Vol 5| Issue 3| 2015 | 163-169.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

URINARY TRACT INFECTIONS: ETIOLOGY AND MANAGEMENT

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ABSTRACT

Urinary tract infection (UTI) is the second most type of infection in the body. There are estimated 150 million UTIs per year worldwide. Urinary tract bacterial infections are common in women because they have a shorter urethra than men. UTIs are the most common bacterial infections affecting humans throughout their lifespan. The clinical symptoms of UTI usually include dysuria, pyuria, abdominal pain, back pain, fever or urgency. But none of these symptoms alone is sufficient to establish UTI diagnosis in human. UTIs encompass a spectrum of clinical entities ranging in severity from asymptomatic infection to acute cystitis, prostatitis, pyelonephritis and urethritis. The most common cause of UTI is a gram-negative bacteria that belong to the family Enterobacteriaceae. *E. coli* is one of the most common bacteria capable of causing infection in humans, particularly UTIs. The antibiotics were usually prescribed for its treatment. Antibiotic therapy in recent years has faced difficulties due to the rapid emergence of multidrug resistance among bacteria causing several life threatening infections and this in turn, making the future management of infectious diseases uncertain. Thus it necessitates the understanding of the etiology of urinary tract infections and searching for medicinal plant therapy.

Key words: Urinary tract infections, Etiology, *E. coli*, Antibiotic therapy, Enterobacteriaceae.

INTRODUCTION

Urinary tract infections (UTI) are one of the most common types of bacterial infections in humans occurring both in the community and the health care settings and ranks high amongst the common reasons that compel an individual to seek medical attention [1-4]. UTI is a term applied to a variety of clinical conditions ranging from asymptomatic presence of bacteria in the urine to severe infection in the kidney with resultant sepsis [5]. UTIs are a serious health problem affecting millions of people each year. Infections of the urinary tract are the second most common type of infection in the body. These are one of the most common bacterial infections affecting humans throughout their lifespan.

UTIs account for more than 8 million visits to physician's offices, 1.5 million emergency room visits, and 3,00,000 hospitals admissions in the United States annually [6]. UTIs are the second most common infection of any organ system and the most common urological disease in the United States, with a total annual cost of more than $3.5 billion [7]. These infections are more common in females than in males. Incidence of women in the of 20-40 years ranges from 25-30% whereas, in older women above 60 years of age it ranges from 40-43% [8].

UTIs can be classified as complicated or uncomplicated. It represents one of the most common diseases encountered in medical practice today, affecting people of all ages, from the neonate to the geriatric age group [9]. Most infections are caused by

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retrograde ascent of bacteria from the fecal flora via the urethra to the bladder and kidney especially in the females who have a shorter and a wider urethra is more readily transversed by microorganisms. The structure of the female urethra and vagina makes it susceptible to trauma during sexual intercourse as well bacteria being massaged up the urethra and into the bladder during pregnancy and/or child birth .

UTIs are categorized into either lower tract infection, located in the bladder and/or urethra (Cystitis and urethritis), and upper tract infection, located in the ureters, collecting system and parenchyma. It is necessary to understand the difference between the two types to make an accurate diagnosis. Cystitis is define as an inflammatory condition of the urinary bladder whereas, pyelonephritis is define as a diffuse pyogenic infection of the pelvis and parenchyma of the kidney. Signs and symptoms of cystitis include dysuria frequency, urgency, malodorous urine, enuresis, hemateuria, and suprapubic pain. On the other hand the signs and symptoms of pyelonephritis include fever over 38.5˚c, chills along width costo-vertebral angle or flank pain and tenderness with pyuria and positive urine culture.

UTI symptoms include abdominal pain, back pain, dysuria, frequency, new-onset incontinence, but none of these symptoms alone is sufficient to establish UTI diagnosis in human. The infection can further be classified as complicated or uncomplicated infection. When a UTI occurs in a healthy person with a normal, unobstructed urinary tract, the term uncomplicated is used. Most women have uncomplicated UTIs which can be cured within 2-3 days of treatment. Complicated UTIs occur when a person, for example, a pregnant woman or a transplant patient is weakened by another condition. A UTI is also complicated when the person have a structural or functional abnormality of the urinary tract, such as obstructive kidney stone or prostate enlargement that squeezes the urethra.

