

**Assessment of Bacterial Profile and Antimicrobial  
Susceptibility Pattern of Catheter-Associated Urinary  
Tract Infections in Comparison with non-Catheterized  
Urinary tract infections in Jimma University Hospital,  
Southwest Ethiopia**

***BY***

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**JUNE 2005**

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**IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR  
THE DEGREE OF MASTER OF SCIENCE  
IN  
MEDICAL MICROBIOLOGY**

***BY***

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**JUNE 2005**

## DECLARATION

I, the undersigned, declare that this M. Sc thesis is my original work, has not been presented for a degree in any other university and that all sources of materials used for the thesis have been duly acknowledged.

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## Abbreviations

BHI	Brain Heart Infusion
CAMH	Cation - Adjusted Muller-Hinton
CFU	Colony Forming Unit
CAUTI	Catheter Associated Urinary Tract Infection
CLED	Cystine lactose electrolyte-deficient
ES $\beta$ L	Extended-Spectrum Beta Lactamase
ES $\beta$ LEC	Extended-Spectrum Beta Lactamase- Producing <i>Escherichia coli</i>
GPS-SA	Gram-Positive Susceptibility <i>Staphylococcus aureus</i>
NCCLS	National Committee for Clinical Laboratory Standards
QREC	Quinolone-resistant <i>Escherichia coli</i>
Spp	Species
TMP-SMX	Trimethprime-Sulfamethoxazole
UPEC	Uropathgenic <i>Escherichia coli</i>
UTI	Urinary Tract Infection
VRE	Vancomycin - Resistant <i>Enterococcus</i>
VREF	Vancomycin Resistant <i>Enterococcus faecium</i>

## ABSTRACT

Urinary tract infections (UTIs) are among the most common bacterial infection. They have become the most common hospital acquired infections, accounting for as many as 35% of nosocomial infections, and are usually associated with catheterization. The aim of this study is to assess the bacterial profile and antimicrobial resistance pattern of catheter associated urinary tract infection in comparison with non-catheter associated UTI. One hundred and twenty urine specimens (30 from catheterized patients and 90 from non-catheterized patients with symptoms of UTI) were screened for the presence of significant bacteruria from January to March 2005. Bacteriological screening of catheterized urine and clean catch mid-stream urine revealed that 13/30 (43.3%) and 20/90 (22.3%) had significant bacteriuria, respectively ( $P < 0.05$ ). All samples taken from patients who have been catheterized for 2 weeks or more showed significant bacteruria. In both group the rate of infection was higher in female patients. Older patients (>50years old) were found to be the most affected age group (46%) among catheterized patients whereas most of the non-catheterized patients with significant bacteruria belonged to age group 11-12 years. Among catheterized patients, *Escherichia coli* and *Klebsiella species* were found to be the most frequently isolated pathogens (each of them accounts 23 %) followed by coagulase negative *Staphylococci* (15 %). The most frequently isolated species from non-catheterized patients was *Klebsiella* (40 %) followed by *E. coli* (30 %). Resistance rates (56.3 % to 100%) to Ampicillin, amoxicillin, cephalexin, carbenicillin, and Trimethoprim/sulfamethoxazole were observed in all organisms isolated from both groups. In addition, resistance rates to gentamicin, nitrofurantoin, and nalidixic acid were observed in all bacteria isolated from catheterized patients. In general, in this study, high level multidrug resistance in both groups indicated that it is time to reconsider the empirical use of the commonly used antimicrobial agents in Ethiopia. Particularly, increasing

resistance in pathogens isolated from catheterized patients is frustrating. Because the most important risk factors for UTI is duration of catheterization indwelling urinary catheterization should be avoided or at least minimized.

## CHAPTER I. INTRODUCTION

### ***1.1. General Introduction***

Urinary tract infections (UTIs) are among the most common bacterial infection. It has been estimated that symptomatic UTIs result in as many as 7 million visits to outpatient clinics, one million visits to emergency departments, and 100,000 hospitalizations annually in the United states (Wilson & Gaido, 2004). The vast majority of UTIs arise in female out patients; physicians treat many of whom empirically if their symptoms suggest acute uncomplicated bacterial cystitis (Sahm *et al.*, 2001). Besides, recurrent UTIs are common clinical problems. Up to 25% of women who present with an acute UTI will have a recurrence within 6 months, despite receiving appropriate antibiotic therapy (Schilling, *et al.*, 2002).

On the other hand, an infection due to extended spectrum-beta-lactamase (ESBL)-producing *Escherichia coli* (ESBLEC) in non-hospitalized patients seem to be emerging in different countries (Bano *et al.*, 2004). The emergence of antibiotic-resistant strains is a major therapeutic problem that is multifactorial and that could be explained by several nonexhaustive hypotheses. The influence of excessive and/or inappropriate antibiotic use, particularly of broad-spectrum agents prescribed empirically has been demonstrated. Reducing the number of prescriptions of a particular antibiotic can lead to a decrease in resistance rates (Sotto *et al.*, 2001). Apart from this, the annual cost to the health care system of the United States attributable to community-acquired UTI alone is estimated to be approximately \$ 1.6 billion (Foxman, 2002).

Urinary tract infections have become the most common hospital acquired infections, accounting for as many as 35% of nosocomial infections, and they are the second most common cause of bacteriemia in hospitalized patients (Stamm, 2002). Nosocomial urinary tract infection is usually associated with catheterization. The infection would be even more common but for the use of the closed catheter system (Warren, 2001). The associated morbidity and mortality are major drains on hospital resources (Kalsi *et al.*, 2003). The overall health care costs caused by urinary catheter-related infections are

sizable given how often urinary catheters are used in acute care settings, extended care facilities, and in persons with injured spinal cords (Saint & Chenoweth, 2003).

The type of organisms associated with catheter associated urinary tract infections (CAUTIs) have changed over time, as have the patterns of antibiotic resistance (Wazait *et al.*, 2003). Many infecting strains isolated from CAUTIs display markedly greater antimicrobial resistance than organisms that cause community-acquired UTIs (Braunwald *et al.*, 2001).

In Ethiopia, Wolday and Erge (1997), reported that high incidence of resistance to the commonly prescribed antimicrobial agents was observed at Tikur Anbessa hospital. Likewise, a study conducted in Gondar indicated that above 68 % of the isolated pathogens showed resistance from two to nine antimicrobials and 15.7 % were resistant to one antibiotic (Moges *et al.*, 2002). In this study, catheterization predisposed patients 4.4 times in the development of UTI and hence resistance. The same holds true for hospitalization hence nosocomial infections, which increased 2.73 times UTIs.

In general, because of the continuous evolution of antibiotic resistance, regular monitoring of this phenomenon appears to be necessary to improve guidelines for empirical antibiotic therapy, which must consider the most probable microorganisms, their susceptibility according to the characteristics of the population concerned, without forgetting side effects, and ecological and economic consequences (Sotto *et al.*, 2001).

## **1.2. Literature Review**

### **1.2.1. Etiologic agents of UTI**

The etiological agents of community- acquired and hospital acquired UTIs are different. Only a limited amount of data has been published regarding changes in the frequency of causative agents among outpatients (Wilson & Gaido, 2004).

Many different organisms can infect the urinary tract, but by far the most common agents are the gram-negative bacilli (Braunwald *et al.*, 2001; Wilson & Gaido, 2004) (Table 1.1). *E. coli* is the primary cause of uncomplicated infections of the urinary tract including cystitis (Gunther *et al.*, 2001; Sahm *et al.*, 2001; Haryniewicz *et al.*, 2001). According to an International survey of the antimicrobial susceptibility of pathogens from uncomplicated UTIs, *E. coli* accounts for 77.0% of isolates (Kahlmeter, 2003). However, there is some evidence that the percentage of UTIs caused by *E. coli* is decreasing, being

replaced by other members of the *Enterobacteriaceae* (Haryniewicz *et al.*, 2001; Weber *et al.*, 1997).

On the other hand, another literature by Braunwald *et al.* (2001) indicated that other gram-negative rods, especially *Proteus* and *Klebsiella* and occasionally *Enterobacter*, account for a smaller proportion of uncomplicated infections. These organisms, plus *Serratia* and *Pseudomonas*, assume increasing importance in recurrent infections, associated with urologic manipulation, calculi, or obstruction.

Gram- positive cocci were isolated more frequently from a hospital setting and the most common were *Enterococcus species* (Wilson & Gaido, 2004; Haryniewicz *et al.*, 2001). *Staphylococcus saprophyticus*-novobiocin-resistant, coagulase-negative species-accounts for 10 to 15% of acute symptomatic UTIs in young females. More commonly, *Enterococci* and *Staphylococcus aureus* cause infections in patients with renal stones or previous instrumentation or surgery. Isolation of *S. aureus* from the urine should arouse suspicion of bacteremic infection of the kidney (Braunwald *et al.*, 2001).

**Table 1.1. Percentage distribution of etiologic agents of urinary tract infections among outpatients and inpatients, by bacterial pathogens (Adapted from Wilson & Gaido, 2004)**

<i>Organisms</i>	<i>Outpatients</i>	<i>Inpatients</i>
	Percentage with pathogen	Percentage with pathogen
<i>E. coli</i>	53-72	17.5-56.7
<i>Coagulase-negative staphylococci</i>	2-7.5	2.1-12.5
<i>Klebsiella species</i>	6-12	6.2-15.0
<i>Proteus species</i>	4-6	3.8-8.2
<i>Enterobacter species</i>	0.6-5.8	0.9-6.5
<i>Morganella morganii</i>	3.1-4.4	4.7-6
<i>Citrobacter species</i>	0.1	0.2-3
<i>Enterococcus species</i>	1.7-12	6.5-15.8
<i>Staphylococcus aureus</i>	2	1.6-3.5
<i>Staphylococcus saprophyticus</i>	0.2-2	0.4

*E. coli*, *K. pneumoniae*, *C. freundii*, *Proteus*, *Pseudomonas*, *Serratia*, *Coagulase-negative staphylococcus*, and *Enterococcus faecium* are species implicated in catheter-associated urinary tract infection (Johnson, *et al*, 1999; Braunwald *et al.*, 2001). However, the types of organisms associated with catheter associated urinary tract infection (CAUTI) have changed over the last 5 years in a UK institution (Wazait *et al.* 2003). This study revealed that *E. coli* was the most frequently isolated pathogen in all years, but its frequency declined over time (35.6 %, 32.5 % and 26.6 %, respectively) and *Enterococcus* was the second most frequent overall, with a significant increase in frequency with time (11.8 %, 15.3 % and 22.0 %, respectively).

### **1.2.2. Virulence factors**

All uropathogens are equipped with a variety of virulence factors. The best characterized are those from *E. coli* (Oelschlaeger *et al*, 2002). However, not all strains of *E. coli* are equally capable of infecting the intact urinary tract. Bacterial virulence factors markedly influence the likelihood that a given strain, once introduced into the bladder, will cause UTI. Most *E. coli* strains that cause symptomatic UTIs in non-catheterized patients belong to a small number of specific O, K, and H serogroups. These uropathogenic clones have accumulated a number of virulence genes that are often closely linked on the bacterial chromosome in “virulence islands” (Braunwald *et al.*, 2001).

