A DISSERTATION

ON

Comprehensive Review on MDR status of Urinary Tract Infection (UTI) patients.

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TO WHOM IT MAY CONCERN

This is to certify that **Ms. AFREEN SHUJA**, a student of M. Sc. Biotechnology (II Year, IV semester), Integral University has completed her four months dissertation work entitled "**Comprehensive Review on MDR status of Urinary Tract Infection (UTI) patients.**" successfully. She has completed this work from Department of Biosciences, Integral University, under the guidance of **Dr. M. Salman Khan.**

The dissertation was a compulsory part of her M. Sc. degree. I wish her good luck and future endeavours.

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Abstract

Urinary tract infections (UTIs) are one of the most common pathological conditions in both community and hospital settings. It has been estimated that about 150 million people worldwide develop UTIs each year, with high social costs in terms of hospitalizations and medical expenses. Urinary tract infection (UTI) is a common bacterial infection known to affect the different parts of the urinary tract and the occurrence is found in both males and females. Despite the fact, that both the genders are susceptible to the infection, women are most vulnerable due to their anatomy and reproductive physiology. The infection is usually caused as a consequence of the bacterial invasion of the urinary tract including the lower and the upper urinary tract. UT possesses a variety of virulence factors (VFs), which the organism uses to attach, invade, and injure the host. These VFs include adhesins, toxins, iron acquisition fact lipopolysaccharides capsules, and other invasions. Most studies on UTI pathogenesis have targeted VFs. 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.

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1. **Introduction**

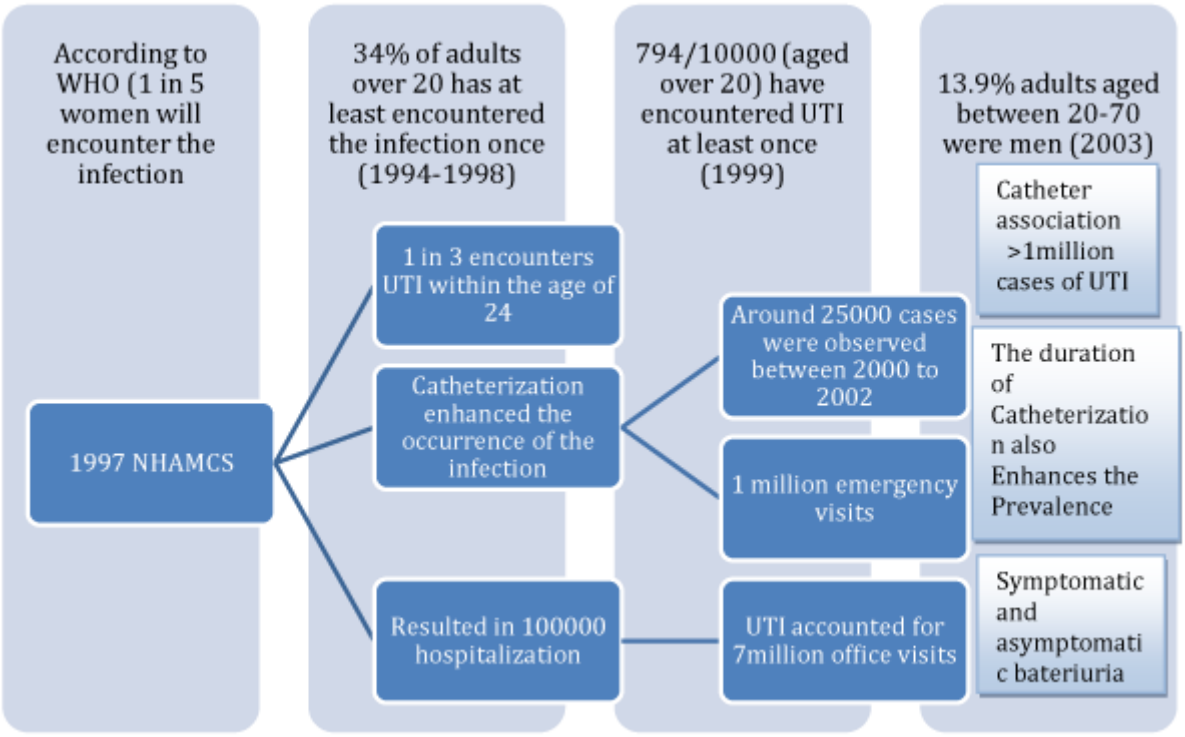
Urinary tract infections (UTIs) are one of the most common infectious diseases ranking next to upper respiratory tract infections. Every year 150 million people suffer from UTI world-wide and the Enterobacteriaceae family contributes 84.3% to UTIs.[1,2,3] The UTI problem has been magnified over time with the emergence of multidrug resistant (MDR) bacteria and it has become a frequently met medical problem. Paradigmatically the transformation of the commensal, Escherichia coli (E. coli) mostly isolated from patients with uncomplicated UTI to be a notorious pathogen is of utmost consternation.[4]

UTI treatment is mainly focused on the use of antibiotics including β-lactams in several countries. However, drug resistance is raising serious concerns. Antibiotic resistance among bacteria is the most prevalent issue and is very common worldwide due to β-lactamase production by various program-negative bacteria especially by Enterobacteriaceae.[5]β-lactamase synthesis by gram-negative bacteria is considered to be the most important crucial mechanism of resistance to β-lactam drugs. Bush discovered and separated these enzymes from Klebsiella in 1983 and designated as extended spectrum β-lactamases (ESBLs). He observed that these enzymes degraded oxyiminao cephalosporin class with a β-lactam ring, like Ceftriaxone, and Aztreonam. The enzymes β-lactamase is thought as the most important cause of drug resistance in gram-negative bacteria. ESBLs breakdowns cephalosporin's of the fourth generation at βlactam ring except for Carbapenems and Cephamycin.[6] Carbapenems such as imipenem, meropenem, ertapenem, and doripenem are considered as the last resort antibiotics to treat ESBL producing Enterobacteriaceae.

Gram-negative bacteria, especially the family Enterobacteriaceae are the common cause of both community and hospital-acquired UTIs. *Escherichia coli* and *Klebsiella* pneumonia are most commonly implicated among patients with UTIs.[7] *Acinetobacter baumannii* (*A*. *baumannii*), *Pseudomonas aeruginosa (P. aeruginosa), Proteus sp., Klebsiella sp.,* Chlamydia trachoma, and Neisseria gonorrhea. Moreover, UTI-fungi, *Candida sp.* (such as *Candida albicans, Candida utilis, Candida glabrata, Candida tropical is*, *Candida kefyr, a*nd *Candida guilliermondii*)

and *Rhodotorula* sp., often burgeon in the mazed environment of infection-source in a hospital, promoting UTI.