UTIs are the most common bacterial infection seen during pregnancy. Asymptomatic bacteriuria is found in 4-10% of pregnant women. Women with a history of UTI have an increased risk for UTI during pregnancy. Pyelonephritis during the third trimester may lead to foetal death or infants born with mental retardation, development delays, or cerebral palsy [10]. Approximately 11-25% of elderly non-institutionalized patients not undergoing catheterization acquire asymptomatic bacteriuria, and about 10% developed symptomatic bacterial UTIs [11].

Causes of urinary tract infections

Catheterization of the urinary tract is one of the most common factor which predisposes the host to complicated UTIs [12]. Catheters interfere with the body's ability to clear microbes from urinary tract. Bacteria travel through or around catheter and establish a place where they can thrive within the bladder. Instillation of catheter may lead to damage of mucosal layer, which disrupts the natural barrier and allows bacterial colonization. The recognized predisposing factors in complicated UTIs are anatomic defects, vesicoureteral reflux (UVR), obstruction, surgery, metabolic diseases like diabetes mellitus and generalized immunosuppression specialy in patient of organ transplant [13-15].

Organism can gain entry *via* extraluminal route by moving across the outer lumen of catheter or by intraluminal route by directly entering the interior of catheter [16]. Catheter-associated UTI (CAUTI) is responsible for 40% of nosocomical infection. CAUTI accounts for more than 1 million cases in hospitals and nursing homes annually and often involves uropathogens other than *E. coli*. The Infectious Diseases Society of America recoments using catheters for the shortest time possible to reduce the risk of a UTI.

The organism most commonly responsible for catheter-associated UTIs are *E. coli*, *Proteus mirabilis*, *Pseudomonas aeuroginosa*, *Klebsiella pneumonia* and *Sreptococcus faeclis* [17]. In case of *E. coli*, the epidemiological, experimental and clinical studies have established the role of multiple virulence factor of *E. coli* like adhesions operative through type-I fimbriae and P fimbriae, O serotypes, K1 capsule, serume resistance hemolysins, cytotoxics necrotizing factors (CNF) and siderophores (enterochelin and aerobactin) in relation to uncomplicated and complicated UTIs [18].

Another cause of UTI is waiting too long to urinate. The bladder is a muscle that stretches to hold urine and contracts when the urine is released. Waiting too long past the time to urinate can cause the bladder to stretch beyond its capacity and overtime this can weaken the bladder muscle, and it may not empty completely and some urine is left in the bladder which increases the risk of UTI or bladder infection.

Etiology of urinary tract infections

Most of the urinary tract infections are caused by gram-negative bacteria like *E. coli*, *Klebsiella sp.*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Acinobacter and Serratia.* 90% of UTI cases are caused by gram(-ve) bacteria while only 10% of the cases are caused by gram-positive bacteria. The most common etological agent of uncomplicated UTI is *E. coli*, which is present in about 80-90% of cases [19]. Gram-positive bacteria include *Enterococcus*, *Staphylococcus and Streptococcus.*

E. coli are the most common gram-negative bacteria responsible for UTI. A Study reported the prevalence of *E. coli* (47%) followed by *Proteus mirabilis* (7%), *Enterococcus faecalis* (6%) and *K. pneumonia* (5%) in 13,774 samples of patients having community-acquired UTI. *P. aeruginosa* is the third most common pathogen associated with hospital-acquired catheter associated UTIs [20]. *Staphylococcus saprophyticus* causes 10-20% infection in young adults. Other members of Enterobacteriacieae, such as, *Klebsiella, Enterobacter, proteus* and rarely *Salmonella and Shigella* also constitute etiology of uncomplicated UTIs.

