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Uropathogenic *Escherichia coli* in urinary tract infections: A review on epidemiology, pathogenesis, clinical manifestation, diagnosis, treatments and prevention

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Abstract

Urinary tract infections (UTIs) are common pathological conditions observed in hospital settings and communities. Uropathogenic *Escherichia coli* (UPEC) is the causative agent of most of the UTIs, such as pyelonephritis and cystitis. The infectious complications may cause acute renal failure affecting both the healthy and renal transplant patient's. The untreated patients with UTI may exhibit septicemia and bacteremia. Furthermore, the multidrug resistance patterns of UPEC may result in severe septic shock. Factors that contribute to the pathogenesis of UPEC include; secreted proteins, haemolysins, capsule, lipopolysaccharides, biofilm, fimbriae adhesions and iron acquisition systems. In spite of several host protection mechanisms; however, UPEC may persist inside the urinary tract and serve as a reservoir of recurrent infections and complications. Early diagnosis and prompt treatment of UTI with broad spectrum antibiotics are essential before this infection causes other medical complications. Generally, in clinical settings, diagnosis of UTIs involves bacterial culture and antibiotic susceptibility assay, in addition to other medical examinations, which aid the physicians to prescribe the appropriate drugs and measures during UTIs treatments. This review aims to understand the epidemiology, pathogenesis, clinical manifestation, diagnosis, treatment and preventive measures of UTIs caused by the uropathogenic *E. coli*.

Keywords: Uropathogenic *E. coli*, Epidemiology, Pathogenesis, Urinary tract infection, Biofilm

1. Introduction

Escherichia coli shape varies from coccal to long filamentous rods (Nanninga, 1998; Stenutz *et al*., 2006), Gram negative, facultative anaerobe, chemo-oraganotrophic microorganism, which has respiratory and fermentative metabolism. However, its growth is less copious under anaerobic conditions. This

bacterium grows well on ordinary media that contains 1% peptone as carbon and nitrogen sources, with optimum temperature of 37°C. Under optimal conditions, the metabolic activity of E. coli is usually significant between 15 to 45°C, with a recorded generation time of 20 min. (Holt, 1994).

Escherichia coli is one of normal flora of the gastrointestinal tract of human and animal, which causes severe illness (Bien *et al*., 2012). However, in case of immunological disorders of the host, and\or once the duct barriers become violated; even the non-pathogenic commensal strains of *E. coli* can cause infections (Kaper *et al*., 2004). In case of UTI, fecal UPEC colonizes the urethra and spreads up through the urinary tract and then to the bladder, however sometimes it may spread to the kidneys leading to pyelonephritis (Najar *et al*., 2009). The UPEC represents a group of uropathogenic bacterium that is not opportunistic *E. coli*, although both these types (i.e. commensal *E. coli* and UPEC) are found in the intestine and in feces (Shah *et al*., 2019).

The isolates of ST131 *E. coli* are truly pathogenic; due to the large number of virulence-associated genes they contain, in addition to the spectrum of infections they cause in both of the hospital settings and the communities (Nicolas-Chanoine *et al*., 2014). In the family *Enterobacteriacea*, production of the extended-spectrum β-lactamases (ESBLs) has significantly increased; especially in the *E. coli* ST131 clone, which is strongly associated with antibiotic drug resistance and ESBLs production (Pitout and DeVinney, 2017).

A single extra-intestinal pathogenic *E. coli* (ExPEC) clone ST131 is predominantly responsible for pandemic cephalosporin resistance (ceph-R) and global fluoroquinolone resistance (FQ-R), leading to millions of annual antimicrobial-resistant infections (Al-Guranie and Al-Mayahie, 2020). The UPEC sequence type 69 (ST69) is a trimethoprim-sulfamethoxazole-resistant (Yamaji *et al*., 2018).

Based on the host clinical symptoms and types of virulence factors that exist, *E. coli* strains are grouped into entero-invasive (EIEC), entero-toxigenic (ETEC), entero-haemorrhagic (EHEC), entero-pathogenic (EPEC), diffusely adherent *E. coli* (DAEC) and entero-aggregative *E. coli* (EAEC) (Kaper *et al*., 2004). Among all members of *Enterobacteriaceae*, UPEC is the most common pathogen (80-85 %) that is involved in UTIs (Nicolle, 2008; Bhatt *et al*., 2012). Moreover, UPEC is the main cause of a large portion of the nosocomial UTIs (50 %), in addition to the community-acquired urinary tract infections (70-95 %). Moreover, UPEC accounts for the worldwide significant medical costs, morbidity and mortality (Foxman, 2014). UTI is defined as a combination of bacteriuria in the midstream urine, the presence of leucocytes, and the existence of several clinical symptoms in the host; including urgency of urination and dysuria (Ejrnaes *et al*., 2006).