Among the first virulence factors that come into play during establishment of a urinary tract infection are adhesins (Oelschlaeger *et al*, 2002,). *E. coli* which infects and causes disease of the urinary tract expresses several adherence factors including type 1 and P fimbriae (Connell *et al*, 2000). Type 1 fimbriae are hair- like projections that extend from the surface of *E. coli* and other genera of the *enterobacteriaceae* (Gunther *et al.*, 2001). These fimbriae bind mannose-containing oligosaccharides via the Fim H adhesive tip protein and are required for colonization of the urinary tract by uropathogenic *E. coli*. Besides their primary function as adhesion molecules, several other additional functions can now be attributed to these organelles. They may also function as invasins, promote

biofilm formation, and transmit signals to epithelial cells resulting in inflammation (Oelschlaeger *et al*, 2002,).

In addition, uropathogenic *E. coli* strains usually produce hemolysin and aerobactin (a siderophore for scavenging iron) and are resistant to the bactericidal action of human serum. Nearly all *E. coli* strains causing acute pyelonephritis and most of those causing acute cystitis are uropathogenic. In contrast, infections in patients with structural or functional abnormalities of the urinary tract are generally caused by bacterial strain that lack these uropathogenic properties; the implication is that these properties are not needed for infection of the damaged urinary tract (Braunwald *et al.*, 2001).

### **1.2.3 Pathogenesis and pathology**

The urinary tract should be viewed as a single anatomic unit that is united by a continuous column of urine extending from the urethra to the kidney. In the vast majority of UTIs, bacteria gain access to the bladder via the urethra. Ascent of bacteria from the bladder may follow and is probably the pathway for most renal parenchymal infections. The female urethra appears to be particularly prone to colonization with colonic gram-negative bacilli because of its proximity to the anus, its short length (about 4 cm), and its termination beneath the labia. Sexual intercourse causes the introduction of bacteria into the bladder and is temporally associated with the onset of cystitis it thus appears to be important in the pathogenesis of UTIs in younger women. In addition, use of spermicidal-coated condoms dramatically alters the normal bacterial flora and has been associated with marked increases in vaginal colonization with *E. coli* and in the risk of UTI (Braunwald *et al.*, 2001).

Following invasion of superficial bladder epithelial cells, uropathogenic *Escherichia coli* (UPEC) can replicate intracellularly and eventually reemerge from the infected host cells in a manner reminiscent of a lytic virus cycle. Upon exiting the superficial cell, UPEC can interact with and invade surrounding and underlying epithelial cells, leading to the establishment of a quiescent bacterial reservoir within the bladder tissue (Mulvey *et al*, 2001). The ability of uropathogenic *E. coli* to flux out of cells and colonize surrounding cells provides them a mechanism to subvert host defense mechanisms and persist in the bladder epithelium for weeks following the acute infection (Schilling *et al*, 2001).

*Upon histological examination of infected bladders, greater morphological changes were observed in bladder tissue (Gunther et al., 2001). These findings suggest a means by which invasion, rather than promoting bacterial spread across mucosal layers and into other tissues, can facilitate the localized persistence of a bacterial pathogen.*

Studies have demonstrated the importance of the attachment and growth of bacteria on the surfaces of the catheter in the pathogenesis of CAUTI. Such bacteria growing in biofilms on the catheter eventually produce encrustations (Braunwald *et al.*, 2001). Urease producing bacteria, such as *P.mirabilis*, that elevates the urine pH are responsible for catheter encrustation development. The lumen of the catheter becomes blocked by crystal formation from a combination of an elevated urine pH, bacterial film, and calcium and magnesium ions (Madigan and Neff, 2003). These encrustations provide and may protect them from antimicrobial agents and phagocytes (Braunwald *et al.*, 2001).

### **1.2.3. Epidemiology**

Several studies have investigated pathogens from a variety of common infections. In the field of urinary tract infections (UTIs), there has been a steady increase in the level of resistance to commonly used antibiotics, including ampicillin and trimethoprim (Kahlmeter, 2003).

Until recently, most infections caused by extended-spectrum beta-lactamase producing *E. coli* (*ESβLEC*) or *Klebsiella pneumoniae* had mostly been described as nosocomially acquired or nursing home related. However, some recent data suggest that infections due to extended spectrum beta- lactamase (*ESβL*)-producing organisms might be an emergent problem in outpatients in different countries. For example, in a recent nationwide study of (*ESβL*)-producing organisms in Spain, 93% of *ESβL*-producing *K. pneumoniae* strains were isolated from inpatients, while 51 % of *ESβLEC* strains were isolated from outpatients (Bano *et al.*, 2004).

In Canada, resistance among community-acquired (as opposed to nosocomial or hospital-acquired) isolates of *E.coli* varies depending on the antimicrobial agent being tested. Ampicillin has the lowest activity against community-acquired *E. coli* isolates, with resistance rates ranging from 23 % to 41%. TMP/SMX resistance rates ranging from 8.4%

to 19.2%, while the resistance to the fluoroquinolone ciprofloxacin has remained at 0% to 1.8% since its introduction over 10 years ago (Mazzuli, 2001).

Data reviewed in the Southern Netherlands indicated that less than 50 % of isolates of *E. coli* and *Proteus spp* were susceptible to amoxicillin. The highest susceptibility rates were found to be for cefotaxime (85% for *proteus spp*, 95 % for *E.coli* and other *Enterobacteriaceae*). More than 80 % of all *Enterobacteriaceae* and *Providencia stuartii*, and 72 % of *Pseudomonas spp.* were sensitive to gentamicin (Vromen *et al.*, 1999). In this study, the decrease in susceptibility to co-trimoxazole and increase to nitrofurantion are most likely to be due to the pattern of empirical prescribing in the study nursing homes. The first choice agent was and is still, co-trimethoxazole. Nitrofurantion is less frequently used.

Another study conducted in Poland revealed that the resistance pattern of hospital *E. coli* was similar to that of community isolates except for those found to produce extended- spectrum  $\beta$  - lactamases (ES $\beta$ LS). Other species of the *Enterobacteriaceae* were more resistant when isolated from the hospital setting (Haryniewicz *et al.*, 2001). According to this study, multi-resistance was usually related to production of ES $\beta$ L, in both community and hospital isolates. Extended- spectrum  $\beta$  - lactamase producers, however, were recovered only from complicated community UTIs.

In addition, an International survey of the antimicrobial susceptibility of pathogens from uncomplicated UTIs shows overall, *P. mirabilis* were less resistant to ampicillin and more resistant to trimethoprim than *E. coli*, whereas *Klebsiella spp.* were significantly more resistant to ampicillin, nitrofurantion and fosfomycin. The other *Enterobacteriaceae* were much more often resistant to the broad-spectrum  $\beta$ -lactams (ampicillin, co-amoxiclav and cephalosporins), nitrofurantion and fosfomycin (Kahlmeter, 2003). This study also clearly shows that *E. coli* is now resistant to ampicillin in >40 % of cases in Spain, Portugal, Ireland and Luxembourg, to sulfamethxazole in >40 % in Ireland, Portugal and Spain, and to TMP-SMX in >20 % of cases in Germany, Ireland, Portugal and Spain. The results indicate that it is time to seriously reconsider the empirical use of these antibiotic in many countries, or to seriously investigate at which level of resistance the out come of therapy with these antibiotics is influenced, or to develop clear strategies to counteract further resistance development to these drugs.

Moreover, a study conducted in Barcelona, Spain indicated that an increasing proportion of quinolone-resistant *E.coli* (QREC) infections were observed (Garau *et al.*, 1999). In this study, QREC strains were more common in patients with nosocomial infections but also increased in patients with community-acquired infections. A complicated UTI and the presence of a urinary catheter were found to be risk factors associated with QREC infection in patients with UTI. The use of quinolones in patients harboring *E. coli* strains with single-step mutations would select isolates with high levels of resistance to ciprofloxacin. QREC may have emerged in direct response to the selective pressure exerted by antibiotic use. The lack of patient-to-patient spread of resistant organisms clearly indicates the presence of QREC strains that were colonizing these patients.

Apart from this, many infecting strains isolated from CAUTIs display markedly greater antimicrobial resistance than organisms that cause community-acquired UTIs (Braunwald *et al.*, 2001). The mechanisms of CAUTI, in a group of hospitalized patients, were determined as extra-luminal, in which the organisms migrated along the outside of the catheter (66%), and intra-luminal (34%), in which the bacteria migrated into the bladder as a result of opening the catheter system (Madigan and Neff, 2003). Hospital-acquired pathogens reach the patient's catheter or urine-collecting tube junction or at the drainage bag portal. The organisms then ascend intraluminally into the bladder within 24 to 72h. Alternatively, the patient's own flora may colonize the perineal skin and periurethral area and reach the bladder via the external surface of the catheter. This route is particularly common in women (Braunwald *et al.*, 2001).

On the other hand, a study performed at the medical college of Virginia hospitals indicated that from 1992 to 1997 the rate of isolation of vancomycin - resistant *Enterococcus faecium* (VREF) increased from 1.1 per 1,000 to 3.3 per 1, 000, patient admissions and clinical isolates were obtained mostly from urine (52 %) and catheter tips (6%) (Bischoff *et al.*, 1999). As demonstrated in this study, *VRE* are usually transmitted by contact and could survive for at least 1h on gloved and ungloved fingertips and 5 to7 days on environmental surface. They can also exist in stool specimens of a carrier for up to 2

years, providing a source for environmental spread. These characteristics can result in the wide dissemination of *VRE*.

In a related study, numerous isolations of *VRE* in the University Hospital in Gdansk in 1997 to 1999 indicated that the first nosocomial outbreak of *VRE* had occurred in the country (Kawalec *et al*, 2000). The isolates were found to be multidrug resistant, uniformly demonstrating additional resistance to penicillins, ciprofloxacin, and high concentration of aminoglycosides. Several lines of evidence obtained in this study of representative isolates suggested that multiple selection events, transposition to different replicons, plasmid - mediated horizontal transfer and clonal dissemination of epidemic strains were major factors of vancomycin resistance spread in enterococcal population.

In addition, the *VRE* isolated in Australia to date show considerable diversity in their phenotypes, genotypes, and geographic locations. All four combinations genotype and species have been found, with the commonest being *E. faecium* van B. While the clinical profiles of *VRE* affected patients appear to be similar to those recorded in the United States and elsewhere, the predominance *E. faecium* van B. rather than *E. faecium* van A suggests an epidemiology different from that in either Europe or the United States (Bell *et al*, 1998).

In Africa, a prospective study performed in Fann University Teaching Hospital, in Dakar, indicated that *Enterobacteriaceae* (87.5%) were the most frequent etiology and *E.coli* (48.7%) was the leading species in this family. The strains of *E. coli* present more resistant profile to beta-lactams (70.2%). Fluoroquinolones are active on more than 80% of the strains responsible for UTI in this study area (Sow *et al.*, 2000).

Similarly, a study conducted at the Tikur Anbassa University Hospital, Addis Ababa, Ethiopia, showed that the strains of *E. coli* isolated were considerably more resistant to all antibiotics tested (Ringertz *et al.*, 1990). In this study, the strain biotypes and antibiograms, together with the length of patients' hospitalization before a positive urine culture was obtained, suggested that the majority of the strains from Tikur Anbessa hospital were of nosocomial origin. In line with this, another study conducted at the same hospital indicated that among patients with mixed infections, majority of them had predisposing underlying disorders & were subjected to chronic urethral catheterization (Wolday and Erge, 1997).