At least 80% of the uncomplicated cystitis and pyelonephritis are due to *E. coli*, whereas, *Proteus mirabilis and K. pneumonia* infections account 10% and 6% respectively. 78% of community acquired UTI are due to *E. coli* and 12% by *Klebsiella*; whereas, in hospital-acquired UTI 65% are caused by *E. coli* and other pathogens including *Pseudomonas.* Most UTIs in children are monomicrobic, often caused by *E. coli* (60-80% of cases), *Proteus, Klebsiella, Enterococcus* and coagulase negative *Stapylococci.*

The complicated infection occurs in individuals of both sexes, who have either structural abnormalities of the voiding mechanism, prostatic calculi or underlying diseases that predispose the kidneyto infection. The underlying diseases include diabetes mellitus, sickle cell anemia, and polycystics real disease. Complicated infection may also occur in recipients of renal transplants. The infection is also usually associated with indwelling catheters or other draining devices. The main causative organisms are *E. coli,* (21-54%) *Klebsiella, Proteus* and *Pseudomonas.* Coagulase negative *Sreptococci*, group B and group D *Sreptococci*, *Mycobacteria,* some viruses and yeasts can also be isolated from complicated UTI patients. *Nocardia asteroids, Oligella urethritis* and *Mycobacterium terrae* have also been reported recently in patients with structural abnormalities of Urinary tract. Occasionally non-typhoidal *Salmonella* can also cause complicated UTI.

Virulence factors of uropathogens

Uropathogens possess a wide spectrum of virulence factors. *P. aeruginosa* possesses a multitude of virulence factors. Virulence of *P.aeruginosa* is multifactorial and has been attributed to cell-associated factors like alginate, lipopolysaccharide (LPS), flagellum, pilus and npo-pilusadhesins as well as with exoenzymes or secretory virulence factor like protease, phospholipase, elastase, pyocyanin, exotoxin A, exoenzyme S, hemolysins (rhamnolipids) and siderophores [21, 22].

These factors have been shown to play an important role in pathogenesis of *P. aeruginosa* and included infections like respiratory tract infections, burn wound infections and keratitis . However, limited reports are available role of these virulence trait in urinary tract infections.

Wood showed high production of elastase and protease in strains isolated from urinary tract infection in comparison to isolates from other infection like burn wounds infection, skin wounds infection and acute pneumonia [23]. Quantitative analysis of elastase, phospholipase C, toxin A, and exoenzymes S was assessed in *P. aeruginosa* isolated from wound infections, respiratory tract infections and urinary tract infection by [24]. It was observed that most of the isolates produces all the four virulence traits. However, depending on infection site, the isolates produced varied levels of these virulence determinants. It was observed that persistent infection isolates from different sites produces significantly higher levels of exoenzymes S. these worker conclude that elastase, phospholipase C, toxin A, and exoenzymes S are important virulence traits which help *P. aeruginosa* to cause a variety of persistent infections. The uropathogenic strains of *P. Aeruginosa* produces atleast one type of siderophore i.e. pyochelin and/or pyoverdin. However, all the uropathogenic strains do not produce both siderophores.

E. coli is the most common causative agents of recurrent, uncomplicated urinary tract infections. Triplex PCR and the disc diffusion method were used to determined and correlate among the phylogenetic group, virulence determinants and antimicrobial resistance in 100 uropathogens. Group B2 represented 58% of the tested isolated with no isolates belonging to group B1. Isolates with the highest percentage of susceptibility to all antimicrobial agents used were within the B2 phylogenetic groups. 38% of the tested population were resistant to trimethoprim, 29% to ciprofloxacin and only 8% to nitrofurantoin. The majority of the isolates resistant to trimethoprim were from group B2 (52.7%), with 45% being positive to the three tested virulence determinants (efu, fbp and picU). These findings suggest that although virulence and antimicrobial resistance are mutually exclusive in *E. coli* clinical isolates, the relationship between virulence and resistance to antimicrobial agents can vary according to the particular resistance phenotype.