The outer membrane of *E. coli* contains lipid A, phospholipids and proteins from which the lipopolysaccharide (LPS) chains arise; overlaid with capsular polysaccharides (CP) (Wang and Quinn, 2010). LPS and CP contribute to the pathogenicity of this bacterium, and represent the chemical basis for O and K antigens, respectively. Lipid A represents the sole chemical structure in *E. coli* that acts as an endotoxin responsible for several in vivo potentials, such as; local Shwartzman reactivity, pyrogenicity, macrophage activation, tumor necrosis factor and lethal toxicity adjuvant activity. Moreover, this endotoxin causes several pathophysiological effects in humans including; hypotension, fever, septic shock and disseminated intravascular coagulation (Rietschel *et al*., 1987; Mahapatra and Heffner, 2019).

2. Epidemiology

UTI is the most common infectious disease in the different community practices leading to significant morbidity and mortality. Throughout the world, almost 150 million individuals are diagnosed every year with UTI infections. The incidence of UTI is age and sex dependent; as females that fall within the sexually active and reproductive age group express UTI more frequently (Foxman *et al*., 2002). The short urethra of

women compared to the men and mechanical activity of the sexual intercourse aid in movement of the bacteria into the bladder, and thus makes the rate of UTI 50-times larger in women than in men (Lentz, 2009). The UPEC strains recovered from sexually active patients often match with the fecal isolates isolated from their partners, indicating that UTI may be sexually transmitted (Foxman *et al*., 2002; Johnson and Delavari, 2002). Furthermore, the use of certain types of contraceptives, spermicidal coated condoms significantly alter the normal flora, and cause the increase in colonization of the vaginal tract epithelium with UPEC, thus increase the risk of UTI (Braunwald *et al*., 2001; Yadav *et al*., 2015).

UTI can affect the gender of all the age groups. Several previous studies conducted by Magliano *et al*., (2012); Thattil and Santhosh, (2018) revealed the higher prevalence of UTI in younger age groups of 15-35 years; including both the males and females, followed by the older age group above 55 years. Moreover, a recent study of Lamsal and Bhandari, (2019) highlighted that maximum number of elderly patients of ≥ 60 years; who complain with abdominal pain, have got diagnosed with UTI. About 60 % of the adult women have UTI once in their lifetime; however, the risk of UTI are raised 4 times in the postmenopausal women that have the history of UTI, compared to those having no previous UTI (Medina and Castillo-Pino, 2019; Lamsal and Bhandari, 2019). In postmenopausal women, several factors including age; health status, use of antibiotics and presence of chronic disease, can affect the incidence of UTI (Medina and Castillo-Pino, 2019).

In Nepal, two previous studies conducted by Ganesh *et al*., (2019); Sharma *et al*., (2019) reported the prevalence of UTI among children of ages ranging from 6 months to 15 years visiting different hospitals. The UTI infected children suffered from several symptoms such as; abdominal pain, fever, dysuria, vomiting, convulsion, diarrhea, screaming attack and irritation, etc. Accordingly, these studies confirm the urgent need for precise diagnosis of UTI infection among the children and elderly people before it leads to any harmful consequences.

The previous studies of Neupane *et al*., (2016); Khatri *et al*., (2017) confirmed the low prevalence of *E. coli* isolates recovered from urine samples of UTI suspected patients. Basically, the usual diagnosis of UTI is based on a quantitative estimation of bacteria in urine culture that yield greater than 10^5 cfu/ ml (Kass, 1957). However, bacterial counts of 100 cfu/ ml of urine even have a high positive incidence of cystitis in symptomatic women (Orenstein and Wong, 1999).

The incidence of UPEC associated with high multi drug resistance (MDR) has increased dramatically, which thus creates therapeutic challenges (Zorc *et al*., 2005; Robinson and Le Saux, 2016). In a study conducted by Chaudhari *et al*., (2016), *E. coli* demonstrated significant resistance against several antibiotics mainly; co-trimoxazole, fluoroquinolones, amoxicillin, in addition to the third generation cephalosporins; however, it expressed moderate resistance against gentamicin and low resistance towards nitrofurantoin. The upmost reasons behind infection with MDR *E. coli* include; overstay in hospitals, antibiotic exposure, improper use of third generation cephalosporin, increased use of intravenous devices and catheters, and severe illness (Kumar *et al*., 2014; Chaudhari *et al*., 2016). Generally, the acquired hospital urinary tract infection is caused by the indwelling of devices and catheters, which represent entry for colonization by the different microorganisms (WHO. 2002).

3. Biofilm formation

Biofilm formation is a phenomenon of bacteria to aid them to survive under severe environments and to establish infections in humans. Biofilm formation protects the bacteria from the host defenses and antibiotics, thus making their treatments more difficult (Neupane *et al*., 2016). According to Subramanian *et al*., (2012), biofilm formation is advantageous for the bacterial uropathogens to colonize the indwelling catheter and the host tissue, to withstand the stress

conditions in the urinary tract environment, and to raise the incidence of urinary tract infections. Ponnusamy *et al*., (2012) added that bacterial biofilm formation is not the only cause of resistance of *E. coli* against the antibacterial drugs, but also related to the incidence of UTI disease.

