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URINARY TRACT INFECTIONS IN FEMALES: A REVIEW

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ABSTRACT

Urinary tract infections (UTIs) are common bacterial infections particularly in females. UTIs can be classified by anatomic site of involvement into lower and upper urinary tract infections. UTIs can also be divided into two major categories, uncomplicated and complicated. UTIs include a variety of clinical conditions such as urethritis, cystitis, pyelonephritis etc. The main symptoms of UTIs include urgency, increased frequency, pain on urination and a foul odor of urine. The microbial etiology of UTIs is reasonably consistent. *E.coli* remains the predominant uropathogen followed by *S.saprophyticus, Klebsiella pneumoniae,* Enterobacter, Proteus and Enterococcus species. Age of the patient, diabetes, catheterization, pregnancy, menopause, sexual intercourse, renal calculi, and tumors etc are the main predisposing factors for UTIs in women. For the diagnosis of UTI, the counting of number of bacteria and white blood cells in urine specimen has been accepted as a routine procedure. The bacterial count of $>10^5$ CFU/ml of clean voided, midstream urine specimen is considered as significant bacteriuria while clinically significant pyuria has been defined as $>10^6$ leucocytes per liter of urine. For the treatment of UTI, fluoroquinolones, sulfonamides, cephalosporins, nitrofurantoin and fosfomycin are the most common antibiotics.

Key words: Urinary tract infections, pyelonephritis, cystitis, *E.coli*,

INTRODUCTION

Urinary tract infection (UTI) is a most common health problem, affecting millions of people each year (Kristen, 2004). The urinary tract is the most common site of bacterial infection, especially in females and cause significant morbidity.(Ribeiro *et al.*, 2002).

Urinary tract infections include a variety of clinical conditions. These include urethritis (inflammation of urethra), cystitis (inflammation of bladder), as well as acute and chronic pyelonephritis (inflammation of kidney), bacteraemia (microorganisms in blood), and sepsis (a severe illness usually with bateraemia and characterized by fever, fall in blood pressure and confusion). The main symptoms of urethritis and cystitis include urgency, increased frequency, pain on urination, bladder pressure and a foul odor of urine. The urine may be bloody and cloudy. Pyelonephritis is characterized by flank pain or tenderness just below ribs (costo-vertebral or Loin pain), fever and chills. Sign and symptomps of cystitis may be present (Mims *et al.*, 1995).

TYPES OF URINARY TRACT INFECTIONS

Urinary tract infections can be classified by anatomic site of involvement into lower and upper UTIs. Infections of the lower urinary tract include cystitis and those of the upper urinary tract include pyelonephritis (Mims *et al.*, 1995). Urinary tract infections can also be divided into two major catagories, uncomplicated and complicated. Uncomplicated UTIs usually occur in urinary tract that is functionally and structurally normal, while complicated UTIs occur in patients who have structurally or functionally abnormal urinary tract. The patients with complicated UTIs can be exceedingly difficult to treat (Jancel and Dudas, 2002). In females, the number of patients aged less than 20 years is few. Complicated UTIs without indwelling catheter are the most frequent among female patients aged between 40 to 59 years. In other age groups, uncomplicated UTIs are most frequent (Kumamoto *et al.*, 2001).

PREDISPOSING FACTORS

A number of predisposing factors render individuals susceptible to UTIs (Mims *et al.*, 1995). Any thing that disrupts normal urine flow or complete emptying of bladder, or facilitate access of organisms to the bladder, will predispose an individual to infection (Jackson *et al.*, 2000). For example, pregnancy acts as a risk factor for UTI as it causes anatomic and hormonal changes which favour development of UTI. The physiological changes associated with pregnancy are the relaxation of ureter under the effect of hormon and increase urinary output. The chemical composition of urine is also affected and results in increased urinary contraction of substances e.g. glucose and amino acids, which may facilitate bacterial growth (Sheikh *et al.*, 2000). Furthermore, pregnant women with kidney infection have a greater chance of delivering their babies prematurely with low weight (Santos *et al.*, 2002 ; Kristen,

2004). Sometimes, it results in fetal and maternal morbidity (Santos *et al.*, 2002). Postmenopausal women are also susceptible to UTI due to lack of estrogen, which plays important role in pathogenesis (Hu *et al.*, 2004).