Likewise, the multidrug resistance, which is extremely high to the commonly used antibiotics in Gondar College of Medical Sciences Hospital, is frustrating. Resistance was high among patients who had a history of catheterization (Moges *et al.*, 2002).

In general, factors associated with increased risk of CAUTIs include female sex, older age, prolonged catheterization, severe underlying illness, disconnection of the catheter and drainage tube, other types of faulty catheter care, and lack of systemic antimicrobial therapy (Braunwald *et al.*, 2001; Madigan & Neff, 2003). The high consumption of often inappropriately prescribed antibiotics, combined with crowding, multiple pathology and frequent use of invasive device, is a major factor contributing to high levels of resistance (Vromen, *et al.*, 1999).

#### ***1.2.5. Clinical features***

Urinary tract infections have traditionally been viewed as acute and often self-limiting infections. However, this concept has been challenged by recent findings demonstrating that an acute bladder infection results from a complex series of host-pathogen interactions that can lead to bacterial invasion and persistence and that ultimately can determine the course of the infectious disease (Schilling *et al.*, 2001). In general, UTIs can be classified as asymptomatic bacteriuria, cystitis, or acute pyelonephrities. Cystitis predominantly involves colonization of the bladder (Gunther *et al.*, 2001).

Patients with cystitis usually report dysuria, frequency, urgency, and supra-pubic pain. The urine often becomes grossly cloudy and malodorous, and it is bloody in about 30% of cases. White blood cells and bacteria can be detected by examination of unspun urine in most cases. However, some women with cystitis have only  $10^2$  to  $10^4$  bacteria per milliliter of urine, and in these instances bacteria cannot be seen in a Gram stained preparation. Physical examination generally reveals only tenderness of the suprapubic area (Braunwald *et al.*, 2001).

The more severe upper urinary tract disease acute pyelonephrities involves colonization of the kidneys and represents an infection capable of progressing to bacteremia (Gunther *et al.*, 2001). Symptoms of acute pyelonephrities generally develop rapidly over a few hours or a day and include fever, chills, nausea, vomiting, and diarrhea. Symptoms of cystitis may or may not be present. Besides fever, tachycardia, and

generalized muscle tenderness, physical examination reveals marked tenderness on deep pressure in one or both costovertebral angles or no deep abdominal palpation. In some patient, signs and symptoms of gram-negative sepsis predominate. Most patients have significant leukocytosis and bacteria detectable in Gram-stained unspun urine. Leukocyte casts are present in the urine of some patients, and the detection of these casts is pathognomonic. Hematuria may be demonstrated during the acute phase of the disease; if it persists after acute manifestations of infection have subsided, a stone, a tumor, or tuberculosis should be considered (Braunwald *et al.*, 2001).

Most catheter-associated bacteriurias are asymptomatic (Warren, 1997). Two studies of hospitalized patients with catheter related UTI found that the majority were asymptomatic; and that patients with and without UTI did not differ in signs and symptoms of fever, dysuria, urgency, and flank pain. Importantly, patients' reports of UTI symptoms, fever, and elevated plasma white blood cell count did not predict catheter-associated UTI. Urinary white blood cell count was the best predictor of CAUTI (Madigan & Neff, 2003). The complications in short-term catheterized patients include fever, acute pyelonephritis, bacteremia and death; patients with long term catheters in place are at risk for these complications and catheter obstruction, urinary tract stones, local periurinary infections, chronic renal inflammation, chronic pyelonephritis, and over years, bladder cancer (Warren, 1997).

#### **1.2.6. Immunity**

Data from various experimental systems indicated that invasion of eukaryotic cells can provide bacterial pathogens refuge from both innate and adaptive host defenses and may facilitate the dissemination of microbes within and across tissue barriers. Within the urinary tract, the bladder epithelium functions as a formidable physical barrier, preventing the diffusion of urine and other substances from within the bladder lumen. The bladder epithelium, which is composed of a single layer of large, highly differentiated superficial cells overlying two or three layers of small, relatively undifferentiated basal and intermediate epithelial cells, also serves as an active component of the innate immune system (Mulvey *et al.*, 2001). Under normal circumstances, bacteria placed in the bladder are rapidly cleared, partly through the flushing and dilutional effects of voiding but also as a result of the antibacterial properties of urine and the bladder mucosa. Owing mostly to a

high urea concentration and high osmolality, the bladder urine of many normal persons inhibits or kills bacteria. Prostatic secretions possess antibacterial properties as well. Polymorphnuclear leukocytes enter the bladder epithelium and the urine soon after infection arises and plays a role in clearing bacteruria (Braunwald *et al.*, 2001).

The role of locally produced antibody remains unclear (Braunwald *et al.*, 2001). However, interactions between type 1- piliated UPEC and bladder epithelial cells can stimulate cytokine (IL-6) and chemokine (IL-8) production and can trigger the exfoliation and clearance of superficial epithelial cells (Braunwald *et al.*, 2001; Schilling *et al.*, 2001). Exfoliation of infected bladder cells occurs via an apoptosis like mechanism and appears to be effective host defense strategy (Mulvey *et al.*, 2001).

### ***1.2.7. Laboratory diagnosis of UTI***

The diagnosis of UTIs begins with the screening of patients with symptoms suggestive of UTIs by a physician (Bell *et al.*, 1998). Determination of the number and types of bacteria in the urine is an extremely important diagnostic procedure (Braunwald *et al.*, 2001). Thus, only patients who had pyuria and significant bacteriuria obtained from appropriate urine samples (a clean-catch midstream and catheter samples of urine) are included in the microbiological analysis (Wazait *et al.*, 2003; Kahlmeter, 2003; Haryniewicz *et al.*, 2001). Bacteruria refers the presence of bacteria in the urine. It is regarded as significant when the urine contains  $10^5$  organisms or more per ml ( $10^8/l$ ) in pure culture (Cheesbrough, 2001). This is true usually in symptomatic patients. In asymptomatic patients, two consecutive urine specimens should be examined bacteriologically before therapy is instituted, and  $\geq 10^5$  bacteria of a single specimen per milliliter should be demonstrable in both specimens (Braunwald *et al.*, 2001). Since the large number of bacteria in the bladder urine is due in part to bacterial multiplication during residence in the bladder cavity, samples of urine from the ureters, or renal pelvis may contain  $< 10^5$  bacteria per milliliter and yet indicate infection. Similarly, the presence of bacteruria of any degree in suprapubic aspirates or of  $\geq 10^2$  bacteria per milliliter of urine obtained by catheterization usually indicates infection (Cheesbrough, 2001; Braunwald *et al.*, 2001).

Routine urine culture should be plated using calibrated loops for the semi quantitative method. This method has the advantage of providing information regarding the

number of CFU/ml, as well as providing isolated colonies for identification and susceptibility testing (Wilson and Gaido, 2004).

The types of media used for routine cultures should be limited to blood agar and MacConkey agar (Wilson and Gaido, 2004; Manges *et al.*, 2001). For urine specimens obtained from outpatients, it is not necessary to routinely inoculate a medium that is selective for gram-positive bacteria (Wilson and Gaido, 2004; Haryniewicz *et al.*, 2001).

In contrast, urine specimen obtained from hospitalized patients are likely to contain *Enterococcus*, which have emerged as the second most common cause of nosocomial infections (Wilson and Gaido, 2004; Wazait *et al.*, 2003; Haryniewicz *et al.*, 2001; Kawalec *et al.*, 2000). Laboratories may want to consider inoculating urine specimens obtained from hospitalized patients, or from patients in whom gram-positive bacterial infection is suspected but not documented, to a medium that is selective for gram-positive cocci. A medium such as phenyl-ethyl alcohol agar suppress the growth of swarming *proteus spp* and other gram negative bacilli that can overgrow gram positive cocci in the specimen. Furthermore, Cystine lactose electrolyte-deficient (CLED) agar is now used by most laboratories to isolate urinary pathogens because it gives consistent results and allows the growth of both Gram-negative and Gram-positive pathogens. The indicator in CLED agar is bromothymol blue and therefore lactose-fermenting colonies appear yellow. The medium is electrolyte-deficient to prevent the swarming phenomenon of *Proteus species* (Cheesbrough, 2001). Urine culture should be incubated overnight at 35°C-37°C in ambient air before being read (Wilson and Gaido, 2004).

Rapid methods of detection of bacteruria have been developed as alternatives to standard culture methods. These methods detect bacterial growth by photometry, bioluminescence, or other means and provide results rapidly, usually in 1 to 2 hour. Compared with urine cultures, these techniques generally exhibit a sensitivity of 95 to 98% and a negative predictive value of > 99% when bacteruria is defined as 10<sup>5</sup> colony-forming unit per milliliter is the standard of comparison (Braunwald *et al.*, 2001).

Microscopy of urine from symptomatic patients can be of great diagnostic value (Cheesbrough, 2001; Wilson & Gaido, 2004; Braunwald *et al.*, 2001). Bacteruria can be detected microscopically using Gram staining of uncentrifuged urine specimens, Gram

staining of centrifuged specimens, or direct observation of bacteria in urine specimen. Gram stain of uncentrifuged urine specimens is a simple method (Wilson & Gaido, 2004). Detecting bacteria in uncentrifuged (fresh) urine indicates urinary infection, i.e bacteruria in excess of  $10^4$ /ml (Cheesbrough, 2001). However, bacteria can not usually be detected microscopically in infections with lower colony count ( $10^2$  to  $10^4$ ). The detection of bacteria by urinary microscopy thus constitutes firm evidence of infection, but the absence of microscopically detectable bacteria does not exclude the diagnosis (Braunwald *et al.*, 2001).

Bacteriuria can be detected chemically when bacteria produce nitrite from nitrate. The biochemical reaction that is detected by the nitrite test is associated with members of the family *Enterobacteriaceae* (Wilson & Gaido, 2004). Urinary pathogens, e.g. *E. coli*, *Proteus*, and *Klebsiella species*, are able to reduce the nitrite normally present in urine in sufficient concentration. When first morning urine is tested, about 80 to 90% of UTI caused by nitrate reducing pathogens can be detected. The test is negative when the infection is caused by pathogens that do not reduce nitrate such as *Enterococcus faecalis*, *Pseudomonas*, and *Staphylococcus* species or when as previously mentioned the bacteria are too few in the urine (Cheesbrough, 2001). Another limitation to the test is that it requires testing a specimen of the first urine produced in the morning, as  $\geq 4$  hour is required for bacteria to convert nitrate to nitrite at levels that are reliably detectable (Wilson & Gaido, 2004). Occasionally the nitrite test is negative because nitrate is lacking in the urine due to person being on diet lacking vegetables (Cheesbrough, 2001).

When carefully sought by means of chamber-count microscopy, pyuria is a highly sensitive indicator of UTI in symptomatic patients. Pyuria is demonstrated in nearly all acute bacterial UTIs, and its absence calls the diagnosis into question (Braunwald *et al.*, 2001). The advantages to urine microscopy are that leukocytes, leukocyte casts, and other cellular elements are observed directly. One disadvantage to urine microscopy is that leukocytes deteriorate quickly in urine that is not fresh or that has not been adequately preserved. In addition, each of these methods has disadvantages that limit its usefulness as a routine test (Carroll *et al.*, 1994). Because of these disadvantages, urine microscopy should be limited to patients in whom pyelonephrities or other more serious infections are suspected.