A previous study of Romling and Balsalobre, (2012) documented that biofilms are responsible for 80 % of the microbial infections and more than 65 % of the nosocomial infections. Attachment of the bacteria to the host tissue is influenced by the presence of attractive or repelling forces, which vary according to the pH, nutrient levels, and temperature of the infected site, where the flagella and chemotaxis play major roles in this step (Donlan, 2002; Lemon *et al*., 2007). In the case of *E. coli*, attachment is mediated by curli fibers, type 1 pili and antigen 43, which also favor the bacterial interactions (Danese *et al*., 2000). When biofilms reach maturity, they acquire a three-dimensional structure. However, when biofilms become fully mature; detachment may occur, which allows the bacterial cells to return to the planktonic state again, and thereby can re-form biofilms in other settings (Serra *et al*., 2013).

Bacteria that adhere to the uroepithelium and form biofilm can invade the renal tissue, thus causing pyelonephritis and may be even responsible for the chronic bacterial prostatitis (Nickel *et al*., 1985). Biofilms not only develop into the urethral stents, but they may also be formed within the catheters thus causing their blockage. Tambyah, (2004) reported that catheter-associated UTI (CAUTI) represents one of the most common care-associated infections worldwide. Within this type of medical device, the bacteria produce urease enzyme, which hydrolyzes the urea to ammonium ions, thus causing the formation of infected bladder calculi, urinary obstruction and encrustation. Formation of ammonium ions increases the pH level of the urine, leading to the precipitation of calcium phosphate crystals and magnesium. The calcium phosphate crystals form a layer that protects the bacteria from effects of the antimicrobial compounds that are used to coat or impregnate the catheters (Soto, 2014).

Several antibacterial agents are unable to diffuse into the biofilm matrix and\or the time required for the antibiotic to penetrate the biofilm is longer than the antibiotic lifetime or the duration of treatment. The factors associated with UPEC include efflux pump mechanism of the antibiotic drug resistance; persisters cells capable of antibiotics tolerance, transfer of antibiotic resistance gene, inactivation of the diffused antibiotics within pH of the biofilms and biofilm rebuilding ability (Keren *et al*., 2004; Soto, 2013).

4. Virulence factor of UPEC

Although the UPEC expresses several virulence factors that help it to invade, colonize the host issue and establish an infection. The common and major virulence factors are presented in Table (1).

5. Pathogenesis of UPEC

When UPEC of gut contaminates the periurethral and vaginal areas, it colonizes the urethra, and then the bacteria ascend to the bladder lumen with the aid of adhesins and fimbriae. Bacterial colonization takes place through adherence on the surface epithelium and then interacting with the bladder epithelium defense system. The host inflammatory response tries to eject the bacteria, however those bacteria that can evade the immune response of host through host cell invasion and\ or through morphological changes can persist to survive, multiply and form biofilms. The invading bacterial pathogens replicate through forming bladder intracellular bacterial communities (IBCs) within which the bacteria may reach 10^5 cfu\ cell (Spaulding and Hultgren, 2016). The bacteria can migrate to colonize the kidney, and then produce toxins that lead to kidney cell injury. If not treated, the bacteria may cross the tubular epithelial barriers in the kidneys that lead to bacteremia. This pathogenesis pathway is the same for both complicated and uncomplicated UTI (Rousseau *et al*., 2016). Flores-Mireles *et al*., (2015) revealed that the most important cause of a compromised bladder is catheterization that may

Table 1: Virulence factors of the UPEC (Terlizzi *et al*. 2017)

Virulence factor	Major function
Flagella	Adhesion of *E. coli* in the urinary tract
Type 1 fimbriae	Adhesion to bladder epithelial cells
P fimbriae	Adhesion to kidney epithelial cells
Dr fimbriae	Cell invasion
Cytotoxic Necrotizing Factor 1	Adhesion, invasion, apoptosis of host cells
Haemolysin	Invasion, tissue damage
Secrete auto transporter toxins	Tissue damage
LPS	Immune response activator
Curli fimbriae	Adhesion, biofilm formation, invasion
Cellulose	Biofilm formation
Iron and zinc acquisition	Nutrition
Capsule	Resistance to phagocytosis
F1C fimbriae	Unknown

induce Catheter associated UTI (CAUTI). Despite the strong inflammatory response associated with urinary catheterization; however, *E. coli* colonizes the urinary catheter and forms biofilms inside, which resist clearance from the host (Rousseau *et al*., 2016).

Several UPEC phylogroups (species with genetic diversity) (i.e. A, B_1, B_2, and D) have been detected; with effective expression of virulence factors including the adhesins; pili, toxins, flagella, surface polysaccharides, iron-acquisition, outer membrane proteins and secreted toxins, which establish these bacterial strains in UTI (Bien *et al*., 2012). These surface structural components represent important bacterial virulence factors. The pili are involved in the initial attachment of UPEC to the urinary tract mucosa, and then UPEC elaborates numerous other fimbria adhesins. P fimbria is the second common virulence factor of UPEC that plays an important role in pathogenesis of the ascending UTIs and pyelonephritis in humans. Moreover, it is responsible for bacterial adhesion to the mucosal and tissue matrix (Bien *et al*., 2012). The flagella confer adhesive and invasive properties to some EPEC strains, and play a key role in the dynamics of biofilms (Pratt and Kolter, 1998; Giron *et al*., 2002).