Sexual intercourse is also a common cause of UTIs because during sexual intercourse bacteria in the vaginal area could be messaged into the urethra. This problem can be avoided by urinating after sexual intercourse (Cornforth, 2002). Women who change sexual partners or have sexual intercourse more frequently may experience more frequent bladder infections (Fihn, 2003).

Several studies have shown that women who use a diaphragm are more likely to develop UTIs than women who use other forms of birth control. More recently, investigators have demonstrated that women whose life partners use a condom with spermicidal foam also tend to have growth of *E.coli* in the vagina (Jancel and Dudas, 2002).

Renal calculi, tumors, and stricture of any sort are also the main predisposing factors. All these factors cause obstruction to complete emptying of bladder (Mims *et al.*, 1995). Urological complications after renal transplantation are also frequently associated with UTIs (Lyerova *et al.*, 2001).

Another common source of infection is catheter or tube placed in the bladder (Orrett and Shurland, 2001). Bacteria on the outside of the catheter can climb up the device into the bladder and cause infection (Pawelczyk *et al.*, 2002). Infection associated with an indwelling catheter is a representative type of biofilm infection occurring in the urinary tract (Evans *et al.*, 2001). These infections are rarely symptomatic and infrequently cause blood stream infection (Tambyah and Maki, 2000). UTI is also the most frequent medical complication in patients with neurologic bladder dysfunction leading to high morbidity, poor quality of life and limited life expectancy (Matsumoto *et al.*, 2001).

Certain diseases also predisposes UTIs e.g. HIV infection (Padoveze *et al.*, 2002). Asymptomatic bacteriuria (ASB). UTIs occur more frequently in women with diabetes mellitus than women without diabetes mellitus because of the changes in the immune system secondary to the high sugar concentration (Geerlings *et al.*, 2002). However, gestational diabetes mellitus is not associated with increased risk of UTIs (Rizk *et al.*, 2001). Although asymptomatic bacteriuria is not associated with serious health outcomes in healthy persons, further research needs to be undertaken regarding the impact of asymptomatic bacteriuria in patients with diabetes (Geerlings *et al.*, 2002). Moreover, the use of calcium supplements also increases the risk of UTI, since calcium ions significantly increases bacterial adherence to uroepithelial cells (Apicella and Sobota, 1990).

Women are especially prone to UTIs probably because of the shortness of urethra and closer to anus. The study has also shown that women with UTIs tend to have certain blood types (Jackson *et al.*, 2000). The presence or absence of blood group determinants on the surface of uroepithelial cells may influence an individual's susceptibility to UTI. (Schaeffer *et al.*, 2001). Besides, severe protein malnutrition, poor fluid intake, and poor hygiene result in decrease immunity (e.g. cancer) and, thus, are also associated with UTIs (Gerberding, 2002).

CAUSATIVE AGENTS

UTIs may be caused by bacteria, viruses, fungi, protozoa and a variety of other parasites (Mims *et al.*, 1995) Bacterial UTIs are usually acquired by the ascending route from the urethra to the bladder or may extend to kidney (*Collier et al.*, 1998). The common gram negative microorganisms causing UTIs are *Escherichia coli* (Moore *et al.*, 2002; Sader *et al.*, 2005), Enterobacter (Honkinen *et al.*, 1999), *Klebsiella pneumoniae* (Honkinen *et al.*, 1999 ; Lavanya and Jogalakshmi, 2002), *Klebsiella aerogenes* (Lavanya and Jogalakshmi, 2002), *Proteus mirabilis* (Honkinen *et al.*, 1999 ; Mohanty *et al.*, 2003), *Proteus vulgaris* , *Serratia marcescens*, *Pseudomonas aeruginosa* (Mohanty *et al.*, 2003). Some less common organisms are Acinetobacter species (Mohanty *et al.*, 2003), *Pseudomonas putida* (Yang *et al.*, 1996), *Shigella sonnei* (Papasian *et al.*, 1995), *Erwinia persicinus* (Hara *et al.*, 1998), and non-typhoidal Salmonella (Abbott *et al.*, 1999). Among gram negative cocci *Neisseria gonorrhoeae* also causes urinary tract infection (Tao *et al.*, 1997).