Leukocyte esterase tests are based on the hydrolysis of ester substrates by proteins with esteriolytic activity. These proteins react with ester substrates to produce alcohols & acids that then react with other chemicals to produce a color change that is proportional to the amount of esterase in the specimen (Wilson & Gaido, 2004). The leukocyte esterase method is less sensitive than microscopy in identifying pyuria but is useful alternative where microscopy is not feasible (Braunwald *et al.*, 2001). Leukocyte esterase can be detected using a reagent strip test such as the BM-Test-LN , which detects with nitrite & leucocytes (LE) or a multi-test reagent strip with an area for leucocytes detection (Cheesbrough, 2001).

Leukocyte esterase tests can yield false-positive test results when the urine is contaminated with bacteria present in vaginal fluid; when the specimen contains eosinophils or *Trichomonas species*, both of which can act as sources of esterase; and when oxidizing agents or formalin react with the test strips to generate false-positive test results. Leukocyte esterase tests may show a decrease in positive test results when the specimen has an elevated specific gravity and/or elevated levels of protein and glucose; when boric acid preservatives are present; when large amounts of ascorbic or oxalic acid are present; and when the patient has received antimicrobial agents, such as cephalothin, cephalexin, or tetracycline (Wilson and Gaido, 2004).

Although many authorities have recommended that urine culture and antimicrobial susceptibility testing be performed for any patient with a suspected UTI, it may be more practical and cost effective to manage women who have symptoms characteristic of acute uncomplicated cystitis without an initial culture. A positive result for pyuria and/or bacteruria provides enough evidence of infection to indicate that urine culture and susceptibility testing can be omitted and the patient treated empirically. Urine should be cultured, however, when a woman's symptoms and urine examination findings leave the diagnosis of cystitis in question. Pre-therapy culture and susceptibility testing are also essential in the management of all patients with suspected upper tract infections and of those with complicating factors, as in these situations any of a variety of pathogens may be involved and antibiotic therapy is best tailored to the individual organisms (Braunwald *et al.*, 2001). Susceptibility testing is also essential in the management of patients with a history of recurring UTI (Cheesbrough, 2001). Thus, each laboratory should have

guidelines by which pathogens are tested for antimicrobial susceptibility. These guidelines should be developed and antimicrobial susceptibility tests should be performed and reported according to the most recent version of the NCCLS guidelines [NCCLS, 2002].

### **1.2.8. Treatment**

Antimicrobial therapy is seldom indicated for asymptomatic infection, but usually indicated for amelioration of symptoms (Nicolle, 2003). Except in acute uncomplicated cystitis in women, a quantitative urine culture, a gram stain, or an alternative rapid diagnostic test should be performed to confirm infection before treatment is begun. When culture results become available, antimicrobial sensitivity testing should be used to direct therapy (Braunwald *et al.*, 2001).

Management of uncomplicated UTIs has traditionally been on two important principles: the spectrum of organisms causing acute UTI is highly predictable (*E. coli* accounts for 75% to 90% and *Staphylococcus saprophyticus* accounts for 5% to 15% isolates), and the susceptibility patterns of these organisms have also been relatively predictable. As a result, empiric therapy with short-course TMP-SMX has been a standard management approach for uncomplicated cystitis or TMP alone for patients with sulfa allergies (Gupta, 2002; Nicolle, 2003). However, antibiotic resistance is now becoming a major factor not only in nosocomial UTIs, but also in uncomplicated community-acquired UTIs (Gupta, 2002).

Another study reported that ciprofloxacin, ofloxacin, and TMP-SMX have similar efficacy when given for 3 days to treat acute symptomatic, uncomplicated lower urinary tract infection in women (MacCarty, 1999). In fact, guidelines recommended TMP-SMX for empirical treatment of uncomplicated UTI unless TMP-SMX resistance in a community exceeds 10% to 20%. The rationale for this 10% to 20% cutoff appears to be related to clinical and economical considerations and to concerns about the emergence of fluoroquinolone-resistant bacteria. In patients with uncomplicated UTIs caused by uropathogens resistant to TMP-SMX who were treated with this drug combination, clinical outcomes were clarified recently and found to be suboptimal (< 60% clinical cure) (Miller and Tang, 2004; Perfetto *et al.*, 2004).

On the other hand, the emergence and dissemination of antimicrobial resistance can be reduced with the use of agents that have favorable pharmacokinetic/pharmacodynamic

profiles and convenient dose (Blondeau, 2004). Fluoroquinolone antimicrobial agents have taken on an expanding management role for UTIs. In fact, the recent Infectious Diseases Society of America clinical management guidelines for UTI recommend fluoroquinolones as first-line therapy for uncomplicated UTI in areas where resistance is likely to be of concern. Fluoroquinolones have demonstrated high bacteriologic and clinical cure rates, as well as low rates of resistance, among most common uropathogens (Schaeffer, 2002). They are indicated for the management of acute uncomplicated UTIs, as well as complicated and severe UTI and pyelonephritis, in adults. Use of fluoroquinolones is recommended for uncomplicated UTIs in areas where the incidence of cotrimoxazole resistance exceeds 10%, and in patients who cannot tolerate sulfonamides or TMP, (Blondeau, 2004; Schaeffer, 2002).

There are currently seven fluoroquinolones with indications for UTI in the United States. However, only three are commonly used: levofloxacin, ciprofloxacin, and to a lesser extent, gatifloxacin (Schaeffer, 2002). Ciprofloxacin is a widely used fluoroquinolone with high bacterial activity against uropathogens and well-established clinical efficacy in the treatment of UTIs (Blondeau, 2004).

Many of the fluoroquinolone agents have once-daily dosing regimens, enhancing patients adherence. In addition, levofloxacin and gatifloxacin have same-dose bioequivalency between their intravenous and oral formulations, allowing for “switch” or step-down therapy from parenteral to oral formulations of the same agent at the same dose. Fluoroquinolone properties include a broad spectrum of coverage, low rates of resistance, and good safety profiles (Schaeffer, 2002).

A new, extended-release formulation of ciprofloxacin (Cipro XR) provides systemic drug exposure comparable with that achieved with twice-daily administration of conventional, immediate-release ciprofloxacin, while also attaining higher maximum plasma concentrations with less interpatient variability. Therapeutic drug concentrations with extended-release ciprofloxacin are established immediately after dose administration and maintained throughout the 24-hour dosage interval, permitting convenient, once-daily treatment. Clinical trial results confirm that extended-release ciprofloxacin is as safely used and effective as the conventional, immediate-release formulation of ciprofloxacin in patients with uncomplicated UTIs, complicated UTIs or acute uncomplicated

pyelonephritis. These findings support the use of extended-release ciprofloxacin as a well tolerated, effective and convenient therapy for UTIs, which may improve patients adherence to therapy and, thereby, reduce the risk of infection recurrence and emergence of antimicrobial resistance (Blondeau, 2004).

Alternative first line agents include nitrofurantoin, and fosfomycin (McCarty *et al.*, 1999). Nitrofurantoin was the first truly effective and safe antimicrobial therapy for UTI but its spectrum of activity is limited (Nickel, 2005). On the other hand, another study by Hooton (2003) indicated that use of nitrofurantoin does not share cross-resistance with more commonly prescribed antimicrobials and its more widespread use is justified from a public health perspective as a fluoroquinolone-sparing agent. Beta-lactams and fosfomycin should be considered second-line agents for empirical treatment of cystitis.

Complicating UTIs (those arising in a setting of catheterization, instrumentation, urologic anatomic or functional abnormalities, stones, obstruction, immunosuppression, renal disease, or diabetes) are typically due to hospital-acquired bacteria, including *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Pseudomonas*, *Enterococci*, and *Staphylococci*. Many of the infecting strains are antibiotic resistant. Empirical antibiotic therapy ideally provides broad-spectrum coverage against these pathogens. In patients with minimal or mild symptoms, oral therapy with more severe illness, including acute pyelonephritis or suspected urosepsis, hospitalization and parenteral therapy should be undertaken. Commonly used empirical regimens include imipenem alone, penicillin or cephalosporin plus an aminoglycoside, and (when the involvement of *Enterococci* is unlikely) ceftriaxone or ceftazidime (Braunwald *et al.*, 2001). Specifically, for the empirical management of CAUTIs, currently, the most appropriate agent seems to be co-amoxiclavate, ciprofloxacin, and nitrofurantoin (Wazait *et al.*, 2003). When information on the antimicrobial sensitivity pattern of the infecting strain becomes available, a more specific antimicrobial regimen can be selected. Therapy should generally be administered for 10 to 12 days, with the exact duration depending on the severity of the infection and the susceptibility of the infecting strain. Follow-up cultures 2 to 4 weeks after cessation of therapy should be performed to demonstrate cure (Braunwald *et al.*, 2001).

In addition, there are special considerations in the management of UTI among selected populations, including postmenopausal and pregnant women, and women with

frequent recurrent UTIs (Nicolle, 2003). In pregnancy, acute cystitis can be managed within 7 days of treatment with amoxicillin, nitrofurantoin, or a cephalosporin. All pregnant women should be treated with oral amoxicillin, macrocrystalline nitrofurantoin, cefpodoxime proxetil, or TMP-SMX. After treatment, a culture should be performed to ensure cure, and culture should be repeated monthly thereafter until delivery. Acute pyelonephritis in pregnancy should be managed with hospitalization and parenteral antibiotic therapy, generally with cephalosporin or extended-spectrum penicillin. Continuous low-dose prophylaxis with nitrofurantoin should be given to women who have recurrent infections during pregnancy (Braunwald *et al.*, 2001).

In general, factors to be considered in the selection of appropriate antimicrobial therapy include pharmacokinetics, spectrum of activity of the antimicrobial agent, resistance prevalence of the community, potential for adverse effects, and duration of therapy. Ideal antimicrobial agents for UTI management have primary excretion routes through the urinary tract to achieve high urinary drug levels (Nicolle, 2003).

#### **1.2.9. Prevention**

Women who experience frequent symptomatic UTIs ( $\geq 3$  per year on average) are candidates for long-term administration of low-dose antibiotics directed at preventing recurrences. Such women should be advised to avoid spermicide use and to void soon after intercourse. Daily or thrice-weekly administration of a single-dose of TMP-SMX (80/400 mg), TMP alone (100 mg), or nitrofurantoin (50 mg) has been particularly effective. Norfloxacin and other fluoroquinolones have also been used for prophylaxis. Prophylaxis should be initiated only after bacteriuria has been eradicated with a full-dose treatment regimen. The same prophylactic regimen can be used after sexual intercourse to prevent episodes of symptomatic infection in women in whom UTIs are temporally related to intercourse. Other patients for whom prophylaxis appear to have some merit include men with chronic prostates; patients underlining prostatectomy, both during the operation and in the postoperative period; and pregnant women with symptomatic bacteriuria. All pregnant women should be screened for bacteriuria in the first trimester and should be treated if bacteriuria is demonstrated (Braunwald *et al.*, 2001).

Non-antibiotic means of preventing UTI, such as increasing colonization resistance with lactobacilli, or the use of vaccines, which provide inhibition of adherence of

uropathogens to uroepithelial cells, show very promising experimental results (Malinverni, 2002).