Overview of UTI



Prevalence of UTI among different groups of people over the last few years.

2. URINARY TRACT INFECTIONS (UTIs)

Urinary tract infections (UTIs) are widespread and affect a large proportion of the human population. About 150 million people worldwide develop UTIs each year, with high social costs. It is estimated that 40% of women develop at least one UTI during their lifetime and that 11% of women over 18 years have an episode of UTI per year [8,9]. With roughly eleven million cases reported in the sole U.S. each year, the costs are estimated at $5 billion annually **(Figure 1)**. Urinary tract infection is a common contagion among men and women but the incidence is quite high among women due to their physiology. In simple terms, it can be referred as a condition that a woman will certainly encounter during the span of a life time and the prevalence is higher among women during pregnancy. The UTI refers to the presence of a certain number of bacteria in the urine (generally > 105 /ml) and symptomatic UTIs are classified in order of severity as urosepsis syndrome, pyelonephritis (or upper UTI, with infection in the kidney) and cystitis (or lower UTI, with bacteria into the bladder.[10] The symptoms associated with the bladder and kidney infections are contrasting which include painful and frequent urination in case of cystitis as a result of bladder infection whereas conditions like high fever and flank pain are commonly experienced in case of kidney contagion was referred to as pyelonephritis prevalence of the infection among children and elderly people is not clearly understood and is currently under study.[11]

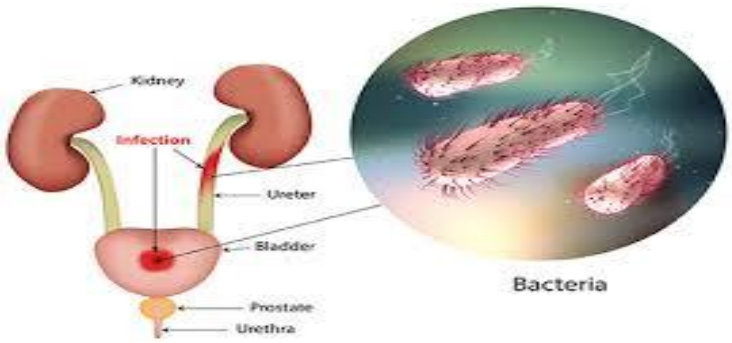


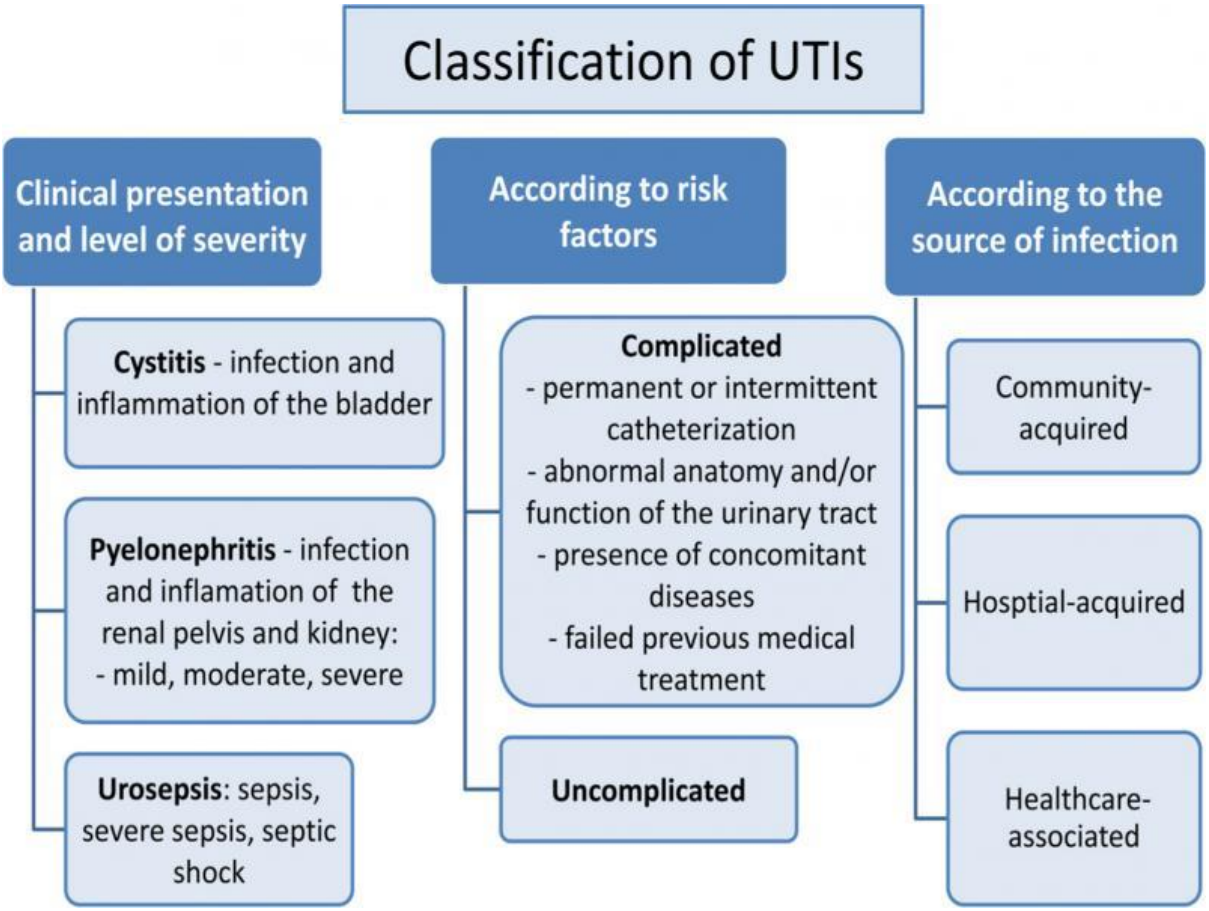
Figure. 1. The Urinary tract and sites of infection.