Among gram positive cocci, *Staphylococcus saprophyticus* is a leading cause of cystitis in young women (Raz *et al.*, 2005). Other common causative agents are *Staphylococcus aureus* (Lavanya and Jogalakshmi, 2002) and *Staphylococcus epidermidis* (Famurewa, 1992). *Staphylococcus lugdunensis*; which is also associated with serious infections in human; is an unrecognized and infrequent cause of UTIs (Haile *et al.*, 2002). *Enterococcus faecalis* has also been isolated from urine specimens (Famurewa, 1992 ; Moore *et al.*, 2002 ; Mohanty *et al.*, 2003 ; Taneja *et al.*, 2004). *Mycobacterium tuberculosis* (acid fast bacilli) has also been reported as urinary pathogen (Shkuratov and Kulchavenia, 1990). Besides, some newly reported organisms are Corynebacterium group D2 (CGD2) (Soriano *et al.*, 1990), *Corynebacterium macginleyi* (Villanueva *et al.*, 2002). *Aerococcus urinae* (Grude and Tveten, 2002), *Aerococcus viridans* (Gopalchar *et al.*, 2004), and *Aerococus urinaehominis* (Lawson *et al.*, 2001), small bacteria i.e *Chlamydia trachomatis* (Morre *et al.*, 1999) and *Ureaplasma urealyticum* (Tao *et al.*, 1997).

Non-bacterial causes of UTIs are fungi, viruses, actinomycetes, and protozoa. Among viruses, some serotypes of Adenovirus has been implicated as cause of haemorrhagic cystitis (Mims *et al.*, 1995). Among fungi, *Candida albicans*, *Candida utilis*, *Candida tropicalis*, *Candida glabrata* (Baran *et al.*, 2000), *Candida parapsilosis*, *Candida krusei*, *Candida robusta*, and *Candida catenulata* have been reported associated with chronic symptomatic UTIs. Rarely *Cryptococcus neoformans* also causes UTI (Dorko *et al.*, 2002). *Actinomycetes europaeus* has also been detected in patients with UTI (Sabee *et al.*, 1999). Among protozoa, *Trichomonas vaginalis* causes urethritis. Infection with *Schistosoma haematobium* results in inflammation of bladder and commonly causes haematuria (Mims *et al.*, 1995).

Ascending infections of urinary tract are most commonly caused by *E.coli*. For instance, in a study of positive urine specimens 79% cultures were found positive for *E.coli* (Honkinen *et al.*, 1999). However, the ability to cause UTI is limited to certain serotypes of *E.coli*, particularly O1, O2, O4, O6, O7, O75 (Mims *et al.*, 1995). Virulence factors are P-fimbriae which enable them to adhere to urethral and bladder epithelium. Other important virulence factors are alpha-haemolysin, antigenic structure, resistance to antibiotics, production of colicins, siderophores (Durovicova *et al.*, 1992), production of cytotoxic necrotizing factor, verocytotoxin (Ludwing *et al.*, 1996), and mannose resistant P-fimbriae. Adherence of type 1 piliated *E.coli* to carbohydrate structures of vaginal mucosa plays a major role in the pathogenesis of ascending UTIs in women (Backhed *et al.*, 2002). In another study, Schembri and Klemm (2001) indicated that fim-H variants posses adaptations that enhance biofilm formation and suggest a novel role for fim-H of *E.coli* in UTIs. Fim-H also plays role in adhesion to epithelial cells of bladder (Hoepelman *et al.*, 2001).

Beside *E.coli*, Honkinen *et al.* (1999) reported the incidence of other members of enterobacteriaceae as Enterobacter 5.3%, Klebsiella 4.4%, Proteus and other species 3.2%. It was observed that urea hydrolysis by *P.mirabilis* in the urinary tract leads directly to urolithiasis (stone formation) and contributes to the development of acute pyelonephritis (Mobley *et al.*, 1995). *P.mirabilis* and *P.vulgaris* produce urease that is active within urinary tract. Some strains of Klebsiella also produce urease. Urease is also a significant virulence factor for *S.saprophyticus* in bladder infection (*Collier etal.*, 1998). Fimriation, haemagglutination and adherence properties of *S.marcescens* play important role in causing UTIs (Leranoz *et al.*, 1997). *E.faecalis* has ability to adhere human bladder carcinoma T24-cells and cause UTIs (Shiono and Ike, 1999).