Bladder colonization by UPEC is mediated by several virulence factors, which has a crucial role in UTI pathogenesis. In addition to mediating adherence to the bladder epithelium, the FimH adhesin located at the tip of type 1 pili mediates invasion of the bladder epithelial and mast cells into the caveolae, which protects the bacteria from the host defenses and antibiotics (McLellan *et al*., 2021).

Lipopolysaccharides (LPS) are known to be associated with the bladder colonization, evoke the innate and adaptive immune system, and provide resistance against the hydrophobic antibiotics (Lee *et al*., 2020). Iron acquisition is a critical requirement for UPEC survival especially in iron limited environment such as the urinary tract (Skaar, 2010). Accordingly, siderophores are small iron chelator molecules that are

produced by the UPEC strains to withdraw the ferric ion (Fe^{3+}), as proposed by O'Brien *et al*., (2016).

Generally, the UPEC toxins play different pathogenic roles during infection. The α-hemolysin toxin is associated with scarring and renal damage, which induces Ca^{2+} oscillations in the renal tubular epithelial cells, thus effectively enhancing colonization and ascension of the kidney parenchyma and ureters, through disrupting the normal flow of urine (Terlizzi *et al*., 2017).

6. UTI in pregnancy

UTI is common during pregnancy, which may lead to serious health complications to the mother as well as to the child. UTI associated with MDR in pregnancy is a major clinical challenge for the physicians (Matuszkiewicz-Rowińska *et al*., 2015). There is a high risk of pyelonephritis during pregnancy, where prompt antibiotic treatment in the asymptomatic bacteriuria can reduce the risk of low birth weight (Wingert *et al*., 2019). Relatedness of UTI during pregnancy is due to the structural and physiological changes that take place during pregnancy, and encompass hydronephrosis and hydroureter in 80 % of the pregnant women. This may be attributed to mechanical compression of the enlarged uterus and to high level of the circulating progesterone hormone. Accordingly, urine stasis, retention of urine in the bladder along with impairment of the anti-reflux mechanism allow for bacterial growth. Furthermore, the induced biochemical changes in urine during pregnancy, such as pH, in addition to increased glucose level and amino acids also facilitate the bacterial growth (Jeyabalan and Lain, 2007; Matuszkiewicz-Rowińska *et al*., 2015; Widmer *et al*., 2015). In the context of Nepal, recent researches conducted by Yadav and Yadav, (2018); Thakur and Nagpal, (2020) concluded the prevalence of UTI (asymptomatic bacteriuria) in pregnant women. However, in other countries such as Bangladesh, Iran and India, the prevalence of UTI is comparatively lower in the pregnant women according to the investigations carried out by Lee *et al*., (2020) (8.9 %); Amiri *et al*., (2015) (5 %); Kant *et al*., (2017) (3.3 %), which included both symptomatic and asymptomatic bacteriuria.

7. Clinical manifestation

Uropathogenic *E. coli* is mainly responsible for the complicated and uncomplicated UTI; involving any part of the urinary tract including the kidneys; ureters, urethra and the urinary bladder.

7.1. Uncomplicated urinary tract infections

Uncomplicated UTIs are associated with the healthy individuals and\or those with no urinary tract abnormalities (Hooton, 2012). These infections are further differentiated into lower urinary tract infection or cystitis, and upper UTI known as pyelonephritis.

7.1.1. Cystitis

Cystitis refers to the inflammation and irritation of the urethra and bladder upon infection with bacteria. It affects people of all ages and of both sexes. However, in females; vaginal infection, sexual activity, obesity, diabetes, and genetic susceptibility are the main factors that affect cystitis (Foxman, 2014). Meanwhile, frequent urination, burning sensation during urination without vaginal discharge, and pain above the pubic bone and\or in the lower back, are the major symptoms of cystitis (Lee *et al*., 2020).

7.1.2. Pyelonephritis

Pyelonephritis means inflammation of the kidneys due to infection with bacteria. Diabetes; prior urinary tract infection, spermicide use, structural problems in the urinary tract, and sexual intercourse are the common risk factors associated with pyelonephritis (McKinney, 2011; Colgan *et al*., 2011). The clinical signs of pyelonephritis include, fever; nausea, vomiting, flank pain, in addition to lower UTI symptoms (Lane and Takhar, 2011).

7.2. Complicated urinary tract infections

Complicated UTI is defined as infection that takes place in those patients who have anatomically, metabolically or functionally abnormal urinary tract, and in patients suffering from infections caused by pathogens that resist treatments with antibiotics (Nicolle, 2005). The clinical symptoms range from a mild cystitis to life-threatening urosepsis and even a long period of asymptomatic bacteriuria. Complicated UTIs are associated with several factors that compromise the urinary tract and\or host defense such as; urinary obstruction, urinary retention caused by a neurological disease, renal failure, pregnancy, renal transplantation, presence of calculi and indwelling catheters, and immunosuppression (Lichtenberger and Hooton, 2008).