It was suggested that besides considering levels of all extracellular enzymes, high levels of hemolysis production *in vitro* could be used as surrogate information for assessing pyelonephritic potential of *P. aeruginosa.* In addition to virulence factor, *P. aeruginosa* has a tendency to form biofilms on the surface of urinary catheters. Growth of *P. aeruginosa* begins in the form of microcolonies, which latr coalesce together to form biofilms. Alginate which is an acetylated polymer of beta-D-mannouronic acid and alpha-L-guluronicacids, is the most important component *of P. aeruginosa* biofilms. However some other exopolysaccharides like ps1 and pe1 have also been shown to play an important role in biofilm forming ability of non-alginate producing strains of *P. aeruginosa.* Ps1 is a mannose-rich and galactose-rich polysaccharide however, the precise ps1 structure has not been elucidated. This is an area requiring future research. As with Ps1, the Pe1 structure is unknown and further biochemical analysis of Pe1 polysaccharide is necessary.

Biofilms are resistance to antimicrobial as well as to host defense mechanisms and hence are difficult to eradicate. Biofilms contribute towards pathogenicity of *P. aeruginosa* as these often lead to persistent and recurrent infections. Once an opportunistic pathogen like *P. aeruginosa* enters the host, its ability to cause infection has been correlated with its tendency to form biofilms.

P. aeruginosa has an innate propensity to stick to the surface of catheters and form biofilms leading to higher incidence of UTIs in patients with long-term indwelling bladder catheterization. In addition, previous microbial urethral colonization could be the cause of most UTIs where introduction of bacteria into the bladder takes place subsequently at the time of catherization [20]. Besides disruption of normal valvular function of urethra, catheters, can also traumatize urethral and bladder mucosa, hence disrupting the normal mucopolysaccharide coating of the epithelium [25]. This damage of cellular structure renders it susceptible to attachment as well as entry of bacteria through surface erosions. Therefore, catheters serve as a direct conduit for pathogens which may be carried from the external meatus to the bladder when the catheters is introduced.

The pathogenesis of catheter-associated UTIs to the production of biofilms by the infecting organisms was related in which bacterial population adhere to catheter surface through pili and/or exopolysaccharides. The organisms are able to persist in host’s tissue for longer duration and are able to cause continues damage to the host. *In vivo* biofilm formation where colonizing bacterial population was observed embedded in glycocalyx on the external and internal surfaces of Foley’s catheter removed from patient.

The nature of biofilms formed in urease producing and non-urease producing organisms have been compared. It was observed that urease producing organisms, *P. mirabilis, Proteus vulgaris, and Providencia rettgeri* formed crystalline nature of biofilms whereas, urease negative bacteria, *Morganella morganii*, *Klebsiella pneumonia* and *P. Aeruginosa* producing non-crystalline biofilms on urethral catheter.

Iron-limiting conditions have been reported to be prevalent in the milieu of urinary tract, therefore, the ability of uropathogens to sequester iron from the host becomes a significant factor in determining their growth, metabolic process, and pathogenicity. A comparison of adhesion of three uropathogens to Tamm-Horsfall protein (THP) coated renal tubular cells in-vitro, also stressed that THP may not help to remove all uropathogens from urinary tract. In the milieu of the kidney where THP is available in abundance, these observation have immense relevance. Once *P.aeruginosa* reaches renal parenchyma, this ability may help this organism to colonize, get established and persist. Further, in vivo studies using THP knock-out mice are warranted which can shed more light on the precise role of THP in *P. aeruginosa* induced UTIs.

UTIs activate both mucosal and systemic inflammatory responses in which cytokines play a pivotal role [26]. Cytokines both pro-inflammatory and anti-inflammatory, have been reported to produce largely by macrophages. In addition, wide variety of cells including lymphocytes, endothelial cells, pulmonary epithelial cells, and urinary tract epithelial cells produce these cytokines in response to bacteria or their products like lipopolysaccharide (LSP) and fimbriae [20]. Virulence factor expression is more common among certain genetically related groups of *E. coli* which constitute virulence factors a strain expresses, the more severe an infection an infection it is able to cause. Immunological and biochemical anti-virulence factors interventions are effective in animal models of UTI and hold promise for the prevention of UTI and in humans [27].