From the viewpoint of prevention of nosocomial UTI infections, the urinary indwelling catheter should be carefully managed (Arakawa, 2002). Because the most important risk factor for infection is duration of catheterization, indwelling urethral catheterization should be avoided or at least limited whenever possible (Saint and Chenoweth, 2003). Additional methods to prevent this infection include aseptic insertion and maintenance use of a closed drainage system, anti-infective catheters in patients at high risk for infection, and systemic antibiotics in selected patients (Saint and Chenoweth, 2003, Madigan & Neff, 2003; Kumon *et al.*, 2001). In one study, the nitrofurazone-containing urinary catheter was broadly active in-vitro against susceptible and multidrug resistant strains of diverse bacterial species characteristics of catheter associated urinary tract infection and it exhibited persistent inhibitory against some isolates for up to 5 days. On the other hand, systemic antimicrobial prophylaxis is not recommended by authorities in the field because of the associated risk of selecting for resistant microorganisms (Johnson *et al.*, 1999).

Alternative urinary collection strategies may be appropriate in certain patient groups. Specifically, condom catheters should be considered in patients requiring long-term indwelling drainage, and intermittent catheterization seems appropriate in patients with injured spinal cords (Warren, 1997).

#### ***1.2.10. Summary***

Urinary tract infections are one of the most common bacterial infections in humans both in the community and hospital setting. Particularly, catheter-associated urinary tract infection is a major health care problem. It is the single most common type of nosocomial infection, and because of its high incidence, it is responsible for an enormous aggregate burden of morbidity, mortality, and increased health care costs.

Although many different organisms can infect the urinary tract, *E. coli* remains the most frequent cause of both community acquired (non-catheter associated) and catheter associated urinary tract infections. Gram-positive cocci were isolated more frequently from a hospital setting and the most common were *Enterococcus spp.*

Antimicrobial resistance is a growing problem and a cause of major concern in many countries. Strains isolated from CAUTIs display markedly greater antimicrobial resistance than organisms that cause community-acquired UTIs. High-level multidrug resistance to the commonly used antimicrobial agents including quinolones was observed in organisms isolated from catheterized patients. Ironically, antimicrobial therapy given to patients who developed CATUI provides further selection pressure for the emergence of even more highly resistant organisms. Thus, when culture results become available, antimicrobial sensitivity testing should be performed to direct therapy.

Although many interventions have been evaluated as possible ways to prevent CAUTI, only reduced duration of indwelling catheter use, strict maintenance of a closed drainage system, and prophylactic systemic antimicrobial therapy have been consistently found to be effective. However, systemic antimicrobial prophylaxis is not recommended by authorities in the field because of the associated risk of selecting for resistant organisms.

#### ***1.2.11. Significance of the proposed study***

Nosocomial UTIs account for up to 40% of all hospital acquired infection (Kalsi *et al.*, 2003) and is usually associated with catheterization (Warren, 2001). Millions of urethral catheters are used each year (Warren, 1997). However, urinary catheter related infections are commonly seen in several different patient populations and lead to substantial morbidity (Madigan & Neff, 2003). Catheter subverts several host defenses to allow bacterial entry at the rate of 3 % to 10 % incidence per day, and its presence encourages the organism's persistent residence in the urinary tract (Warren, 1997).

Infection associated with an indwelling catheter is a representative type of biofilm infection occurring in the urinary tract (Kumon *et al.*, 2001). Because biofilm has important implication for the pathogenesis, treatment, and prevention of catheter related infection, recent attention has appropriately focused on biofilm development on the catheter surface (Saint and Chenoweth, 2003.).

Research evidence from 1992-2002 indicated that in 1,540 nursing home residents, catheterized residents had three times risk of hospitalization, length of hospitalization and length of antibiotic therapy compared to residents who were never catheterized. Residents who were catheterized for 79-100% of their days in the nursing home were three times more likely to die within a year, compared to those who were never catheterized (Madigan

and Neff, 2003). This study also showed that long-term catheterization (>90 continuous days) is associated with a higher incidence of chronic pyelonephritis and chronic renal inflammation.

Apart from this, resistance rates among common uropathogens continue to evolve and appear to be increasing to many commonly used agents (Mazzulli, 2002). The current trend of rising-TMP-SMX and beta-lactam resistance rate is worrisome (Gupta, 2003). Especially, the increasing prevalence of resistance strains of *E. coli* to TMP-SMX (Manges *et al.*, 2001; Burman *et al.*, 2003; Brown *et al.*, 2002; Raz *et al.*, 2002) and VRE in hospitals (Gunther *et al.*, 2001; Mulvey *et al.*, 2000) complicate the management of urinary tract infections. Of more concern, however, are the emerging issues of fluoroquinolone resistance and multidrug resistance among community-acquired isolates (Gupta, 2003).

In addition, the patterns of antibiotic resistance associated with CAUTI have changed over the last 5 years, as have the types of organism. As a result, in 1996, CAUTIs were least often resistant to ciprofloxacin (8.0%) followed by co-amoxiclav (18.5%) and cephalexin (25.4%). In 2001, CAUTIs were least often resistant to co-amoxiclav (22.5 %), followed by ciprofloxacin (27.2%) and nitrofurantion (28.8%) (Wazait *et al.*, 2003).

Even though there are published information concerning the etiology and resistance pattern of community acquired UTIs (Gedebou, 1983; Ringertz *et al.*, 1990; Woldaye and Erge, 1997; Moges *et al.*, 2002), local data regarding CAUTIs are sparse in Ethiopian patients (Gedebou *et al.*, 1988; Habte-Gebr *et al.*, 1988). Therefore, the present study was undertaken in order to investigate the bacterial profile and the resistance pattern of CAUTI in comparison with non-catheterized UTIs in Jimma University Hospital, Southwest Ethiopia.

### *1.3. Objectives of the study*

#### *General objective*

- **To assess the bacterial profile and pattern of antibiotic resistance of catheter associated and non-catheter associated urinary tract infections.**

#### *Specific objectives*

- **To see the distribution of different bacterial pathogens isolated from both catheterized and non-catheterized patients with UTIs.**
- **To compare the most prevalent bacterial pathogens isolated from both catheterized and non-catheterized patients with UTIs.**
- **To determine the susceptibility pattern of isolates to the commonly used antimicrobial agents by using disk diffusion method.**

## **CHAPTER III. MATERIALS AND METHODS**

### **2.1. Study design, period and area**

A prospective cross sectional study was conducted between January and March 2005. The study was conducted at the Jimma University Hospital located in Jimma town, Southwest Ethiopia.

### **2.2. Study subjects**

*Catheterized patients  $\geq 72$  hrs ( $n_1 = 30$ ) admitted to Medical, Surgical, Gynecology, and Maternity wards and non-catheterized patients ( $n_2 = 90$ ) from the outpatient departments with symptoms of UTI were included in the study. Among the non-catheterized patients, only one person gave history of catheterization.*

Sample size was determined using EPI-6 version statistical soft ware package where  $P_1$  (prevalence of UTI in catheterized study subjects) = 70 %,  $P_2$  (prevalence of UTI in non-catheterized study subjects) = 35 %, Power of test = 90%, 95% confidence interval,  $n_1$  (number of catheterized study subjects):  $n_2$  (number of non-catheterized study subjects) = 1: 3.

Histories were taken from each patient and the hospital charts for every individual included in the study were reviewed. All the relevant data (Demographic, Clinical, and Laboratory data) were recorded and transferred to the questionnaire prepared for this study (see appendix I).

Urinary tract infection is considered when a patient presents with symptoms of dysuria/ frequency of micturition, suprapubic/flank pain with fever. Patients treated with antimicrobials with the preceding one-week were excluded.

### **2.3. Sample collection, handling, and transport**

A freshly voided midstream urine samples (10-20 ml) were collected from non-catheterized patients in a wide mouth sterile container after cleansing the genitals with soap and water. Catheter urine specimens (10-20ml) from catheterized patients were transferred to a sterile container after cleansing the out let of catheter with appropriate disinfectant. The urine specimens were then delivered to the laboratory immediately and processed within one hour.

#### **2.4. Culture and identification**

Urine specimens obtained from both groups were inoculated on blood and MacConkey agar (Oxoid, Ltd., Basingstoke, Hampshire, England) by using calibrated loop (0.001/ml). Cultures were incubated in aerobic atmosphere at 37°C for 24 hrs. A positive urine culture was defined as colony count  $\geq 10^5$  cfu/ml for mid stream urine and  $\geq 10^2$  cfu/ml for catheter urine. All positive cultures were further identified by their characteristics appearance on the media and confirmed by the pattern of biochemical reactions using the standard procedures (Baron & Finegold, 1990). All the isolated uropathogens were kept frozen at  $-20^\circ\text{C}$  in 1 % nutrient agar (Oxoid, Ltd) until antimicrobial sensitivity test was done.

#### **2.5. Antimicrobial susceptibility testing of uropathogens**

The antimicrobial susceptibility testing of all isolates was done by the standard disk diffusion method (Bauer *et al.*, 1966) using commercial disks (Oxoid). Each isolates was taken from the freezing medium and sub cultured on MacConkey/blood agar (Oxoid) and incubated in aerobic atmospheres at 37°C for 24 hours.

When pure culture was obtained, a loopful bacteria was taken from a colony and was transferred to a tube containing 5ml of normal saline and mixed gently until it formed a homogenous suspension. The turbidity of the suspension was then adjusted to the density of a McFarland 0.5 (Mary-l'Etoil, France) in order to standardize the inoculum size. A sterile cotton swab was then dipped into the suspension and the excess was removed by gentle rotation of the swab against the surface of the tube. The swab was then used to distribute the bacteria evenly over the entire surface of Mueller-Hinton agar (Oxoid). The inoculated plates were left at room temperature to dry for 3-5 minutes. With the aid of sterile needle the following concentration of antibiotic discs were put on the surface of Mueller-Hinton

agar (Oxoid): amikacin (30 µg), ampicillin (10µg), amoxicillin (10 µg), amoxicillin-clavulanic acid (30 µg), carbenicillin (30 µg), cephalexin (30 µg), ciprofloxacin(5 µg), gentamicin(10 µg), methicillin(5 µg), nalidixic acid (30 µg ), nitrofurantoin (300 µg), oxacillin(1 µg), Polymixin B (300 units), TMP-SMX (25 µg) and vancomycin (30 µg). The plates were incubated at 37°C for 24 hours.

Reference strains of *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923) and *P. aeruginosa* (ATCC 27853), sensitive to the antimicrobial agents tested were used as a quality control throughout the study. The results were interpreted according to the most recent version of the National Committee for Clinical Laboratory Standards (NCCLS, 2002).

Multi-drug resistance was defined as resistance to three or more of the antimicrobials tested.

## **2.6. Statistical analysis**

SPSS 11.5 version statistical soft ware package was used for statistical analysis. Chi-Square and Fisher's exact test were applied to test whether differences between values are significant. p values < 0.05 was considered as statistically significant.

## **2.7. Ethical consideration**

The M.Sc research project was approved by the Department of Microbiology, Immunology and Parasitology, the Faculty Research Publications Committee, was endorsed by the Faculty Academic commission, and was ethically cleared. Written informed consent was obtained from all patients participating in the study (see Appendix II). The results of culture and sensitivity were given to the attending physicians for subsequent management of patients.