7.3. Recurrent UTI

A previous study of Soto, (2014) reported that acute UTI caused by bacteria can lead to recurrent infection (RUTI) or "reinfection", when it involves a bacterial strain other than that causing the original infection. Recurrent infection is defined also as a "relapse", when it is caused by the same strain that is involved in the original UTI. Relapse caused by uropathogenic *E. coli* has been related to ability of the pathogenic strains to form biofilms (Soto *et al*., 2006). Approximately 25 % of women will have a risk of a second symptomatic episode of UTI within 6 months (Foxman, 2014). Intestinal colonization, vaginal colonization, and intracellular bacteria residing within the transitional epithelial cells are the main reservoirs for reinfection (Johnson and Russo, 2005; Mysorekar and Hultgren, 2006). Periurethral bacterial colonization and the presence of certain *E. coli* virulence factors are pathogen-related factors, whereas high intercourse frequency; voiding dysfunction, spermicide use, and oral contraceptive are the host behavioral risk factors that predispose women to RUTI (Finer and Landau, 2004).

Women with RUTIs need to be well investigated with the aid of using urine cultures, urinalysis and different radiological strategies that allow to determine the reasons of recurrence, in addition it is necessary to evaluate infections caused either by anatomical or urinary tract abnormalities (Al-Badr and Al-Shaikh, 2013). There are several evidences to support that RUTIs may be caused by one of two mechanisms mainly: repeated ascending infections and\or chronic persistent infection in the bladder. Repeated ascending infections are thought to take place by the endogenous rectal flora via a fecal–perineal–urethral route. The bacteria migrate from the gastrointestinal tract to the periurethral area, finally ascending the urethra into the bladder. The other alternative mechanism involves survival of bacteria in the urinary bladder through intracellular bacterial communities (IBC), and even into persistent quiescent intracellular reservoirs (QIR) (Glover *et al*., 2014). Type 1 pilus-associated adhesin FimH is the major facilitator of UPEC entry into the host cells. UPEC mutants that lack FimH are unable to effectively invade the bladder epithelial cells either in mice or in cell culture model systems.

UP1a (Uroplakin 1 A receptor) as a major receptor available to FimH on the bladder surface is presumed to be an important mediator of UPEC entry into the umbrella cells. In addition to the umbrella cells, FimH can mediate UPEC entry into immature uroepithelial cells and many other hosts cell types that lack uroplakins or uroplakin plaques. More than 40 host cell factors have been implicated as regulators of the bladder cell invasion through UPEC downstream of FimH, which binds to either the integrin subunits or UP1a. Different FimH receptors and associated signaling pathways may promote UPEC entry in a synergistic fashion, rather than acting autonomously (Lewis *et al*., 2017).

7.4. Renal scarring

Renal scarring by UPEC strains includes several events such as influx of neutrophils. Accordingly, oxidative burst occurs due to the production of granulocytic cytotoxic products including; elastase, myeloperoxidasem and lysozyme (Heinzelmann *et al*., 1999). These mechanisms that are targeted to destroy the pathogens may be harmful to the host, through causing tissue destruction along with fibrosis.

However, delay in treatment may lead to kidney failure (Jahnukainen *et al*., 2005).

Renal scarring is most common in young children; however, children less than 2 years are prone to UTI (Beiraghdar *et al*., 2012). The more common risk factors associated with RUTI and renal scarring include; febrile UTI, antenatal HUN (high grades), children less than 5 years age, female gender, congenital abnormalities (PUV and duplex kidney), infection with UPEC and increasing grades of vesicoureteral reflux (VUR) (Bandari *et al*., 2019). However, the major risk factors associated with renal infection include; the presence of bladder and bowel dysfunction, the presence of VUR, in addition to defects in the ability of the host immune response to clear the bacteria (Murugapoopathy *et al*., 2020). A previous study conducted by Li *et al*., (2017) suggests that the acquired renal scarring occurs in patients with proteinuria; febrile urinary tract infections, hypertension and having chronic kidney disease.

Patients with VUR are more prone to renal scarring. Moreover, the severity of renal scarring is associated with the severity of VUR. In children, the risk factors for renal scarring involve those with older age of VUR diagnosis; primary VUR, higher grade of VUR and higher number of UTIs. On the other hand, the risk factors associated with deteriorating the renal function include a history of Acute phosphate nephropathy (APN); a younger age of VUR diagnosis and renal scarring (Chen *et al*., 2013).