Treatment of urinary tract infections

Antibiotic therapy rapid in recent years has faced difficulties due to emergence of multidrug resistance among bacteria causing several life threatening infections and this in turn, making the future management of infectious diseases uncertain. The increasing failure of chemotherapeutics, unsatisfactory therapeutic options in recurrent urinary tract infection (RUTI), antibiotic resistance exhibited by pathogenic microbial infectious agents and the spiraling cost of antibiotic therapy has led to the screening of several medicinal plant for potencial antimicrobial activity. One promising alternative is the use of live microorganisms (probiotics) to prevent and treat recurrent complicated and uncomplicated UTI [19].

Nature has been a source of medicinal agents for thousands of years and use of medicinal plants, especially in traditional medicine, is currently well acknowledged and established [28]. Down the ages, spices have evoked interest as sources of natural products fort their potential uses as alternative remedies to heal many infectious disease (Parekh *et al.*, 2005). Spices are the common dietary adjuncts that contribute to the taste and flavour of foods as well as are recognized to stabilize the foods from the microbial deterioration [29]. Several scientific reports have described the inhibitory effect of spices on a variety of microorganisms, although considerable variation for resistance of different microorganisms to a given spices and of the same microorganisms to different spices has been observed [30].

Spices are rich source of biologically active antimicrobial compounds. The gram-positive bacterial strains are more sensitive to the antimicrobial compound of spices than gram negative bacteria [31-33]. The extent of antimicrobial activity of spices depend on several factor which include kind of spices, composition and concentration of spices, microbial spices and its occurrence level, substrate composition and processing conditions and storage.

Saeed and Tariq investigated the potential of using aqueous infusion, decocation and essential oil of clove (*Syzygium aromaticum*) as natural antibacterial agents against 100 isolates belonging to 10 different spices of gram-negative bacilli viz., *E. coli* , *Proteus mirabilis* (6), *Pseudomonas aeruginosa* (10), *Enterobacter aerogenes* (5), *Klebsiella pneumoniae* (24), *Serratia marcescens* (4), *Salmonella typhi* (3), *Shigella dysentriae* (5), *Vibrio cholorae* (5). The screening was performed by standard disc diffusion method. The aqueous infusion and decocation of clove exhibited maximum activity against *P. Aeruginosa* (10.43mm and 10.86mm) whereas, the essential oil of clove exhibitd maximum activity against *V. chlorae* (23.75mm).*K. ozaenae, K. pneumoniae, S. marcescens, S. typhi, S. dysentriae and V. chlorae* were found resistant to aqueous infusion and decocation while essential oil showed strong antibacterial activity against all bacterial isolates tested.

Durairaj [34] evaluated the antibacterial effects of aqueous garlic extract (AGE) against 17 multidrug resistant gram positive and gram-negative bacterial isolates including *Staphylococcuc aureus, Pseudomonas aeruginosa, Salmonella typhii, Escherichia coli* and *Proteus* sp. by agar well diffusion assay. Antibacterial activity of different concentrations of AGE was characterized by inhibition zones of 15 gram-positive and 2 gram-negative pathogenic bacteria. All test organisms were inhibited by AGE up to 25% concentration and the activity was a linear function of concentration. At 100% concentration, the maximum zone of inhibition was observed in *Bacillus subtilis* (54mm) and the minimum was observed for *Proteus mirabilis* (22mm).

Sharma [35] evaluated seventeen Indian folklore medicinal plants for their antibacterial activity. The aqueous, ethanol and acetone extracts of the seventeen plants were investigated against 66 multidrug resistant isolates of major urinary tract pathogens (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Enterococcus faecalis*) by disc diffusion method. Ethanol extract of *Zingiber officinale* and *Punicagranatum* showed strong antibacterial activity against *Escherichia coli.* Ethanol extracts of *Terminalia chebula* and *Ocimum sanctum* exhibited antibacterial activity against *Klebsiella pneumoniae*. Ethanol extract of *Cinnamomum cassia* showed maximum antibacterial activity against *Pseudomonas aeruginosa* while ethanol extract of *Azadirachta indica* and *Ocimum sanctum* exhibited antibacterial activity against *Enterococcus faecalis*.