Bacterial cystitis (also called acute cystitis) can occur in both women and men and some people develop recurrent infections of the urinary tract.[12] Three or more

urinary tract infections within 12 months define a recurring UTI, as well as two or more recurrences within 6 months. The same bacterial species that caused previous us infection is typically responsible for relapses. Approximately 20–30% of adult women with an initial UTI will experience a recurrence within 3–4 months; whereas, in children, about one third experiencing a UTI before the age of one, will experience a recurrence within 3 years, and 18% of them will have a recurrence within a few months.[13] In patients suffering from recurrent UTIs, maintenance is ensured by antibiotic prophylaxis; however, in some cases, T I needs to be treated by surgery. During pregnancy, recurrent UTIs may be frequent and can cause severe adverse outcomes for the mother and the baby, including preterm birth. The interventions in this setting can be pharmacologic (antibiotics) or non-pharmacological (alternative remedies).[14] In pre-menopausal women, sexual activities three or more times a week, the use of spermicides, new or multiple sexual partners and having suffered from UTI before age 15 are the main risk factors in UTI development and recurrence. In menopausal women, systemic hormonal therapy is not an effective prevention, and usually asymptomatic bacteriuria during this period does not require treatment.[15] In women after menopause, the risk increases mainly by low estragon levels after-effects, which associated to vaginal atrophy. Women over the age of 61–65 years, so suffer of genital-urinary symptoms while 29% had episodes of urinary incontinence, all symptoms associated with bacteriuria.[16]

3. Classification of UTI

Many microorganisms are continuously threatening to infect the urinary tract, but their virulence is balanced by host-protective mechanisms. Most UTIs are caused by the ascent of microorganisms through the urethra, although some microorganisms can reach the urinary tract by the haematogenous or lymphatic spread.



Classification of UTIs

Classification of UTIs is important for clinical decisions, research, quality measurement, and teaching. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings and usually have been divided into uncomplicated and complicated UTIs, and urosepsis however, most UTIs are uncomplicated.

Uncomplicated and complicated urinary tract infection: This is a consequence of bacterial infection and the prevalence is higher in women than men. This includes the common form of the infection like cystitis and pyelonephritis which affects the

lower and the upper tracts leading to bladder and kidney infections. In contrast, complicated urinary tract infection occurs in men and women at any point in their life and tends to produce severe outcomes resulting in death under serious circumstances. Patients with urinary tract infection are often subjected to medical devices and one such device commonly employed among the patients are the urinary catheters which serve as a common means of infection. In addition, bladder and kidney malfunction and kidney transplants are the other factors for complicated urinary tract infections. The first three months after a kidney transplant is very crucial and the patient is vulnerable to developing such complications.

Recurrent urinary tract infection: This is a common phenomenon that is observed among women who have experienced uncomplicated UTIs and they are classified as re-infection and relapse. Major cases of UTIs are referred to as re-infections and the condition is encountered by the patient after several weeks of antibiotic treatment. Knowledge about risk factors is important for treatment decisions, for instance, treatment of asymptomatic bacteraemia in women with recurrent symptomatic UTIs is no longer recommended if there are no identified risk factors. Treatment strategy depends on the clinical severity grade, and both appropriate antimicrobial therapy and resolution of risk factors are mandatory. Her selection of antibiotics is mostly based one standard culture test. Increasing antimicrobial resistance might require the development of more targeted approaches for successful antimicrobial therapy in the future.

4. Symptoms of UTI

UTI can be manifested as an asymptomatic or symptomatic infection based on the presence and absence of the symptoms. Urinary tract infections are caused by microorganisms usually bacteria that enter the urethra and bladder, causing inflammation and infection. [17]Though a UTI most commonly happens in the urethra and bladder, bacteria can also travel up the ureters and infect your kidneys. Hence symptoms enhance the diagnosis process among young healthy women. The infection is less common in children.

Symptoms of urinary tract infection

A) Cystitis: This is commonly called a lower urinary tract infection or bladder infection and affects the bladder. It causes the following symptoms

i. Pressure in lower pelvis pain

ii. Dysuria (painful urination)

iii. Polyuria (frequent urination)

iv. Urinary urgency

v. Nocturia (urination during the night)

vi. Haematuria (urine with traces of blood)

Cystitis is further classified based on the etiology and therapeutic approach and traumatic cystitis is considered the common form of cystitis among females causing the bruising of the bladder. This is often followed by bacterial cystitis. The coliform bacteria are transferred to the bladder from the bowel through the urethra.

B) Pyelonephritis: Kidney infection is a type of urinary tract infection (UTI) that commonly begins in your bladder and moves upstream to one or both of your kidneys. In rare cases, kidney infections can lead to serious health problems, but quick treatment prevents most complications. It is also known as “pyelitis**”.** Severe incidence causes the accumulation of pus around kidneys and is known as “pyonephrosis”. Symptoms of pyelonephritis include fever and flank pain in addition to symptoms seen in lower urinary tract infections. Among young children, high

fever is the only symptom of urinary tract infection and the symptoms are difficult to detect in elderly people. Hence it is recommended to carry out an analysis of the urine culture.