7.5. Asymptomatic bacteriuria (ABU)

Asymptomatic bacteriuria (ABU) is defined as that condition where a specified number of bacteria are isolated from an appropriately collected urine sample without any clinical symptoms or adverse effects of UTI. A specimen of midstream clean catch urine collected from a man or a woman recording isolated bacterial count of $\geq 10^5$ cfu/ ml of urine address UTI. However, for those Catheterized male and female patients with quantitative bacterial count lower ($\geq 10^2$ to $<10^5$ cfu/ml) collected from two consecutive urine specimens within two weeks following insertion of new catheter, establish an ABU. For males; a single specimen collection is enough for diagnosis. However, incomplete bladder emptying in elderly women may develop ABU. It is highly recommended for ABU to be treated during pregnancy, after renal transplantation and before urological surgery (Nicolle *et al*., 2019; Givler and Givler, 2022).

Asymptomatic bacteriuria means the presence of bacteria in urine without symptoms of acute urinary tract infection, which predisposes pregnant women to the development of urinary tract infections and pyelonephritis, associated with an attendant pregnancy related complications. ABU occurs commonly in both of pregnant and non-pregnant women. However, when it takes place in pregnant women; anatomical and hormonal changes from the pregnancy cause dilatation of the renal pelvis and ureters, associated with an attendant urinary stasis (Schnarr and Smaill, 2008). There is an association between ABU and sexual activity during pregnancy, in consistent with several studies that recorded sexual activity as a risk factor for developing UTI in women (Sheffield and Cuningham, 2005).

Increased prevalence of ABU is observed in sickle trait; low socio-economic status, grand multiparity and diabetes mellitus, where each of them is associated with two-fold increase in the rate of bacteriuria. The prevalence of ABU in pregnant women varies between 4-7 % (range 2-11 %), and is similar to that observed in non-pregnant women (Patterson and Andriole, 1997). In young premenopausal non-pregnant women, the prevalence of ABU ranges from 1 % - 5 %. Generally, the prevalence of ABU increases with age, thus in elderly women aged 68−79 years; the prevalence is 13.6 %, which increases to 22.4 % in those aged 90 years (Ferroni and Taylor, 2015). Several traits of pregnancy act as predisposing factors for ABU, including slowed peristalsis; increased progesterone, urinary stasis in ureters, increased volume of residual urine, uterine growth and bladder displacement (Schneeberger *et al*., 2014).

7.6. Catheter associated UTI (CAUTI)

Bacteria initiate the formation of biofilms as they adhere to the surface of catheters (Nickel and Costerton, 1992). If catheterization is performed for more than 30 days, almost all cauterized patients are likely to have bacteriuria (Albu *et al*., 2018). Catheter-associated urinary tract infections (CAUTIs) are one of the most common nosocomial infections, which may lead to numerous medical complications that range from mild catheter encrustation and bladder stones, to endotoxic shock; pyelonephritis and severe septicemia (Cortese *et al*., 2018). CAUTIs may lead to more serious complications like sepsis and endocarditis, and more than 13,000 deaths each year are associated with healthcare associated UTIs (Klevens *et al*., 2007). A recent study of Letica-Kriegel *et al*., (2019) revealed that approximately 12 % of patients who have a catheter inserted for 30 days will develop a CAUTI. However, when an episode of CAUTI becomes symptomatic, the resulting sequelae range from mild (fever, cystitis and urethritis), to severe (renal scarring, acute pyelonephritis, bacteremia, and calculus formation). These infections when left untreated may lead to urosepsis and death (Niel-Weise *et al*., 2012).

Expression of type 1 fimbriae, which is found in 80-100 % of UPEC strains, represents a virulence factor of UPEC (Niel-Weise *et al*., 2012). This adhesin factor allows UPEC strains and other uropathogens to adhere to the uroepithelial cells lining the urinary tract as well as the surface of a catheter. The ability to adhere to the catheter allows for establishment of a UPEC infection, which can then support complex biofilm formation by UPEC and other strains. Moreover, attachment to the uroepithelial cells may lead to invasion and deterioration of the uroepithelial layer, in addition to perpetuation of CAUTIs after removal of the catheter. UPEC strains are also capable of avoiding the host immune response through the formation of capsule and production of LPS. According to Cortese *et al*., (2018), the capsules produced by UPEC play important roles in UTIs and CAUTIs, as they aid in masking the bacterial cells with surface structural similarities to the human cells; host immune avoidance and providing resistance against phagocytosis by the immune cells.

8. Antibiotic drug resistance (ADR)

A study of Alqasim *et al*., (2018) revealed that all extended spectrum beta-lactamase (ESBL) positive *E. coli* isolates express high resistance towards front-line antibiotics used to treat UTI patients. High co-resistance to the different classes of antibiotics is recorded from ESBL-producing UPEC, which remains a serious clinical challenge (Halaji *et al*., 2020). Higher percentages of ESBL producing UPEC are associated with UTI. Moreover, Ali *et al*., (2016) added that most of these bacterial isolates are multi-drug resistant (MDR) and fluoroquinolone-resistant. The average resistance of UPEC to the different classes of antibiotics is demonstrated in the Table (2).