Al- Jiffri [36] evaluated the antibacterial activities of natural extracts against pathogenic *E. coli* causing urinary tract infections. A total 130 urine samples was collected from patients examined for urinary tract infection. Ciprofloxacin, levofloxacin and norfloxacin were the best antibiotics used against *E. coli* isolates. Clove, ginger (dry, fresh), peppermint, spearmint and thyme alcoholic extracts were the most effective plant extracts against selected isolates of *E. coli.* It was concluded that combination between clove alcoholic extract and antibiotics as gentamicin, levofloxacin, amikacin and norfloxacin increase the synergistic effect of antibiotics against selected *E. coli* isolates.

Saleem [37] reported that urinary tract infection is a common infection prevalent among patients with diabetes. Diabetes raises a risk of UTI as a consequence of malfunctioned gentito urinary tract. The growing concern associated with the management of UTI in diabetic patients is the multidrug resistance in Uropathogens to conventional antibacterial therapy. Recent changing trends in antimicrobial resistance demands quick alternative regime for the control of frequent UTI in patients with Diabetes Mellitus. In this prospective study it investigated that turmeric shows good antimicrobial efficacy on various multi resistant UTI pathogens of *Pseudomonas aeruginosa*, Methicillin resistant *S. aureus* (MRSA), Vancomycin resistant *Enterococcus faecalis* (VRE) and *E. coli.*

Sethi [38] investigated that antimicrobial activity of three medicinal plants (*Murraya*, *Azadirachta*, and *Ocimum*) on Urinary tract pathogens. The methanolic extracts of leaf of all three medicinal plants were the potent antimicrobial agent than ethanolic extract. Methanolic extract of all the three plants inhibited the growth of *Kliebsiella*, *Escherichia* and *Serratia* while the ethanolic extract inhibited less. The highest antibacterial activity was found against *Escherichia* with methanolic extract of Leaf and Bark of *Murraya* and Leaf extract of *Azadirachta*. Bark extract of *Azadirachta* showed highest inhibitory activity against *Serratia* with methanolic extract and least with *Escherichia*. *Ocimum* leaf extract possess maximum antibacterial activity against *Serratia* with methanolic extract and least with *Kleibsiella.*

Escherichia was found to be most sensitive than *Kleibsiella* and *Serratia*. The highest antibacterial activity was found against all the Urinary tract pathogens with methanolic extract of leaf and bark of *Murraya*.

Kumar *et al.* [39] investigated the antibacterial activity of some medicinal plants used against UTI causing pathogens. Bacteria were isolate from the UTI infected patient and characterized by using microscopic, staining, morphological and biochemical methods. Oils from plants were extracted using Clevenger and these oils were than used to check their antibacterial activity against the bacteria isolated from UTI infected patients and the zone of inhibition were compared with the zone of inhibition of standard antibiotics. Results from the present study showed that ajwain oil had more antibacterial activity compared to other oils we used and Fennel oil had lowest antibacterial activity.

Sharma *et al.* [40] investigated *in vitro* antibacterial activity of seven ethanolic extracts of spices against the clinical isolates of enterococci. Ethanolic extracts of Cumin *(Cuminumcyminum*), Cinnamon (*Cinnamomum zeylanicum*), Ginger (*Zingiber officinale*), Fenugreek (*Trigonella foenum graecum*), Cloves (*Syzygium aromaticum*), Cardamom (*Elettaria cardamomum* Maton) and Black pepper (*Piper nigrum*) were prepared. The antibacterial effect of the extracts was studied using well diffusion method. Cinnamon and ginger were found to have activity against all the isolates whereas Cumin and cloves had varied effect on the strains. Fenugreek, black pepper and cardamom did not show any effect on the isolates. It was concluded that cinnamon and ginger showed the maximum antibacterial activity against the enterococcal isolates followed by clove and cumin.

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