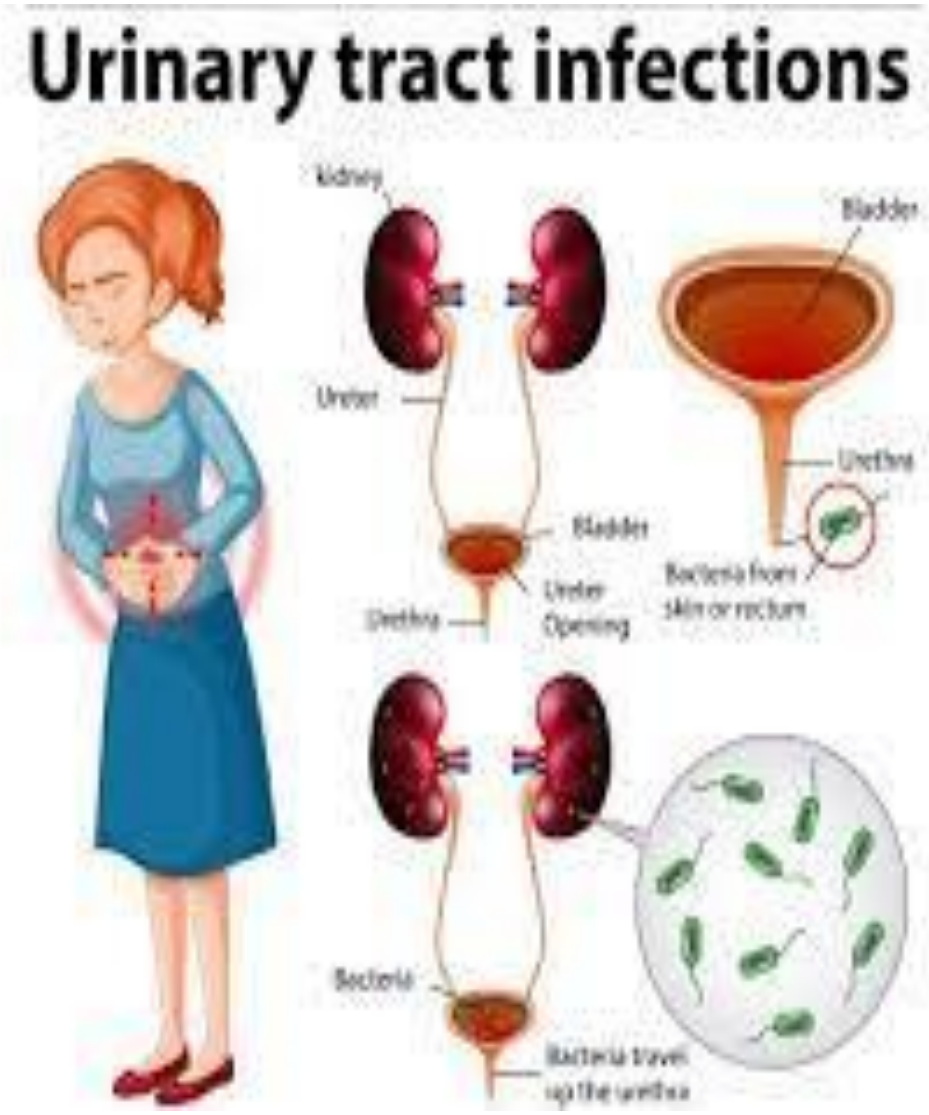


Figure.2 Symptoms of UTI

Asymptomatic and symptomatic UTI

Asymptomatic UTI

ASB is essentially an asymptomatic UTI. In other words, it is the presence of significant bacteriuria without symptoms or signs, such as frequency, urgency, dysuria, pyuria, or haematuria. Significant bacteriuria is defined as greater than or equal to 105 colony-forming units of a single pathogen per millilitre of urine in two consecutive midstream urine samples.[18]

ASB is not considered clinically significant in most patient populations; however, this is not the case with pregnant women. The number of pregnant women who develop pyelonephritis is significantly higher than their non-pregnant counterparts. If untreated, as many as 20% to 40% of pregnant women with ASB will develop pyelonephritis.[19, 20] Although it is known that bacteriuria can lead to pyelonephritis in pregnancy, other adverse effects of bacteriuria are less well-established. In various studies, untreated bacteriuria has been linked with prematurity, low birth weight, intrauterine growth retardation, and neonatal death.[21] However, poor outcomes may be the result of coexisting risk factors, such as low socioeconomic status, rather than bacteriuria alone. To date, this suggestion remains controversial.[19]

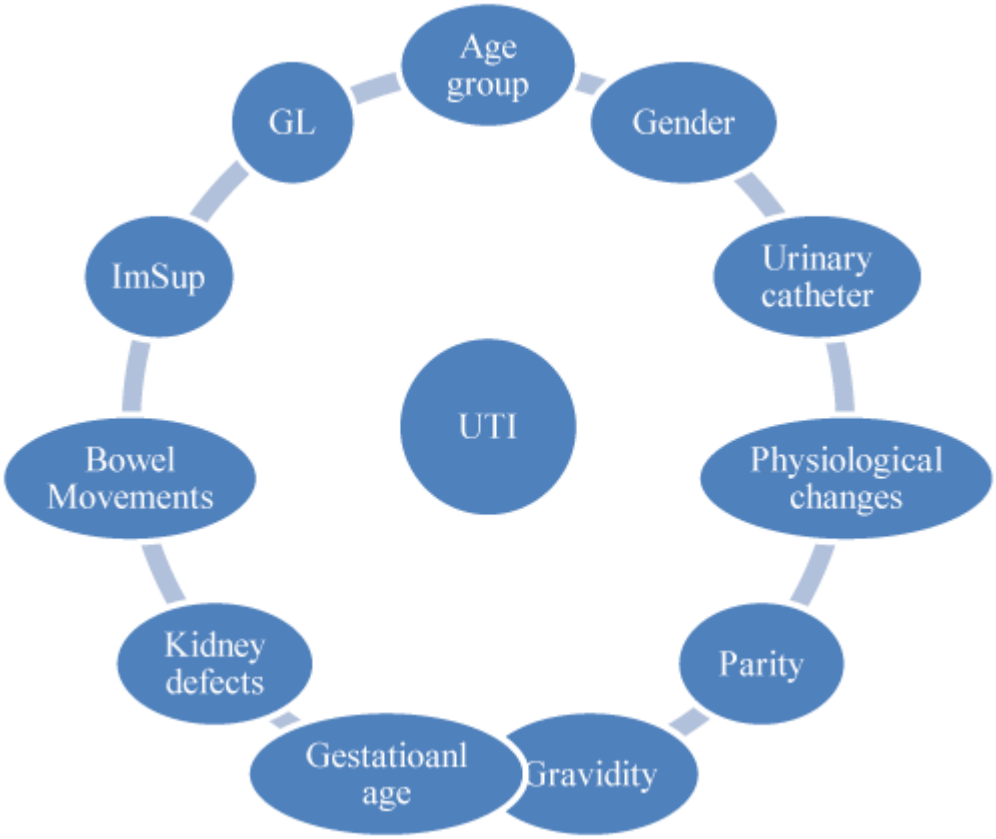
Symptomatic UTI

The incidence of cystitis during pregnancy has been approximated at 1% to 2%. Diagnosis of cystitis is based on a combination of bacteriuria and signs and symptoms of frequency, urgency, dysuria, hematuria, and pyuria. Treatment of cystitis is the same as treatment for ASB. Again, follow-up, as outlined above, is important because up to third women may experience UTIs during pregnancy.[21] Incidence of pyelonephritis during pregnancy is approximately 1% to 2%. However, 20% to 40% of women with untreated bacteriuria will develop pyelonephritis during pregnancy.[21] Pyelonephritis is seen most commonly during this trimester whether stasis and hydronephrosis are most evident.[23]

Bacteriuria and clinical signs and symptoms establish a diagnosis of pyelonephritis. The signs and symptoms are similar to those of non-pregnant women and include fever, nausea, vomiting, chills, and costovertebral angle (CVA) tenderness.

All patients who have pyelonephritis during pregnancy should be admitted and treated with parenteral agents.[24] Initial antimicrobial therapy is typically ampicillin plus gentamicin or cephalosporin's. Second- or third-generation cephalosporin may also be considered for single-agent therapy.[25] With these treatment regimens, more than 95% of women will respond within 72 hours. [26, 27] Resistant organisms must be considered in women who do not respond appropriately to treatment, and antimicrobials should be changed according to culture results. If treatment response is suboptimal despite culture-specific treatment, an ultrasound should be obtained to rule out nephrolithiasis, structural abnormality, or renal abscess. Once afebrile, women may be switched to a 2-week outpatient course of an oral antimicrobial. This course should be followed by suppressive therapy until delivery.[28,29] As with ASB and cystitis, follow-up after treatment is important. Women should be monitored closely throughout their pregnancy because there is an increased risk of recurrent pyelonephritis.[30]

Demographic parameters



Demographic parameters associated with UTI ImSup, immune suppressants GL, geographic location.