The study conducted by Reygaert, (2018) highlighted that antibiotic drug resistance (ADR) to β-lactam antibiotics is conferred by the production of beta lactamase enzymes by UPEC, which could hydrolase β-lactam ring structure causing the ring to open. Thus, the β-lactam drugs such as; cephalosporin, penicillin, carbapenems and monobactams fail to bind to the specific penicillin binding proteins (PBP). The genes (i.e. *bla* genes) responsible for coding the different types of β-lactamase are usually found in the bacterial plasmid (Kot, 2019). Extended Spectrum β-lactamase (ESBL) produced by *E. coli* confers resistance to the extended spectrum drugs such as penicillin and the 3rd- 4th generation cephalosporins. ESBL enzymes are classified into 3 groups: $ESBL_A$, $ESBL_M$ and $ESBL_{CARBA}$. $ESBL_A$ includes the most frequently detected CTX-M enzymes, in addition to Sulphydryl variable (SHV) and Temoniera (TEM) enzymes that can be degraded by clavulanic acid. $ESBL_M$ are miscellaneous ESBLs that represent the most common type. $ESBL_A$ and $ESBL_M$ confer resistance to most of the β-lactam antibiotics except of carbapenems. However, $ESBL_{CARBA}$ enzymes bear carbapenemase potentials, which account for the $ESBL_{CARBA}$ efficacies to confer resistance to all the β-lactam antibiotics (Giske *et al*., 2009).

Table 2: Average resistance of UPEC to the different antibiotics (Kot, 2019)

Antibiotics	Average resistance
Nitrofurantoin	<1.5 %-13.3 %
Fosfomycin	<1.5 %
Amoxicillin-Clavulanic acid	
Developed countries	3.1 %-40 %
Developing countries	48 %-83 %
Ciprofloxacin	
Developed countries	5.1 %-39.8 %
Developing countries	55.5 %-85.5 %
Trimethoprim-sulfamethoxazole	
Developed countries	14.6 %-37.1 %
Developing countries	54 %-82 %

In UPEC, mutation in the Fluoroquinolone (FQ) target enzymes, mainly; DNA topoisomerase II (DNA gyrase) and topoisomerase IV, leads to drug resistance towards Quinolones and fluoroquinolones, which are the drugs extensively used in UTIs. Mutations in *gyr*A and *gyr*B genes have played major role in in bacterial resistance towards quinolones and fluoroquinolones. However increased resistance to these antibiotics is also conferred by several mechanisms such as efflux pump mechanism; decreased uptake of drugs due to loss of the membrane bound porin, and plasmid-mediated quinolone resistance (PMQR) (Karczmarczyk *et al*., 2011).

Nitrofurantoin drug is used as the first empirical antibiotic used in treatment of uncomplicated cystitis. This is the antibiotic of choice; as resistance towards it is low, because this antibiotic attacks the target bacteria from multiple sites, and is safe for use even during pregnancy. Resistance towards nitrofurantoin is mediated by mutations in the *nsf*A and *nfs*B genes that encode for oxygen-insensitive nitro-reductases. According to Sandegren *et al*., (2008), the nitrofurantoin resistant mutants have expressed reduced growth even in the presence of clinical concentrations of nitrofurantoin, thus making it effective for treatment of infections caused even by the mutant strains. Due to the growing resistance of trimethoprim-sulfamethoxazole, this antibiotic is no more recommended as a therapy for treatment of the UTIs (Olson *et al*., 2009).

9. Treatment of UTIs

The US Food and Drug Administration (FDA) have categorized medications during pregnancy as demonstrated in Table (3).

Treatment with antibiotics should be started only after arrival of the urine culture and antibiotic susceptibility test reports; however, if antibiotic therapy has already begun; it should be checked whether the antibiotic is appropriate as per the report or should be stopped.

Examples of several antibiotics that are used for treatment of the UTIs include;

a)-Nitrofurantoin: It is best recommended for treatment of cystitis and is regarded safe to be used even during pregnancy. However, this antibiotic is not

preferred for treatment of pyelonephritis, as it does not penetrate well into the renal parenchyma. The use of nitrofurantoin for prolonged suppression of UTI is not considered appropriate in elderly patients, due to its adverse effects. The side effects are minimal and may include cough; malaise and dyspnea (Jancel and Dudas, 2002).

Table 3: Antibiotics categorized as risky by the FDA (Matuszkiewicz-Rowińska *et al*., 2015; Widmer *et al*., 2015)

Antibiotic	FDA risk category	Antibiotic	FDA risk category
Amoxicillin	B	Vancomycin	B
Cephalosporins	B	Metronidazole	B
Piperacillin	B	Trimethoprim	C
Azithromycin	B	Ciprofloxacin	C
Erythromycin	B	Gentamycin	D
Nitrofurantoin	B	Amikacin	D
Clindamycin	B	Tetracyclines	D
Meropenem	B	Tobramycin	D
Daptomycin	B	Trimethoprim-sulfamethoxazole	D
Fosfomycin	B		

Where; A: no adverse effects observed in human pregnancies; B: no adverse effects observed in human pregnancies but with adverse effect seen in animal pregnancies; C: no pregnancy related data available in human pregnancies; D: adverse effects observed in human pregnancies

b)-Trimethoprim/ Sulfamethoxazole: This antibiotic has long been considered as the standard for therapy of acute and recurrent UTIs (Jancel and Dudas, 2002).