## **CHAPTER III. RESULTS**

### **3.1. Study subjects**

A total of 120 study subjects with symptoms of UTI were investigated during the study period. Of these, 90 were non-catheterized (age range 7-60 years) and 30 were catheterized (age range 20-78 years). Distribution of study subjects by sex is shown in Table 1. Of the 90 non-catheterized patients, 66 (73.4%) were females and 24 (26.6%) were males. The ratio of male to female was 0.36: 1. Of the 30 catheterized patients, 10 (33.3%) were females and 20 (66.7%) were males. The ratio of male to female was 2 to 1. Non-catheterized patients aged 21-30 years predominated and represented 31.1 % of all, whereas in catheterized patients the age group > 50 years old predominated and represented 33.3%.

**Table 3.1. Sex distribution of patients investigated for UTIs in Jimma University Hospital, Southwest Ethiopia**

Study subjects	SEX		Total
	Males no. (%)	Females no. (%)	
<b>Non-Catheterized</b>	24 (26.6)	66 (73.4)	90
<b>Catheterized</b>	20 (66.7)	10 (33.3)	30
<b>Total</b>	44 (36.6)	76 (63.4)	120

### ***3.2. Rate of UTI among non-catheterized and catheterized patients***

The rates of UTIs among non-catheterized and catheterized patients are shown in Table 3.2. Significant bacteruria was observed in 20/90 (22.2%) and 13/30 (43.3%) of non-catheterized and catheterized patients, respectively ( $p < 0.05$ ). The overall prevalence of UTI in both groups was 33/120 (27.5%). The overall prevalence of UTI is higher in females (20%) than in males (7.5%), but there was no statistical significant difference between the two groups ( $p > 0.05$ ). However, statistically significant association was observed only in the non-catheterized group ( $p < 0.05$ ). In this study, UTI is more common

in the elderly patients (aged > 50 years) among catheterized patients, whereas in the non-catheterized patients more common in the age groups between 11 and 20 years.

**Table 3.2. Rate of UTI among non-catheterized and catheterized patients in Jimma University Hospital, Southwest Ethiopia**

Study groups	Significant Bacteruria		Total
	Yes	No	
	no. (%)	no. (%)	
<b><u>Non-catheterized</u></b>			
Male	1 (4.3)	23 (96.7)	24 (100)
Female	19 (28.3)	47 (71.7)	66 (100)
Total	20 (22.2)	70 (77.8)	90 (100)
<b><u>Catheterized</u></b>			
Male	8 (40)	12 (60)	20 (100)
Female	5 (50)	5 (50)	10 (100)
Total	13 (43.3)	17 (56.7)	30 (100)

As shown in Table 3.3, the rate of UTI is increased as the duration of catheterization is increased. All patients who had been catheterized for one week and more, showed significant bacteruria.

**Table 3.3. Rate of UTI with respect to duration of catheterization**

Duration of catheterization	Significant Bacteruria		Total No. (%)
	Yes no. (%)	No no. (%)	
3 days	0 (0)	10 (100)	10 (100)
1 week	4 (36)	7 (64)	11 (100)
2 weeks	3 (100)	- -	3 (100)
>2 weeks	6 (100)	- -	6 (100)

### 3.3. Causative organisms

The number and percentage of each uropathogen isolated from mid-stream and catheter urine samples are shown in Table 3.4. A total of 33 uropathogens were isolated, 20 from non-catheterized and 13 from catheterized patients (22.2% vs. 43.3%,  $p < 0.05$ ). *Klebsiella spp.* (33.3%) and *E. coli* (27.7%) were the most common bacteria pathogens isolated from both groups. The most frequently isolated species from non-catheterized patients was *Klebsiella* (40%) followed by *E. coli* (30%). Among catheterized patients, *E. coli* and *Klebsiella* species were found to be the most frequently isolated pathogens (each of them accounts 23%). In addition, *Proteus spp.*, *Pseudomonas spp.* and coagulase negative *Staphylococci* were isolated only from catheterized patients. More than one bacteria (mixed type) were isolated in equal proportions (15%) from both groups. The gram positive and negative bacteria constituted 3 (9%) and 25 (76%), respectively. There are no statistical significant differences in the isolation frequency of each pathogen between non-catheterized and catheterized patients ( $p > 0.05$ ).

**Table 3.4. Distribution of uropathogens isolated from mid-stream and catheter urine samples in Jimma University Hospital, Southwest Ethiopia**

<u>Uropathogen</u>	<b>Type of urine specimen</b>		
	<b>Mid stream urine</b>	<b>Catheter urine</b>	<b>Total</b>
	No. (%)	No. (%)	No. (%)
<i>Klebsiella spp.</i>	8 (40)	3(23)	11 (33.3)
<i>E. coli</i>	6 (30)	3(23)	9 (27.7)
<i>Enterobacter spp.</i>	1 (5)	1(8)	2 (6)
<i>Proteus spp.</i>	- -	1(8)	1 (3)
<i>Pseudomonas spp.</i>	- -	1(8)	1 (3)
<i>Citrobacter spp.</i>	1(5)	- -	1 (3)
CONs*	- -	2(15)	2 (6)
<i>S. aureus</i>	1(5)	- -	1 (3)
Mixed type	3 (15)	2(15)	5 (15)
<b>Total</b>	<b>20 (100)</b>	<b>13 (100)</b>	<b>33 (100)</b>

\* Coagulase negative *Staphylococci*

\* Mixed type: more than one type of bacteria

### **3.4. Antimicrobial susceptibility testing**

The resistance pattern of gram-negative bacteria isolated from non catheterized and catheterized patients against 11 antimicrobial agents are shown in Table 3.5a and 3.5b, respectively. Gram-negative isolates from both groups of patients (non-catheterized vs. catheterized) showed a high level (>80%) of resistance to ampicillin (93.4% vs.100%), amoxicillin (82% vs.100%), carbencillin (93.5% vs. 100%) and cephalexin (100% vs.100%). Intermediate level (60-80%) of resistance was found against trimethoprim-sulphamethoxazole (62.5% vs. 77.8%) and low level (< 60%) of resistance observed for amikacin (12.5% vs. 22.2%) and ciprofloxacin (6.3% vs. 33.3%), nitrofurantoin (0% vs. 55.6%), nalidixic acid (12.5% vs. 44.4%) and amoxicillin-clavulanic acid (56.3% vs.

33.3%). Low level (25%) and high level (100%) of resistance to gentamicin was observed in non-catheterized and catheterized patients, respectively.

The resistance pattern of three-gram positive isolates (one *S. aureus* from non-catheterized and two coagulase negative *Staphylococci* from catheterized patients) is presented in Table 3.5c. All the isolates showed a high level of resistance (>80%) to ampicillin, amoxicillin, cephalixin, methicillin, oxacillin, nalidixic acid and ciprofloxacin. All the strains were sensitive to amoxicillin-clavulnic acid and polymyxin B. Vancomycin

Multidrug resistance to the commonly used antibiotics (ampicillin, amoxicillin, cephalixin, & carbenicillin) was observed in all (100%) and 68.7 % of gram negative bacteria isolated from catheterized and non-catheterized patients, respectively. In addition, Multidrug resistance (resistance to 7 antimicrobial agents) was observed in all (100 %) of gram positive isolates.

**Table 3.5a. Resistance pattern of gram-negative bacteria isolated from non-catheterized patients against 11 antimicrobial agents**

Organisms	No.	Antimicrobial agents (% resistance)										
		AK	AMP	AML	AMC	CL	CIP	CAR	CN	F	SXT	NA
<i>E. coli</i>	6	1(16.7)	6(100)	5(83.3)	3(50)	6(100)	1(16.7)	5(83.3)	1(16.7)	- -	3(50)	1(16.7)
<i>Klebsiella spp</i>	8	- -	8(100)	8(100)	5(62.5)	8(100)	- -	8(100)	3(37.5)	- -	6(75)	- -
<i>Enterobacter spp</i>	1	- -	1(100)	- -	1(100)	1(100)	- -	1(100)	- -	- -	1(100)	- -
<i>Citrobacter spp</i>	1	1(100)	- -	- -	- -	1(100)	- -	1(100)	- -	- -	- -	1(100)
<i>Total</i>	16	2(12)	15(93.75)	13(82)	9(56.2)	16(100)	1(6.3)	15(93.7)	4(25)	- -	10(62.5)	2(12.5)

AK: Amikacin, AMP: Ampicillin, AML: Amoxicillin, AMC: Amoxicillin-clavulanic acid, CL: Cephalexin, CIP: Ciprofloxacin, CAR: Carbenicillin, CN: Gentamicine, F: Nitrofurantoin, SXT: Ttrimethoprim/sulfamethoxazole, NA: Nalidixic acid,

**Table 3.5b. Resistance pattern of gram-negative bacteria isolated from catheterized patients against 11 antimicrobial agents**

Organisms	No.	Antimicrobial agents (% resistance)										
		AK	AMP	AML	AMC	CL	CIP	CAR	CN	F	SXT	NA
<i>E. coli</i>	3	2(66.7)	3(100)	3(100)	2(66.7)	3(100)	3(100)	3(100)	3(100)	1(33.3)	2(66.7)	3(100)
<i>Klebsiella</i>	3	- -	3(100)	3(100)	1(33.3)	3(100)	- -	3(100)	3(100)	1(33.3)	2(66.7)	- -
<i>Proteus</i>	1	- -	1(100)	1(100)	- -	1(100)	- -	1(100)	1(100)	1(100)	1(100)	- -
<i>Pseudomonas</i>	1	- -	1(100)	1(100)	- -	1(100)	- -	1(100)	1(100)	1(100)	1(100)	1(100)
<i>Enterobacter</i>	1	- -	1(100)	1(100)	- -	1(100)	- -	1(100)	1(100)	1(100)	1(100)	- -
Total	9	2(22.2)	9(100)	9(100)	3(33.3)	9(100)	3(33.3)	9(100)	9(100)	5(55.6)	7(77.8)	4(44.4)

AK: Amikacin, AMP: Ampicillin, AML: Amoxicillin, AMC: Amoxicillin-clavulanic acid, CL: Cephalexin, CIP: Ciprofloxacin, CAR: Carbenicillin, CN: Gentamicine, F: Nitrofurantoin, SXT: Ttrimethoprim/sulfamethoxazole, NA: Nalidixic acid,

**Table 3.5c. Resistance pattern of gram-positive bacteria isolated from non-catheterized and catheterized patients against 10 antimicrobial agents**

Organisms	No.	Antimicrobial agents (% resistance)										
		AMP	AML	AMC	CL	MET	OX	VA	PB	NA	CIP	
Coagulase negative staphylococcus	•	2	2(100)	2(100)	- -	2(100)	2(100)	2(100)	2(100)	- -	2(100)	2(100)
<i>S. aureus</i>	••	1	1(100)	1(100)	- -	1(100)	1(100)	1(100)	1(100)	- -	1(100)	1(100)
Total		3	3(100)	3(100)	- -	3(100)	3(100)	3(100)	3(100)	- -	3(100)	3(100)

AK: Amikacin, AMP: Ampicillin, AML: Amoxicillin, AMC: Amoxicillin-clavulanic acid, CL: Cephalexin, CIP: Ciprofloxacin, CAR: Carbenicillin, CN: Gentamicine, F: Nitrofurantoin, SXT: Trimethoprim/sulfamethoxazole, NA: Nalidixic acid, MET: Methicillin, OX: Oxacillin, VA: Vancomycin, PB: Polymixin-B

- : Isolated from catheterized patients
- : Isolated from non-catheterized patients

## CHAPTER IV. DISCUSSION

Catheter associated urinary tract infection (CAUTI) is the most common nosocomial infection in hospitals and nursing homes worldwide with more than one million episodes in the United States alone. Although the costs of catheter-associated urinary tract infections are not as high as for example a deep surgical site infection or a nosocomial pneumonia, CAUTIs are a cause for concern as they are a major reservoir of resistant pathogens. Numerous studies have documented a high prevalence of resistant pathogens in CAUTI and the association between nosocomial CAUTI and surgical site infections has been made (Tambyah, 2004). Complications arising as a result of catheter uses include bacteremia, developed in 5% of catheterized patients, increased risk by 5 fold and case fatality rate in 13% of the same group of patients (Hartstein *et al.*, 1981). Moreover, many catheter associated infecting strains display markedly greater antimicrobial resistance than organisms that cause community-acquired UTIs. As a result, effective management of UTIs particularly in the inpatient settings has been complicated.