5. Etiology of UTI

The microbial etiology of urinary infections has been regarded as well-established and reasonably consistent. *Escherichia coli* remains the predominant uropathogen (80%) isolated in acute community-acquired uncomplicated infections, followed by *Staphylococcus saprophyticus (10%to15%)*. *Klebsiella*, *Enterobacter*, and *Proteus* species and enterococci infrequently cause uncomplicated cystitis and pyelonephritis.[31]

Escherichia coli is a normal constituent of the intestinal micro biota of humans and animals. [32,33]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, invasions, and serum resistance-associated proteins. The presence and numbers of such VFs predict in vivo virulence.[34]

6. Epidemiology and risk factors for E.coli UTI

Urinary tract infections (UTIs) are caused by a wide range of pathogens, including Gram-negative and Gram-positive bacteria, as well as fungi. Uncomplicated UTIs typically affect women, children and see other healthy elderly patients Complicated UTIs are usually associated with indwelling catheters, urinary tract abnormalities, immunosuppressed, ion or exposure to antibiotics. The most common causative agent for both uncomplicated and complicated UTIs is Uropathogenic *Escherichia coli* (UPEC). For uncomplicated UTIs, other causative agents are (in order of prevalence) *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *group B Streptococcus* (GBS), Proteus mirabilis, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida spp*. For complicated UTIs, the other causative agents are (in order of prevalence) *Enterococcus spp., K pneumoniae*, *Candida spp., S. aureus, P. mirabilis, P. aeruginosa* and *GBS.*

Overall, UTI is more prevalent among females than males, attributable to the 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.[35,36] Functional, hormonal, and anatomical changes that occur during pregnancy predispose pregnant women to UTIs. UTIs during pregnancy can result in devastating maternal and neonatal complications, including maternal sepsis, preterm labour, and premature delivery.[37] Thirty per cent of patients with untreated asymptomatic bacteriuria (ASB) develop symptomatic cystitis and up to 50% develop pyelonephritis. ASB is also associated with intrauterine growth retardation and low-birth-weight infants.[36] Up to 27% of preterm births have been associated with UTI pregnancy. [37]

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 UTIs will develop permanent kidney damage, leading to other chronic diseases such as hypertension and renal insufficiency.[38,39] 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.[40,41]

7. E.coli UTI pathogenesis

UTI pathogenesis is a complex process that is influenced by various host biological and behavioural 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 non-compromised 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 per urethral areas to the lower urinary tract (i.e., urethra and bladder) where they may establish colonization. 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.[42] These two mechanisms may not be mutually exclusive but instead may jointly contribute to UTI pathogenesis.

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,[43] but without any evidence of person-to-person transmission. Foods and water have been proposed as possible vehicles for such outbreaks.[44] The VFs of the invading bacteria and the host's defense mechanisms determine the outcome of the infection. [45] 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. 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 acute pyelonephritis.

8. Uropathogenic E.coli [UPEC] and its virulence

UPEC is the main cause of community-acquired UTIs (about 80– 90%).[46] Four main UPEC phylogroups (A, B1, B2, and D) have been identified based on the occurrence of genomic Pathogenicity Islands (PAI) and the expression of virulence factors, such as adhesins, toxins, surface polysaccharides, flagella, and iron-acquisition systems.[47] Usually, many of these virulence factors are required for UPEC to cause UTIs. However, besides UPEC, UTI can be caused by *Klebsiella pneumoniae at* 7%), *Proteus mirabilis* (about 5%), and *Pseudomonas aeruginosa*, *Enterococcus faecalis, Enterobacter cloacae, Streptococcus bovis*, and the fungus *Candida albicans*.[48] During UTIs, UPEC pathogenesis includes: (a) UEC colonization of the periurethral and vaginal areas with colonization of the urethra; (b) ascending into the bladder lumen and growth planktonic cells in the urine; (c) adherence to the surface and interaction with the bladder epithelium defense system (d) biofilm formation; (e) invasion and replication by forming bladder Intracellular Bacterial Communities (IBCs) where quiescent intracellular reservoirs (QIRs) form and reside in the underlying urothelium; (f) kidney colonization and host tissue damage with increased risk for bacteremia septicaemia.

Replication of bacteria in the IBC can easily reach as many as 105 bacteria per cell; furthermore, bacteria in the IBC undergo morphological changes, flux out of the infected cell, and go on to infect neighbouring cells.[49] These include surface structural components, such as lipopolysaccharide (LPS), polysaccharide capsule, flagella, outer-membrane vesicles, pili, curli, non-pilus adhesins, outer membrane proteins (OMPs), as well as secreted toxins, secretion systems, and TonB-dependent iron-uptake receptors, including siderophores receptors (**Figure 2**). All of these components are attractive candidates for the development of new drugs and vaccines.[50]

In UPEC, the film operon encodes type 1 pilus (expressing a hemagglutination which is mannose-sensitive), whereas the pap operon encodes P- or Pap-pili (which are able to interact with the digalactoside unit in the P-blood group antigen). In UPEC clinical isolates, fim operon is constitutive whereas pap is part of a PAI that is also responsible for other putative virulence determinants.

Mannosylated proteins that are present on the bladder epithelium bind to FimH in a Rho GTPases (Rac1)-mediated host actin cytoskeleton rearrangement-dependent manner.[51] This eventually leads to the development of cystitis due to bacterial invasion **(Figure 2)**. In addition, the expression of type 1 pili is strictly controlled by phase variation, which reversibly switches between the type 1 pili active expression (Phase-ON, piliated cells) and loss of expression (Phase-OFF, non-piliated cells).[52]

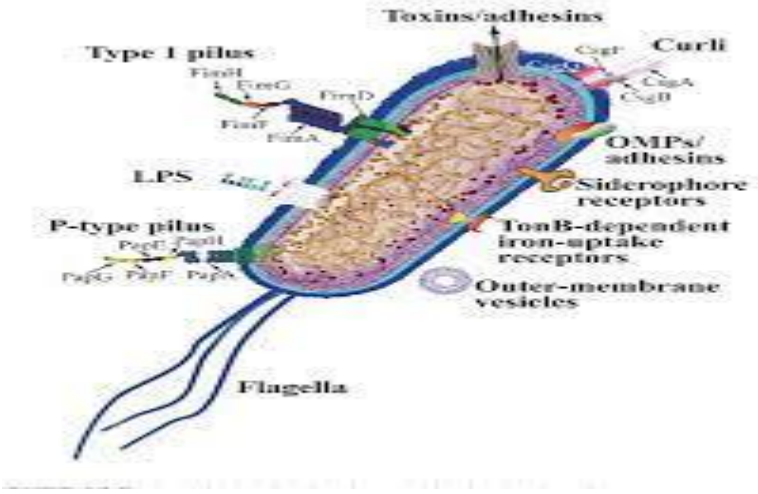


Figure 3. *Escherichia coli* adhesins and motile structure.

