H5 serotype of ST131 strains has recently been identified, as well as other species that are not reproducible for O and H antigens. ST69, ST95, and ST73 strains of UPEC are also the most common causes of UTIs and bloodstream infections [62].

Current Treatment Options for Antibiotic-Resistant and ESBL-Producing UPEC

Antimicrobial Agents

Antimicrobial therapy is suitable for symptomatic UTIs but not for asymptomatic bacteriuria. For uncomplicated cystitis in adult women fosfomycin, pivmecillinam, or nitrofurantoin as first-line treatment was recommended by European Association of Urology (EAU) guidelines on urological infections in 2018. Combination therapy with amoxicillin and an aminoglycoside, or a second-generation cephalosporin plus an aminoglycoside is recommended for the treatment of complicated UTIs. Intravenous injection of third-generation cephalosporins is recommended for complicated UTIs [63]. Carbapenems such as ertapenem may be used for the treatment of chronic or recurrent UTIs due to ESBL-producing ST131 strains, but since these antibiotics are one of our last defenses, they should be used cautiously [64]. In kidney transplant patients, patient intolerance, drug toxicity, and the acquisition of antibiotic resistance may make the treatment of these patients very difficult. Therefore, it is important to choose an effective antibiotic to treat UTIs [22]. In most healthcare settings, after the kidney transplant, co-trimoxazole (TMP/SMX) and ciprofloxacin are used to prevent UTI and other infections, but in people with a history of allergies to these antibiotics, nitrofurantoin is replaced and it is also an effective antibiotic against ESBL-producing UPEC [2]. Recently, an increase in the antibiotic-resistant UPEC isolates has been reported [22], especially resistance towards trimethoprim/sulphamethoxazole. The use of this antibiotic as prophylaxis for most kidney transplant patients may be one of the causes of increased resistance [22]. Therefore, due to the high prevalence of resistance to first-line oral antibiotics including trimethoprim-sulfamethoxazole (STX), amoxicillin/clavulanic acid, and ciprofloxacin (CP), fosfomycin-trometamol (phosphoenolpyruvate analog) is increasingly been considered to treat UTIs caused by multidrug-resistant pathogens in KTPs due to fewer side effects such as non-interference with immunosuppressive drugs and lack of renal toxicity [65, 66].

Mannosides and Pilicides

Mannosides are small-molecule compounds that are designed based on the structure of the FimH adhesin bound to mannose and inhibit the FimH binding to the receptor. Pilicides are small synthetic molecules and inhibit pilus assembly by inhibiting the Chaperone-Usher Pathway, which is responsible for surface structure formation [67, 68]. Mannosides and pilicides have the potential to treat uncomplicated bladder inflammation and recurrent urinary tract infections and may help circumvent the rising trend of antibiotic-resistant bacteria [64].

Cranberry Products

The mechanism of cranberry products' action is unknown and disputed; nevertheless, it has been widely used for many years to treat and prevent urinary tract infections [63, 69, 70]. Microbial-derived metabolites of cranberry polyphenols are claimed to play a role in bacterial adhesion to uroepithelial cells, disabling or preventing UPEC adhesion and, thus, preventing bacterial colonization and the progression of UTIs [71].

Probiotic Bacteria

Another promising therapy considered in UTI prevention and treatment is the use of probiotic bacteria [72], and human intervention studies have evaluated the use of certain strains such as *Lactobacillus* spp. in the prevention or treatment of UTIs [73]. For example, bacteriocinogenic *L. lactis*-GAM217-derived bacteriocin (Bacteriocin-GAM217) has been to have shown an anti-biofilm and antibacterial effect on ESBL producing *E.coli*, *K. pneumoniae*, *Citrobacter amalonaticus*, *C. diversus*, and *Proteus mirabilis* and MBL

producing *E. coli*, *Pseudomonas aeruginosa*, and *K. pneumoniae* clinical isolates through the formation of pores on the bacterial cell wall. Moreover, bacteriocin-GAM127 with phytochemicals such as curcumin and cinnamaldehyde have been observed to display a synergistic effect on the destruction and attenuation of biofilm formation by antibiotic-resistant *E. coli* even at low concentration by permeabilization of the cell membrane [74]. In addition, it has been suggested that combining cranberry with some probiotic strains may be more effective in the management of recurrent UTIs [75].

1, 8-Cineole

1, 8-Cineole is one of the main components of rosemary volatile oil (known as eucalyptol) which at the minimum inhibitory concentration [MIC, 0.8% (v/v)] demonstrates bactericidal activity on planktonic *E. coli* ATCC35218 strain and also exhibits the anti-biofilm activity against MDR ESBL-producing uropathogenic *E. coli* strains by causing cell death into the biofilm-attached and biofilm-released cells [76].

Carbon Monoxide-Releasing Molecules or CORMs

Carbon monoxide (CO), a small gaseous molecule, possesses anti-inflammatory and antimicrobial properties with the ability to penetrate the cell membrane. CO-releasing molecules (CORMs) are one of the metal carbonyl compounds that have been developed for therapeutic applications by releasing CO in a controlled manner. Antibacterial effects of CORM-2 and CORM-3 (ruthenium-based carbonyls) are reported in *E. coli* K-12 strains, *Staphylococcus aureus* and *P. aeruginosa*. CORMs are effective not only in near-anaerobic conditions [77] but, also in aerobic conditions. They inhibit respiration by reacting with cytochrome *bd* and *bo'* by accelerating the transfer of CO into the bacterial cell (such as CORM-3) [78]. Another suggested mechanism for the antibacterial effect of CORMs is the production of intracellular reactive oxygen species by CORM-2 which causes DNA damage and bacterial cell death. Recently it has been shown that CORM-2 has antibacterial effects on planktonic multidrug-resistant ESBL-producing UPEC isolates [79]. According to Charlotte Sahlberg Bang's study [78] in biofilm-like conditions, CORM-2 can decrease the bacterial viability of multidrug-resistant UPEC especially, following colonization of UPEC in human bladder epithelial cells.

Conclusions

To conclude, infections in renal transplant patients pose a problem, and UTI ranks among the most common infections that a recipient post-transplant encounters. UPEC accounts for the majority of these UTIs. ESBL production among UPEC has steadily been increasing in recent years. The role of resistant high-risk clones is a worrisome trend as the occurrence of multidrug-resistant clones may acutely compromise graft function and if left uncontrolled may lead to mortality. Various factors have been implicated in the development of UTI in transplant patients. Immunosuppressive conditions carry a stress-free increased risk for the occurrence of UTI. If UTI is suspected prompt initial empiric antibiotic therapy is recommended, and further thorough investigations are required to identify potential underlying causes of chronically recurring infections. One of the current challenges is the accurate and rapid detection of ESBL production as resistance to cephalosporins may further lead to the development of resistance to other antibiotics. Post-transplant UTI needs a careful revision in terms of careful and selective use of antibiotics. Many novel antibiotic therapies have been proposed along with the use of conjunctive probiotics or the use of natural products. Improvements in UTI prophylaxis and treatment make further studies of post-transplant UTI a necessary and rewarding area of future research.

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