c)-Fluoroquinolones: fluoroquinolones such as levofloxacin and ciprofloxacin are generally used for treatments of the uncomplicated pyelonephritis and complicated UTI. They remain very effective for treatment of acute cystitis, although the increased resistance towards fluoroquinolone among the uropathogens communities is mitigating the usefulness of this antibacterial class (Gupta *et al*., 2011).

d)-Oral β-lactams: They are used for treatment of the uncomplicated UTI as alternative agents. Amoxicillin and ampicillin are not preferred for the empiric therapy, due to the increased prevalence of pathogen resistance; however, they can be used for treatment of those pathogens that show susceptibility (Warren *et al*., 1999).

The choice of an antibiotic is based on the microbial sensitivities recorded through results of the urine culture. One-day antibiotic courses are not recommended in pregnancy, although 3-day courses are effective (Sheffield and Cunningham, 2005). The most commonly used antibiotics include nitrofurantoin; amoxicillin, ampicillin, trimethoprim-sulfamethoxazole and cephalosporins. Short courses of fluoroquinolones treatments are not harmful to the fetus, and thus, it is recommended to use this class of antibiotics in treatment of resistant or recurrent infections (Habak and Griggs, 2021).

Nitrofurantoin is the first choice of antibiotic treatment according to the National Institute for

Health and Care Excellence (NICE) guidelines, unless there is a recorded contraindication to it. Amoxicillin and cefalexin are the second-choice antibiotics, which should be used if contraindication to nitrofurantoin has been recorded (Ghouri and Hollywood, 2020). Nitrofurantoin may still be safe and effective to treat urinary infections in pregnant women. This antibiotic inhibits pyruvyl transferase and then bacterial cell wall synthesis (Gardiner *et al*., 2019).

For treatment of the uncomplicated UTIs caused by the drug resistant microorganisms, Fosfomycin has been recorded as a potential antibiotic. In the situations of emerging MDR pathogens, the use of fosfomycin has gained considerable importance, due to its broad spectrum against the MDR (Gram-positive and Gram-negative) (López-Montesinos and Horcajada, 2019). Regarding the use of fosfomycin in complicated UTIs, there is increasing clinical experience with patients suffering from infections caused by MDR bacteria, those with recurrent urinary tract infections and populations with kidney transplants (López-Montesinos and Horcajada, 2019). Matthews *et al*., (2016) study reported that fosfomycin is safe and effective for treatment of patients with complex comorbidities; even for prolonged periods.

Fosfomycin treatment of UTIs showed an excellent 7-day clinical efficacy (79.7 %). However, when used to treat recurrent or complicated UTIs, there are associated high levels of infection relapse in a total of 20.4 % of patients during the first 2 months of treatment. This indicates that fosfomycin expresses good activity for treatment of the uncomplicated UTIs only (Fajfr *et al*., 2020). Fosfomycin exhibits good efficacy against both ESBL-producing and ESBL-negative E. coli strains. Out of 358 isolates of the tested bacterial pathogens, 338 (94.4 %) are recorded to be susceptible to fosfomycin (Sabharwal and Sharma, 2015).

Escherichia coli remains the predominant uropathogen in acute community-acquired uncomplicated UTIs; however, amoxicillin-clavulanate is regarded as a useful first-line antibiotic (Tan and Chlebicki, 2016). Meanwhile, trimethroprim is considered as the first line option for treatment of recurrent UTI (Holm *et al*., 2019).

10. Prevention of UTIs

-Proper nutrition and hydration are effective in prevention of this infection. Dehydration refers to a condition where the body lacks proper amount of water. This leads to concentrated urine and less frequent voiding, which eventually support bacterial growth in the urinary bladder (Lean *et al*., 2019).

-Personal hygiene is highly advised to prevent contact with the urine and feces. The genital and anal areas should be washed daily with soap and water (Ani and Mgbechi, 2008).

-Complete emptying of the bladder that is available only in relaxed voiding environment; with comfortable toilet seat and at an appropriate height (Kowalik *et al*., 2019).

-Avoid the unnecessary use of urinary catheters for long periods, especially among women, the elderly and patients with impaired immunity (Gould *et al*., 2009).

Conclusion

The increasing incidence of UTI is a serious global health issue. UPEC can ascend to the ureter and may cause cystitis. If not treated, the UPEC can later ascend to the kidneys and cause renal infections; kidney failure and bloodstream infection. Moreover, high prevalence of MDR *E. coli* in UTI suspected patients alarms the urgent need of prescribing the proper antibiotics and the other drugs; based only on urine culture, antibiotic sensitivity and imaging reports. The prevalence of MDR *E. coli* in urine may result in therapeutic challenges, and accounts for greater morbidity and mortality rates. Accordingly, accurate diagnostic procedures and appropriate use of antimicrobials for

the treatment and preventive measures of UTIs are crucial, to reduce the burden and prevent the possible long-term consequences.

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