Curli are bacterial surface appendages that secrete subunits from the cell as soluble monomeric proteins and possess the typical structure and physical characteristics of amyloid fibrils. Which are known to be formed in some human degenerative diseases. The bacterial amyloids may facilitate biofilm formation. In UPEC, curli formation is coordinated by proteins encoded in the operons CSG DEFG. The operon accessory proteins CsgE, CsgF, and CsgG are required to facilitate the secretion of CsgA whereas CsgB nucleates CsgA subunits into curli fibers **(figure.2)**. [53]

Moreover, the large majority of UPEC isolated from women with acute, asymptomatic, or recurrent UTIs shows the presence of flagellum-mediated motility.[54]Flagella are organelles that confer adhesive and invasive properties to some EPEC strains [55] and play a key role in the dynamic of biofilm.[56]

Iron acquisition is a critical requirement for UPEC survival in an environment that is iron-limited as the urinary tract.[57] Thus, is not surprising that IBC UPEC shows up

regulation of redundant systems for the acquisition of iron.[58] In this regard, siderophores are small-molecule iron chelators that are produced by UPEC strains to scavenge ferric iron (Fe3+), thus UPEC expresses yersiniabactin, salmochelin, and aerobatic. Siderophore receptors require the TonB cytoplasmic membrane-localized complex, a high-affinity iron acquisition system that allows binding and chelation of iron at the cell surface to promote its uptake. [59]Lastly, further UPEC factors associated with colonization have been linked to the regulation of metabolic pathways mediated by two-component signalling systems (TCSs). TCSs are the main signal transduction pathways by which bacteria sense and respond to a wide array of environmental stimuli, including quorum sensing signals, nutrients, and antibiotics. TCSs are composed of a membrane-bound sensor histidine kinase (HK) and a cytoplasmic response regulator (RR) that functions by regulating gene expression.[60]

The importance of the above-described UPEC virulence factors in UTI pathogenesis has been further supported, in recent years, by the application of multiple “omics” technologies aimed at investigating the UPEC genomic diversity, the global gene expression in different models of infection both in vitro and in vivo, and to define the occurrence of UPEC-specific proteins as a new candidate therapeutic and vaccine targets.[61]

Transcriptomics investigations by both microarrays and NGS-based RNA sequencing (RNA-seq), on the other hand, have led to the identification of virulence and fitness UPEC genes, expressed during different in vitro and in vivo infection-relevant conditions. In this regard, RNA-seq-based transcriptome analysis of mouse macrophages infected in vitro with two UPEC strains, allowed us to identify strain-specific differentially expressed genes associated with the survival in macrophages, such as those involved in the responses to oxidative stress, as well as those involved in the initial adhesion of UPEC to cells, such as multiple flagella genes.[62]

High-resolution liquid chromatograph-mass spectrometry/mass spectrometry (LC-MS/MS)-based technology has been applied to identify and characterize the surface proteome of UPEC isolates and strains grown in human urine.[63] UPEC core surface proteins, such as integral Outer Membrane (OM) proteins (e.g., OmpA, OmpC, and OmpF) and several iron-uptake proteins were in acted in more than 80% of

strains.[64] The application of this technique, which allows which in situ two-dimensional assessment of protein spatial distribution and abundance, revealed the occurrence of different bacterial subpopulations within biofilms: type-1 pili-expressing cells localized at the air-exposed region and a curli-equipped population localized to the underlying air-liquid interface.[65]

9. Structure & targeting bacterial adhesion

Adhesins, which appear as hair-like fibers called fimbriae (or pili), facilitate the colonization of E. coli in the urinary tract by attaching them 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.[66] 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 calaboose, which is an antigen within the human P blood group system.[67] Different components of the P fimbriae have been described, including four different units that are at the tip of the fibrillium, including PapG, PapE PapF, and PapK. [68,69] 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 larger chromosomal insertion sections called pathogenicity associated islands (PAIs).[70]

As adherence has a key role at nearly every step of UTI pathogenesis, one attractive strategy for the development of antivirulence therapies, including vaccines, has been to target CUP pili. However, adhesins-based vaccines are effective at blocking host-pathogen interactions, thus preventing the establishment of disease. [71,72] Experiments using mouse and cynomolgus monkey models of UTIs determined that immunization with PapG–PapG or FimC–FimH chaperone–adhesin complexes protected against UTIs. Modifications of this vaccine are currently under development, to induce greater immune stimulation.[71,72] For example, one approach has been to fuse FimH to the flagellin FliC in order to induce a more substantial acute inflammatory response which functions through TLR4 signalling MYD88 pathway. A Phase I clinical trial began in January 2014 to evaluate the efficacy of a FimC–FimH vaccine using a synthetic analogue of monophosphoryl lipid A as the adjuvant.

In addition to the UPEC adhesins, adhesins from *P. mirabilis* and *E. faecalis* have also been used as vaccine targets.[73,74] In a mouse model of UTI, vaccination with the *P. mirabilis* MR/P pilus adhesin, MrpH, reduced bacterial burdens compared with those of unvaccinated controls, similar to the results observed with UPEC in the

FimH vaccine trials. [74,75]Moreover, a vaccine strategy that is efficacious against *E. faecalis* CAUTIs is being developed based on vaccination with the Ebp pilus adhesin, EbpA. This strategy induced high antibody titters and reduced bacterial burdens in a mouse model of CAUTI. In conclusion, adhesin-based vaccines represent a promising area for the development of therapeutics against uropathogen. Thus, understanding the molecular basis of host-pathogen interactions is crucial for vaccine development strategies.