Therefore, the present study was undertaken in order to investigate the bacterial profile and the resistance pattern of CAUTI in comparison with non-catheterized UTIs in Jimma University Hospital, Southwest Ethiopia.

All patients (non-catheterized and catheterized) with symptoms and signs of UTI were from the different units of inpatient and outpatient Department of Jimma University Hospital.

The frequency of detection of UTI from 90 non-catheterized and 30 catheterized patients are presented in Table 3.2. The overall prevalence of UTI in both groups was 27.5%. This agrees well with previous studies conducted in Addis, Ababa, Ethiopia (Gedebou, 1983; Wolday and Erge, 1997). However, there is a report from Gondar, Ethiopia with higher prevalence of UTI (40%) (Moges *et al.*, 2002).

In this study, significant bacteruria was observed in 22.2% and 43.3% of non-catheterized and catheterized patients, respectively. These results indicate that there was a statistical difference in the frequency of detection of UTI from non-catheterized and catheterized patients (22.2% vs. 43.3%,  $p < 0.05$ ). Hence, this study confirms the high prevalence of UTI in catheterized patients as in most catheterized patients in previous Ethiopian studies (Gedebou *et al.*, 1988; Habte-Gebr *et al.*, 1988; Moges *et al.*, 2002) and elsewhere in the world (Tambyah, 2004). This may be explained by the fact that catheter

subverts several host defenses to allow bacterial entry at the rate of 3% to 10% incidence per day, and its presence encourages the organism's persistent residence in the urinary tract. A number of prospective studies have conducted multivariate analysis of the risk factors associated with CAUTI with daily urine cultures to detect all CAUTIs in large numbers of patients (Shapiro *et al.*, 1984; Tambyah, 2004). These studies were found to have remarkably similar results. The most important risk factors have been prolonged catheterization and being female. Other risk factors identified have included catheterization outside the sterile environment of the operating room, being on a urology service which might simply mean having a urinary tract abnormality, other infections, diabetes, malnutrition and renal failure. Interestingly, most of the infection control interventions were found to have a minimal impact on the incidence of CAUTI with one exception if the drainage tube was allowed to be above the level of the patient; that was a major risk factor for infection. There are clearly many challenges that face researchers and clinicians working in the field of CAUTI. Foremost among these must be the prevention of these infections. Effective interventions to prevent CAUTI will doubtless help to reduce the reservoir of resistant pathogens in the intensive care units wards and long-term care facilities. This will be a critical step in the battle against antibiotic resistance (Tambyah, 2004).

Anti-infective catheters were found to be effective to prevent CAUTIs. In one study (Johnson *et al.*, 1999), the nitrofurazone-containing urinary catheter was found to be broadly active in-vitro against susceptible and multidrug resistant strains of diverse bacterial species characteristics of catheter associated urinary tract infection and it exhibited persistent inhibitory against some isolates for up to 5 days. Other alternative is using silver coated catheters. Silver is a well-known antiseptic with a long history, as an antiseptic rather than an antibiotic and the risk of generating antibiotic resistance would be expected to be low. Argyrism is a potential concern that has limited the use of silver on the internal coating of catheters and possibly limited its efficacy. On the other hand, systemic antimicrobial prophylaxis is not recommended by authorities in the field because of the associated risk of selecting for resistant microorganisms

In the present study, the prevalence of UTI is higher in females (20%) than in males (7.5%), but there was no statistical significant difference between them ( $p > 0.05$ ). Similar findings have been reported in the earlier studies done in Ethiopia (Gedebou, 1983; Wolday

and Erge, 1997) and elsewhere in the world (Madigan and Neff, 2003). Although everyone is susceptible to UTI, there are specific subpopulations that are at increased risk of UTI, including infants, pregnant women, the elderly patients with spinal cord injuries and/or catheters, patients with diabetes, multiple sclerosis or acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) and patients with underlying urologic abnormalities. Except during the first few months of life, females are far more susceptible than males to UTI. The higher incidence of UTI in women is suggested to be due to short (about 4 cm), wide urethra, and its termination beneath the labia. This route is particularly predisposing for ascending infection by organisms colonizing the perianal area. Recently, a retrospective population-based study investigated the incidence rate of first-time symptomatic UTI in children less than 6 years of age (Foxman, 2002). The cumulative incidence rate of UTI was 3 times greater in girls (6.6%) than boys (1.8%) (Foxman, 2002). In catheterized patients, the patients own bowel flora may colonize the perineal skin and periurethral area and reach the bladder via the external surface of the catheter. This route is particularly common in women.

In this study, UTI is more common in the elderly patients (aged > 50 years) among catheterized patients, whereas in the non-catheterized patients more common in the age groups between 11 and 20 years. Similar findings have been reported among the non-institutionalized elderly populations, in which genitourinary infections are the second most common form of infection, accounting for nearly 25% of all identified infections (Madigan and Neff, 2003; Foxman, 2003). This suggested that elders residing in long-term care facilities have a high prevalence of chronic genitourinary symptoms and bacteriuria, and are at risk for urinary catheter-associated infections. Asymptomatic bacteriuria is believed to affect up to 50% of geriatric women and 30% of geriatric men. Approximately 11% to 25% of elderly non-catheterized patients develop asymptomatic bacteriuria that generally spontaneously resolves. Similarly, 12% of elderly ambulatory men are determined to have asymptomatic bacteriuria (ASB), frequently with gram-positive uropathogens (Foxman, 2002). Although the majority of cases (76%) spontaneously resolve, infections with urea-splitting bacteria (such as *Proteus*) are more likely to have significant sequelae, including stone formation and permanent renal damage. However, symptomatic UTI among the elderly requires anti microbial therapy (Foxman, 2002).

Whereas the high rate of infection in the age groups between 11 and 20 years (in young females) suggested that sexual intercourse causes the introduction of bacteria into the bladder and is temporally associated with the onset of cystitis it thus appears to be important in the pathogenesis of UTIs in younger women. In addition, use of spermicidal coated condoms dramatically alters the normal bacterial flora and has been associated with marked increases in vaginal colonization with *E. coli* and in the risk of UTI (Braunwald *et al.*, 2001).

The present study also showed that the rate of UTI is increased with duration of catheterization as presented in Table 3.3. This finding is in agreement to those studies reported that nosocomial UTI among newly catheterized is frequently asymptomatic (90%) and the risk of UTI increases with increasing duration of catheterization (Foxman, 2002, Madigan and Neff, 2003; Tambyah, 2004). The overall incidence of bacteriuria is 8% and ranges from 3% to 10% per day (Foxman, 2002).

Detection of bacteriuria within 1 week of catheterization in this study may be related to inadequate precautions. Because, catheter associated urinary tract infections can sometimes be prevented in patients catheterized for < 2 weeks by use of a sterile closed collecting system, by attention to aseptic technique during insertion and care of the catheter, and by measures to minimize cross-infection (Braunwald *et al.*, 2001). The fact that significant bacteriuria was detected in all patients catheterized for 2 weeks and more than 2 weeks suggested that despite precautions, the majority of patients catheterized for > 2 weeks eventually develop bacteriuria.

The number and percentage of each uropathogen isolated from mid-stream and catheter urine samples are shown in Table 3.4. A total of 33 (27.5%) uropathogens were isolated from 90 (22.2%) non-catheterized patients and 13 (43.3%) from 30 catheterized patients ( $p < 0.05$ ). The results of the present study showed that the etiologic pathogens of UTIs mainly belong to gram-negative enteric bacteria (76%). This agrees well with the previous studies conducted in Ethiopia (Gedebou, 1983, Gedebou *et al.*, 1988; Habte-Gabr, 1988; Wolday & Erge, 1997; Moges *et al.*, 2002) and elsewhere in the world (Ronald, 2002).

Among catheterized patients, *E. coli* and *Klebsiella* species were found to be the most frequently isolated pathogens (each of them accounts 23%). Although Wazait *et al.*, (2003) reported that *E. coli* was the most frequently isolated pathogen in all years, in agreement with this study, its frequency declined over time. In contrast to other investigator (Wazait *et al.*,

2003), coagulase negative Staphylococcus was found to be the second most frequent pathogen in this study. However, compared to the non-catheterized UTI isolates, the frequency of gram-positive cocci among catheterized patients is in agreement with Wazait *et al* (2003) report. In both studies, gram-positive cocci were the second most frequent pathogens.

Isolates of *Pseudomonas* and *Proteus*, in this study were found exclusively in catheter-associated urinary tract infections. According to a study conducted at Tikur Anbessa Hospital (Wolday & Erge, 1997), these bacteria were also isolated most frequently from patients in surgical ward. Since both studies indicated that the bacteria were of nosocomial origin, the results of the two studies agree each other. This is supported by other literature (Cheesbrough, 2001), suggesting that urinary tract infections caused by *Pseudomonas* & *Proteus* are associated with hospital-acquired infections, often following catheterization or gynecological surgery.

In contrast to the previous studies done in Addis Ababa and Gondar (Wolday & Erge, 1997; Moges *et al*, 2002), the most frequently isolated species from non-catheterized patients was *Klebsiella* followed by *E. coli*. Some have shown, however, that the percentage of *E. coli* is slowly declining, being replaced by other members of the *Enterobacteriaceae* (Weber *et al.*, 1997; Hryniewicz *et al.*, 2001).

It has been documented that, almost all of the causative organisms of UTIs (uncomplicated and complicated) originate from faecal material or the periurethral environment. The organisms ascend the urinary tract from the urethral opening or from the insertion site of catheters. The etiology of uncomplicated UTIs has generally remained constant over the past 2 decades, albeit with a noticeable increase in antimicrobial resistance in both community-acquired and nosocomial UTIs. The etiology of complicated UTI is more diverse and directly affected by underlying host characteristics than that of uncomplicated UTI.

UTI in the vast majority of patients is caused by a single species, but occasionally there may be a mixed infection. Some microbiologists regard urine cultures with polymicrobial (mixed) growth as contaminants (Denman and Greenough, 1991). However, polymicrobial growth from mid stream urine has been found among patients with confirmed bladder infection. Mixed infections are more likely to occur with underlying disorders that interfere with free urine flow and is frequent also patients with indwelling catheter (Denman and Greenough, 1991). These suggestions agree well with the present study showed that more

than one, bacteria (mixed type) was isolated in equal proportions (15%) from both midstream and catheter urine samples. When mixed infection occurs and contamination is suspected, a repeat should be performed from a carefully collected mid stream urine or preferably by catheterization or suprapubic aspiration.