LABORATORY DIAGNOSIS

For the diagnosis of UTI, quantitative evaluation of urine by means of bacterial count has been accepted as a routine procedure. The number of bacteria and white blood cells in urine specimen are the basis for diagnosing UTIs. A pelvic examination may also be necessary (Cornforth, 2002). The bacterial count of $>10^5$ CFU/ml of clean-voided, midstream urine specimen is generally indicative of infection of urinary tract and this count is considered as significant bacteriuria (Okada, 2000). Grude *et al.* (2001) reported 10^4 CFU/ml of urine as significant bacteriuria. The urine is normally sterile. A bacterial count of 10^3 CFU/ml of urine has a high positive predictive value for cystitis in symptomatic women. Unfortunately, some clinical laboratories do not report counts of less than 10^4 CFU/ml of urine (Orenstein and Wong, 1999). The aim of imaging a UTI is to detect conditions that must be treated in order to avoid immediate deterioration or recurrences and probable long-term kidney damage (Johansen, 2002). Kunin and Buesching (2000) described a filter paper dilution system technique to diagnose common urinary pathogens in urine. Furthermore, Gram staining of unspun urine can be used to detect bacteriuria. In this semi-quantitative test, one organism per oil immersion field correlates with 10^5 CFU/ml by culture. This procedure is time-consuming and has low sensitivity. Thus, it is not routinely performed in most clinical laboratories unless it is specifically requested (Orenstein and Wong, 1999). In the last few years several chromogenic media have been developed, allowing for more specific direct isolation, differentiation and presumptive identification of urinary tract pathogens on primary plates (Chaux *et al.*, 2002).

Dipstreak is another new urine culture device. Researchers concluded that dipstreak device represents an attractive and excellent screening method for reliable detection, counting and presumptive identification of urinary tract pathogen (Scarparo *et al.*, 2002). Asymptomatic bacteriuria (silent infection) is defined as the presence of $>10^5$ CFU/ml of clean voided urine in persons with no symptoms of UTIs. Asymptomatic bacteriuria is several-fold more common among women than men (Ronald and Ludwig, 2001). But it rarely requires treatment and is not associated with increased morbidity in elderly patients (Orenstein and Wong, 1999).

Pyuria is a good marker for detection of significant bacteriuria (Tambyah and Maki, 2000). Clinically significant pyuria has been defined as $>10^6$ leukocytes per liter of urine (Turner and Caulihard, 1995). However, pyuria is not a totally reliable index of presence of UTI because it may be absent during bacterial UTI or may occur in disorders other than bacterial infections such as extreme dehydration, trauma secondary to instrumentation or

calculi, chemical inflammation, renal tuberculosis, acute glomerulonephritis, non-bacterial gastroenteritis and respiratory infections due to some other reasons (Isenberg *et al.*, 1985). Pyuria in the absence of positive urine culture can also be due to chlamydia and is also seen in patients receiving antibacterial therapy for UTI as the bacteria are inhibited by the antibacterial agents before the inflammatory response (Mims *et al.*, 1995). Furthermore, urinary leukocytes may disappear rapidly, thus, such screening may produce false negative results (Vickers *et al.*, 1991). According to Ahmad *et al.* (1997) pyuria as predictor of bacteriuria is the least reliable technique to be recommended in routine clinical practice.

Pyuria can be detected by standard microscopic analysis, dipstick leukocyte estrase and nitrate dipstick analysis (Latorre *et al.*, 2001) and haemocytometric cell counting (Turner and Caulthard, 1995). The usefulness of measurements of urinary lactoferrin (LF) released from polymorphonuclear leukocytes and of an immunochromatography test strip devised for measuring urinary LF for the simple and rapid diagnosis of UTIs was evaluated by Arao *et al.* (1999). Their findings indicated that urine LF measurement with the immunochromatography test strip provides a useful tool for the simple and rapid diagnosis of UTI.

TREATMENT

The goal of antimicrobial therapy is to eliminate the infecting organisms from the urinary tract and provide the resolution of symptoms (Jancel and Dudas, 2002). Antimicrobial therapy is seldom indicated for asymptomatic infection but it is usually indicated for amelioration of symptoms (Nicoll, 2003). The most common antibiotics used for the treatment of UTI are sulphonamides and cephalosporins (Prais *et al.*, 2003). First-line of treatment of acute uncomplicated UTI has traditionally involved a 3-day regimen of trimethoprim-sulfamethaxazol (TMP-SMX) or TMP alone for patients with sulfa allergies. Alternative first-line agents include the fluoquinolones, nitrofurantoin, and fosfomycin (Nicoll, 2003).

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