10. Vaccines targeting toxins and proteases

The UPEC pore-forming toxin HlyA has also received attention as a potential vaccine target and was evaluated in a mouse model of pyelonephritis to assess protection against renal damage.[76,77] Vaccination with HlyA reduced the incidence of renal scarring compared with controls; however, it did not protect against UPEC colonization of the kidneys.[77] In addition, in a mouse model of UTI, vaccination with the *P. mirabilis* hemolysinn, HpmA, did not protect against bacterial colonization. However, vaccination with Pta, an alkaline protease with toxic effects on epithelial cells, displayed promising results in a mouse model of UTI, protecting against upper UTI, although bacterial burdens in the bladder remained unaffected. [78] Thus, although haemolysins and proteases might provide effective vaccine targets for preventing upper UTIs, additional studies are needed to determine the effectiveness of these enzymes as targets for vaccines.

11. 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.[79,80] Pathogenic bacteria, including UPEC, have devised ways of accessing iron by producing siderophore-mediated iron transport systems. UPEC exhibits multiple mechanisms for extracting iron from the host, mainly siderophore-siderophore receptor systems, but also heme uptake [81,82] Siderophores, which are secreted low molecular weight molecules, have a high. affinity for ferric (Fe3+) iron, which is insoluble as a free cation. While all E. coli can produce the siderophore enterobactin, the production of alternative siderophores has been shown to increase the virulence of strains causing bacteraemia.[83] Several enter bacteria contain a gene cluster called the high pathogenicity island (HPI), which encodes protected for the biosynthesis of the yersiniabactin siderophore and its uptake system.[84,85] The HPI is widespread among members of the *Enterobacteriaceae* family and is essential for virulence in *Yersinia* and certain pathotypes of E. coli.[84]One of the important genes residing on the fun is fun encoding the 71 kDa outer membrane protein FyuA (ferric siderophore uptake), which act as a receptor for Fe-yersiniabactin uptake. FyuA, which was first described in Yersinia species, is associated with virulence in many members of the Enterobacteriaceae family.[86]

Aerobactic is another important hydroxamate siderophore synthesized from the condensation of two lysine's and one citrate molecule. Successive steps in the biosynthesis of aerobactin are catalysed 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. [87]

Previous studies have shown that the aerobactin system and P fimbriae are commonly found together in UPEC isolates from patients with UTI and urosepsis. [89,90] These observations suggest the association of aerobactin with other VFs differs between plasmid and chromosomal aerobactin. Plasmids carrying the aerobactin region sometimes also carry antimicrobial resistance genes.[89,90] 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.

Finally, UPEC produces salmochelins in order to access iron during the info on o the host. The salmochelin siderophore system, so named because it was first shown to be characteristic of *Salmonella* strains [91], is also present in UPEC. The salmochelin receptor *iro*N may play a dual role as an iron uptake receptor as well as an internalization factor.[83] Using a neonatal rat model, it was shown that *iro*N plays a major role during the bacteremic step of the disease.[92] These findings suggest that *iro*N 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.[93]

12. Biofilm production by UPEC

Bacterial biofilms play an important role in urinary tract infections (UTIs), being responsible for persistent infections causing relapses and acute prostatitis. Bacterial forming biofilm is difficult to eradicate due to the antimicrobial-resistant phenotype that this structure confers being combined therapy recommended for the treatment of biofilm-associated infections.[94, 95, 96]

Curli fibers are thin aggregative surface fibers, connected with adhesion, which bind laminin, fibronectin, plasminogen, human contact phase proteins [97], and major histocompatibility complex (MHC) class I molecules. Curli fibers are coded for by the CSG gene cluster, which is comprised of two divergently transcribed operons. One operon encodes the cage, usage, and CSC genes, while the other encodes used, CsgE, CSF, and can. The assembly of the fibers is unique and involves extracellular self-assembly of the Curli subunit (CsgA), dependent on a specific nucleator protein (CsgB).[98] CBD is a transcriptional activator essential for the expression of the two Curli fiber operons, and CsgG is an outer membrane lipoprotein involved in the extracellular stabilization of CsgA and CsgB. [99]The role of the other CsgG genes has yet to be elucidated. Expression of both curli operons is important for curli fiber assembly. Curli fibers are also essential for the internalization of bacteria during infection.[100]

Co-expressed both biofilm components also harbored fyuA, implying that iron uptake via the yersiniabactin system may play a significant role in biofilm growth.[101] 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. [94, 102]

13. Phylogenetic group and VF distribution among Patient groups and clinical syndromes

The phylogenetic classification of *Escherichia coli* isolates is of great importance not only for understanding the populations of *E. coli* but also for clarifying the relationship between strains and diseases. One categorization of *E. coli* isolates that is frequently determined is the phylogenetic group. *E. coli* strains generally fall into one of four phylogenetic groups—A, B1, B2, and D [103]and early studies using multilocus enzyme electrophoresis (MLEE) indicated that isolates from human feces are not equally distributed between the groups, with group A predominant, whereas among Expect strains, groups B2 and D predominate.[104]A subsequent study using a triplex PCR to determine phylogenetic groups found a predominance of groups A andB1, and it has become common for authors to state that phylogenetic groups A and B1 "predominate" among commensal *E. coli* strains. Most studies quote prevalence rates around 63–65% for group B2 in pathogenic strains, and 10–15% for group D.[105]

Some studies in children showed that pyelonephritis isolates more often belonged to group B2, contained on average higher prevalence 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 [106,107]

In most patient groups, pyelonephritis isolates tend to exhibit the highest prevalence 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 a 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 [108,109] PapiniII has been shown, experimentally, to contribute to the o pathogenesis of pyelonephritis, and OmpT is strongly associated with febrile UTI in men. [110,111]

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 behaviour in UPEC.[112] 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.

14. 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 54 *Escherichia coli* - Recent Advances on Physiology, Pathogenesis and Biotechnological Applications (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 [113]. Studies have demonstrated that certain VFs commonly occur together, in a way that suggests co-selection or direct genetic linkage.[114,115] Direct genetic linkage of VFs has been shown on PAIs and plasmids. [116,117]

15. Antimicrobial drug and Uropathogenic E.coli

Urinary tract infections (UTIs) belong to the most common community-acquired and nosocomial infections. A main etiological factor of UTIs is Uropathogenic *Escherichia coli* (UPEC). [118,119]Although TMP-SMX has traditionally been used as a first-line treatment for UTIs [120], there are reports of increased resistance to this antibiotic, which in some countries is in the range of 15–20%.[121] Nitrofurantoin and fosfomycin are recommended as first-line therapy in the treatment of uncomplicated cystitis, and the resistance to these antimicrobial agents remains low between UPEC[122], 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.[123]