In this study, the resistance pattern of gram-negative and positive bacteria isolated from non-catheterized and catheterized patients against chosen antimicrobial agents are presented in Tables 3.5a, 3.5b and 3.5c, respectively. Gram-negative isolates from both groups of patients (non-catheterized vs. catheterized) showed a high level (>80%) of resistance to ampicillin, amoxicillin, carbencillin and cephalexin. Intermediate level (60-80%) of resistance was found against trimethoprim-sulphamethoxazole and low level (< 60%) of resistance observed for amikacin and ciprofloxacin, nitrofurantoin, nalidixic acid and amoxicillin-clavulanic acid. Low level (25%) and high level (100%) of resistance to gentamicin was observed in non-catheterized and catheterized patients respectively. Compared to previous studied done in Ethiopia (Gedebou, 1983; Wolday & Erge, 1997; Lindtjorn *et al.*, 1989; Moges *et al.*, 2002), the present study showed a high incidence of resistance to the commonly used prescribed antimicrobial agents.

Resistance rates (56.3 to 100 %) to ampicillin, amoxicillin, cephalexin, carbenicillin, & trimethoprim/sulfamethoxazole were observed in all gram-negative bacteria isolated from both catheterized and non-catheterized patients. The possible explanation for this is that most of these drugs are easily available and may be used indiscriminately, which may lead to a shift to increase prevalence of resistant organisms. In addition, resistance (55.5 to 100 %) to gentamicin, nitrofurantoin, and nalidixic acid was observed in all gram-negative bacteria isolated from catheterized patients. Because all strains from catheterized patients were of nosocomial origin, the wide use of antimicrobial agents in the hospital setting may contribute for the particular resistance pattern of catheter urine isolates.

However, the resistance pattern of individual gram-negative bacteria indicated that except for nitrofurantoin, resistance rate (66.6 to 100%) to all drugs including ciprofloxacin and nalidixic acid in *E.coli* strains isolated from catheterized patients was observed. This is also in agreement with Garau *et al* (1999) report, indicating that the presence of a urinary catheter was found to be risk factors associated with quinolone resistance *E. coli*. This may be explained by the fact that the use of quinolones in patients harboring *E. coli* strains with single-step mutations would select isolates with high levels of resistance to ciprofloxacin. The

increase in susceptibility to nitrofurantoin is most likely to be due to the pattern of empirical prescribing. Nitrofurantoin is less frequently used in Jimma university hospital.

On the other hand, all *Klebsiella species* isolated from both catheterized and non-catheterized patients were sensitive to nalidixic acid, amikacin, and ciprofloxacin. In fact, 62 % and all of the *Klebsiella species* isolated from non-catheterized patients were also sensitive to gentamicin and nitrofurantoin respectively. This also corresponds to other previous studies (Wazait *et al.*, 2003; Kadri *et al.*, 2002; Moges *et al.*, 2002; Wolday and Erge, 1997). On the other hand, in agreement with Wazait *et al.*, (2003) report, amoxicillin-clavulanic acid was found to be effective against other gram-negative bacteria (*Proteus*, *Pseudomonas*, & *Enterobacter*) isolated from catheterized patients. Thus, these findings suggest that in a place where laboratory facilities are available, at least, species identification must be done for appropriate treatment of especially catheter associated urinary tract infection.

However, in almost all cases there is a need to start treatment before the final microbiological results are available. Hence, for empirical management, the most effective in-vitro antimicrobial agents against all gram-negative bacteria isolated from catheterized patients were found to be amikacin followed by ciprofloxacin and amoxicillin-clavulanic acid. Except for amikacin, these results are in agreement with other investigators (Wazait *et al.*, 2003). Although high-level resistance of catheter isolates to gentamicin was observed in this study, higher effectivity of amikacin suggests that the majority of gram-negative bacteria do not develop cross-resistance to uncommon aminoglycosides.

For non-catheterized patients, the nitrofurantoin was found to be effective against all gram negative bacteria. Ciprofloxacin is also effective against 93.3 % of these isolates. Other effective antibiotics were amikacin, nalidixic acid, and gentamicin. This also corresponds to the results reported by other investigators (Kadir *et al.*, 2002; Moges *et al.*, 2002; Wolday *et al.* 1997).

Similar resistance pattern was observed between *E. coli* species isolated from a patient who gave history of previous catheterization and pathogens isolated from catheterized patients. This is supported by a study conducted in Gondar (Moges *et al.*, 2002). This suggests that patients who gave history of previous catheterization may acquire UTIs from the hospital during catheterization.

All the gram-positive isolates showed a high level of resistance (>80%) to ampicillin, amoxicillin, cephalexin, methicillin, oxacillin, nalidixic acid, and ciprofloxacin. This may be related to the production of extended spectrum beta lactamase by resistant bacteria. In addition, *Coagulase negative staphylococci* isolated from catheterized patients were found to be resistant to vancomycin. Resistance to vancomycin implies cross resistance to other cell wall synthesis inhibitors since this drug is not easily available in Ethiopia. On the other hand, amoxicillin-clavulanic acid and polymixin B were effective against all gram-positive bacteria isolated from both groups. This corresponds with other investigator (Moges *et al.*, 2002). Effectiveness of amoxicillin-clavulanic acid may be related to the activity of clavulanic acid, which inhibits beta lactamase produced by resistant bacteria. The fact that polymixin B is not used widely in Ethiopia may explain the susceptibility of resistant bacteria to polymixin B.

The high prevalence of resistance among urinary isolates from Jimma University Hospital to most antimicrobial agents is a reason for considerable alarm. Therefore, there is a need to develop locally relevant guidelines for management of UTI, to disseminate current information on issues like susceptibility patterns of bacteria causing UTI in the local population and to supervise antimicrobial usage in order to promote rational drug use. This is especially important in low-income countries where options for safe, effective, and affordable antimicrobial therapy are already limited. Improvement of the Microbiology laboratory services is also urgent in improving the antimicrobial chemotherapeutic approach to infectious diseases.

## **Conclusion and Recommendations**

This study has shown that *Klebsiella* spp. and *E. coli* were the most common cause of UTI in both non-catheterized and catheterized patients in Jimma University Hospital Southwest Ethiopia. Urinary tract infection is more common in catheterized patients than in non-catheterized patients. Risk of UTI increases with increasing duration of catheterization. Species distribution of uropathogens in catheterized and non-catheterized patients is found to be different. More than one, bacteria (mixed type) were isolated in equal proportions (15%) from midstream and catheter urine samples. UTI is common between the age of 11 and 20 years in the non-catheterized groups and in elderly patients (> 50 yrs) in the catheterized groups. UTI is more common in females than males. The present study also showed a high incidence of resistance to most antimicrobial agents tested. Particularly, increasing fluoroquinolone resistance in pathogens isolated from catheterized patients is frustrating.

When antibiotics treatment is needed, the susceptibility, potential availability, simplicity of use, safety and low cost of the antimicrobial agent has to be taken into account.

Based on this study the following recommendations are made:

1. The microbiological investigations of urine from non-catheterized and catheterized patients with symptoms of UTI yielded a total isolation rate of gram negative and positive bacteria of 27.5%. Still some of the UTI episodes were etiologically unexplained. It is well known that other aerobic and anaerobic bacteria, mycobacteria, fungi, viruses, and parasites would account significant number of UTIs. Further studies should be undertaken in order to ascertain the importance of other etiologic agents responsible for UTIs.
2. Physicians who diagnose and treat patients with UTIs, should seriously be aware of the commonest uropathogens responsible for community acquired and nosocomial UTIs.
3. If antibiotic treatment for UTIs is deemed necessary, then positive urine culture (significant bacteruria) should be obtained before hand, and the antimicrobial susceptibility patterns of uropathogens should be ascertained.
4. The best way of preventing a CAUTI is to remove the catheter or to avoid or at least minimize its use. All studies have shown the duration of catheterization as a significant risk factor for nosocomial CAUTI and bacteremia. One problem is that there are few viable alternatives to a urinary catheter for patients who are incontinent or have urinary obstruction.
5. Aseptic insertion, gloves, and hand washing can minimize nosocomial clusters. Besides, daily bag decontamination with a diluted (1:10) bleach solution has been found effective in reducing bacterial colony forming units to a negligible number.

6. Further nationwide and extensive study on catheter associated urinary tract infections should be considered.

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## APPENDIX-I

Questionnaire for assessment of patient identification, clinical profile and laboratory data of patients at Jimma University Hospital, South West, Ethiopia.

### I. Patient Identification

1. Serial No.....
2. Patient name.....
3. Age.....
4. Sex M/F.....
5. Address .....
6. Out patient/Inpatient
7. Ward: Medical \_\_\_\_\_  
Surgical \_\_\_\_\_  
Gyn & ObS \_\_\_\_\_  
Pediatrics \_\_\_\_\_  
Others \_\_\_\_\_
8. Catheterized Patients Yes.....  
No.....
9. If yes, for how long: 3 days.....  
1 week.....  
2 week.....  
More than 2 week.....
10. Indication for catheterization\_\_\_\_\_
11. History of previous catheterization: Yes.....

No.....

12. State reason for previous catheterization \_\_\_\_\_  
13. History previous antibiotic treatment \_\_\_\_\_

**II. Clinical Profile**

	YES	NO
1. Fever	_____	_____
2. Dysuria	_____	_____
3. Urgency	_____	_____
4. Frequency	_____	_____
5. Flank pain	_____	_____
6. Suprapubic pain	_____	_____
7. Others	_____	_____
Specify:	_____	

**III. Laboratory Data**

1. Date of urine collection-----  
2. Type of specimen: Catheter urine sample.....  
Mid stream urine sample.....  
3. Cultures and Identification  
Significant bacteruria: Yes \_\_\_\_\_  
No \_\_\_\_\_  
Name of the bacteria isolated \_\_\_\_\_

4. Antimicrobial susceptibility testing	S	I	R
1 Amikacin	----	-----	-----
2 Ampicillin	----	-----	-----
3 Amoxicillin	-----	-----	-----
4 Amoxicillin-clavulanic acid	----	-----	-----
5 Carbenicillin	-----	-----	-----
6 Cefpalexin	-----	-----	-----
7 Ciprofloxacin	-----	-----	-----
8 Gentamicin	-----	-----	-----
9 Methicillin	-----	-----	-----
10 Nalidixic acid	-----	-----	-----
11 Nitrofurantoin	-----	-----	-----
12 Oxacillin	-----	-----	-----
13 Polymixin B	-----	-----	-----
14 TMP-SMX	-----	-----	-----
15 Vancomycin	-----	-----	-----

**IV. Comments** \_\_\_\_\_  
 \_\_\_\_\_

**APPENDIX-II. CONSENT FORM**

(To be translated in to the patient's language)

The objective of this study is to assess the bacterial profile and pattern of antimicrobial resistance of catheter-associated urinary tract infection in comparison with non-catheterized UTIs. Because the type of organisms and pattern of antimicrobial resistance in catheter-associated and non-catheterized UTIs are different, the results of this study are believed to be important to treat patients appropriately. Therefore, I am requesting you to participate in the study, which would require your response to an interview, physical examination and to provide 10-25 ml urine sample for laboratory examination. Results will be reported to the requesting physician for appropriate treatment and management.

I \_\_\_\_\_ here by give my consent for giving of the requested information and urine specimen as the doctors find best for me.

Signature: \_\_\_\_\_ Date \_\_\_\_\_