16. UTI during pregnancy

The prevalence of symptomatic and asymptomatic bacteriuria among women during pregnancy is very common and the previous history of the infection is a major risk factor.[124] Pregnant women easily develop urinary tract infections (UTIs) because of functional, hormonal, and anatomical changes and also because of the location of the urethral meatus, which allows Uropathogenic bacteria (found in rectal ¯ora) access from the vagina to the lower urinary tract. *Escherichia coli* are the pathogen most frequently isolated in UTIs during pregnancy.[125]The relationship between asymptomatic bacteriuria, preterm delivery, and birth has been well documented. Up to 27% of preterm births have been associated with clinical forms of UTI. However, the pathogenesis of the uterine contraction responsible for preterm labour is not clear. The current treatment for acute pyelonephritis in pregnancy presents problems because of its high resistance to ampicillin, and on a minor scale, to regenerations cephalosporin. Bacterial resistance is the principal cause of failure in antibiotic treatment. It is not well known that lower genital tract infection can impudence this failure.[126] This article briefly examines the risk factors, the microbiology the virulence factors and the usual resistance of Uropathogenic E. *coli* to common antibiotics in UTIs during pregnancy. It analyses the diagnosis and treatment of bacteriuria and acute pyelonephritis, *group B streptococcal* (GBS) infection and recurrent UTI. In particular, it analyses the pathogenesis of preterm labour associated with UTIs.[127]

In females, the urinary tract has a significant affiliation with reproductive organs due to its propinquity. The position of the uterus plays a vital role in conferring the infection. The uterus lies above the bladder in the non-pregnant state and the enlargement of the uterus during pregnancy negatively influences the tissues of the urinary tract.[128] The infection can be diagnosed by isolating the urinary pathogen from the patient. Researchers have reported that the occurrence of the infection during pregnancy may be related to the socioeconomic status of the patient as the indigent group was more prone to the infection.[129] The occurrence of bacteriuria among the non-indigent was found to be 2% compared to 6.5n in the indigent population.[130]Factors like history of the a previous infection, diabetes, and physiological aberrations of the urinary tract also signify the infection.[131]The

pathogens responsible for conferring the infection are similar are pregnant and non.[132] *E. coli* accounts for 80% of the infection and the presence of pili allows the pathogen to attach to the uroepithelial cells and results in tissue invasion.[133]Untreated infection during pregnancy can lead to premature labour which can be fatal to the new-born infant.[134] Babies are considered to be premature if they are born before the 37th week of the pregnancy and this enhances the scope of infection in new born babies. In severe cases preterm delivery can also result in abortion leading to infant death.

17. Emergence of resistance among UTI pathogens

Studies to validate the fact of growing resistance among UTI-causing pathogens have been going on for the last three decades and the available data and reports confirm that the increase in resistance to commonly employed antibiotics is a consequence of inappropriate use of the antimicrobial agent The existence of Gram-negative bacteria exhibiting multidrug resistance among the pregnant women and the extent of antimicrobial resilience among these pathogens has become an issue of concern. Treatment of asymptomatic bacteriuria among elderly and non-pregnant women does not seem to be beneficial but they insist on a prior screening process of the condition before the employment of the antimicrobial agents.[135] However, the extent of antimicrobial resistance shown by the pathogens towards the commonly employed drugs is an issue of global concern and this antimicrobial pattern exhibited by the pathogens varies according to the factors like the site of their isolation, environmental conditions as well as the stage of the infection. This is an indication of the development of surfacing resistance among major pathogens conferring UTI and has made them resilient to the commonly employed antimicrobial agents. Despite the fact of its affectivity, *Proteus* species and *Enterobacter* species are resistant to nitrofurantoin. A Gram-negative bacterium, their study has demonstrated the least activity of trimethoprim against *E. coli* and has substantiated the use of trimethoprim in empirical treatment. Even though the occurrence of UTI is a consequence of *E. coli* infection which accounts for 80%, the involvement of other pathogens cannot be denied. Demographic parameters like maternal, gestational age, gravidity, parity, socioeconomic condition, n, and previous history of the infection can be vital and signifies the infection.[136] However some research studies feel that other pathogens of *Staphylococcal* genus are mistaken to be *S. aureus* but the other species of the genus are capable of causing the infection.[137,138]*S. aureus* colonization among women during pregnancy enhances the rate of morbidity and mortality.[139] The resistance of *S. aureus* against fluoroquinolones such as *ciprofloxacin*, *ofloxacin ,* and *norfloxacin* is a consequence of empirical treatment.

18. E.coli Sequence type 131(ST131)

Multidrug-resistant E. coli sequence type 131 (ST131) has emerged over the past decade as a globally disseminated cause of extra intestinal infections in humans and animals.[140–141] 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. 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.[142, 143] This is consistent with increased neurovirulence and provides epidemiological evidence of increased virulence for ST131, which has been presumed but without evidence from experimental animal models.[144] The antibiotic resistance advantage, in combination with the possible presence of enhanced virulence, could explain the recent worldwide emergence of ST131.

Four VF genes (out, promptness, 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 type O16 is [145]

Resistance of ST131 to extended-spectrum cephalosporins is often due to the 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. [146]

19. Treatment of UTI

Urinary tract infections (UTIs) caused by antibiotic-resistant Gram-negative bacteria are a growing concern due to limited treatment options. Treatment oral options for UTIs due to ESBLs-*E.coli* include nitrofurantoin, fosfomycin, pivmecillinam, amoxicillin-clavulanate, finafloxacin, and sitafloxacin while pivmecillinam, fosfomycin, finafloxacin, and sitafloxacin are treatment oral options for ESBLs- *Klebsiella pneumonia*. Treatment options for UTIs caused by multidrug-resistant (MDR)-*Pseudomonas* spp. include fluoroquinolones, ceftazidime, cefepime, piperacillin-tazobactam, Carbapenems including imipenem-cilastatin/sulbactam, meropenem, and fosfomycin, ceftolozane-tazobactam, ceftazidime-avibactam, aminoglycosides including plazomicin, Aztreonam and ceftazidime-avibactam, cefiderocol, and colistin. It is important to use the new antimicrobials wisely for the treatment of UTIs caused by MDR-organisms to avoid resistance development.

20. Conclusion

Uropathogenic Escherichia coli infections pose a serious problem to human health, with societal costs of tens of billion US$ worldwide. Direct strategies are targeting bacteria viability, bladder epithelium adhesion, and biofilm formation; indirect strategies elicit and enhance immune responses, by stimulating infected tissues and cells to overreact to UPEC invasion. A wide range of UPEC VFs has 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 multiplied determined. 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 behaviour in UPEC. An increasing body of evidence shows that the reduction of adhesion of UPEC to urinary tract tissues reduces recurrence and increases recovery. Future interesting targets might not only be directed to UPEC adhesins, but also to immune-based strategies able to improve cell responses to UPEC infection; in this context, several natural products fit this strategy.

21. References

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