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Prevalence of urinary tract infection and antibiotic susceptibility among women in child bearing age in Northern area of Bangladesh

Zahan, Rozina Aktar

University of Rajshahi

PREVALENCE OF URINARY TRACT INFECTION AND ANTIBIOTIC SUSCEPTIBILITY AMONG WOMEN IN CHILD BEARING AGE IN NORTHERN AREA OF BANGLADESH

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BY

ROZINA AKTAR ZAHAN
(MBBS, University of Rajshahi)

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Molecular Biology laboratory
Institute of Biological Sciences
University of Rajshahi
Rajshahi-6205, Bangladesh

DEDICATED TO

My parents I owe my life and basic learning

My husband for his great patience, co-operations and sacrifices

My children, my inheritance and future

My brothers and sisters for their continuous support and inspiration

My relatives for their love and affections

My neighbors and villagers for whom I am a social being

My colleagues and fellows I feel always

My teachers for their teaching and advices

Philosophers and social reformers for whom I feel life

And mankind whom I interacted in different spheres of life.

DECLARATION

I, hereby, declare that, the research work as a dissertation entitled "**Prevalence of urinary tract infection and antibiotic susceptibility among women in child bearing age in Northern area of Bangladesh** " submitted to the Institute of Biological Sciences, the University of Rajshahi, Rajshahi, Bangladesh for the degree of Master of Philosophy (M. Phil.) is the result of the original research work carried out under the supervision of **Professor Dr. Parvez Hassan,** Institute of Biological Sciences, University of Rajshahi, Rajshahi, Bangladesh and **Dr Abdullah-Al-Baki**, Associate Professor, Armed Forces Medical College, Dhaka, Bangladesh.

I, further, declare that, this dissertation or part thereof has not been the basis for the award of any degree, diploma or associate ship of any other similar title.

(Rozina Aktar Zahan)
Signature of the candidate

CERTIFICATE

We do hereby certify that, **Rozina Aktar Zahan** is the sole author of the dissertation entitled **"Prevalence of urinary tract infection and antibiotic susceptibility among women in child bearing age in Northern area of Bangladesh".** This dissertation or part thereof has not been previously submitted for the award of any degree, diploma or associate ship of any other similar title.

We are forwarding this dissertation to be examined for the degree of Master of Philosophy (M. Phil) to the Institute of Biological Sciences, the University of Rajshahi, Rajshahi, Bangladesh.

Rozina Aktar Zahan has fulfilled all the requirements according to the rules of the University for Submission of a dissertation for M. Phil Degree.

Principal Supervisor

Dr. Parvez Hassan
B.Sc (Hons.), M.Sc. Ph.D (Biochemistry)
Professor, Institute of Biological Sciences,
University of Rajshahi Rajshahi,
Bangladesh

Co-Supervisor

Dr Abdullah-Al-Baki
MBBS,DCP,FCPS (Microbiology)
Associate Professor
Armed Forces Medical College,
Dhaka, Bangladesh

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- The Author

ABSTRACT

Background and Objectives

Urinary tract infection (UTI) is common in women, especially sexually active women *i.e.* in women of child bearing age all over the world including Bangladesh. A large number of women in Bangladesh are reportedly suffering from UTI due to ignorance and not practicing health and hygiene factors properly and it is a significant source of morbidity rate in our country. UTIs in pregnant women pose serious health risks for both mother and child.

Earlier and recent reports globally, as well as in Bangladesh, have shown increasing rates of antibiotic resistance among uropathogens often resulting in treatment failure of UTI. The distribution of uropathogens and their susceptibility pattern to antibiotics vary regionally and even in the same region, they change over time. Due to rising antibiotic resistance among uropathogens; it is important to have local hospital based knowledge of the organisms causing UTI and their antibiotic sensitivity patterns. Therefore, the knowledge on the frequency of the causative microorganisms and their susceptibility to various antibiotics are necessary for a better therapeutic outcome.

In the Northern region of Bangladesh there are four Government owned Tertiary Level hospitals namely - RMCH, Rajshahi, SZMCH, Bogra, Rangpur Medical College Rangpur and Dinajpur Medical College Hospital, Dinajpur. A huge number of female patients from different, social, cultural, educational and economical levels attend the OPD's or get admitted to the above tertiary level hospitals to receive treatment for UTI and other diseases.

As far as our knowledge goes, very few, but no detailed study on the prevalence of UTI, isolation and identification of the uropathogens and the antibiotic susceptibility pattern of the isolates in providing basic guideline in treating UTI's have so far not been conducted on the Tertiary care hospitals in the Northern parts of Bangladesh.

To fill this information gap, the present study was undertaken, with the aim was to study the frequency and distribution of uropathogens and their resistance pattern to antibiotics in tertiary care hospitals located in the Northern parts of Bangladesh.

Settings and Design: Prospective study for a period of 3 year from July 2008 to July 2011carried out in the Molecular Biology Laboratory, Institute of Biological Sciences, University of Rajshahi, Bangladesh .

Patients and Methods: Four hundred fifty (450) female patients aged between 15-45 years who attended the OPDs or got admitted to RMCH, Rajshahi, SZMCH, Bogra, Rangpur Medical College Rangpur and Dinajpur Medical College Hospital, Dinajpur in the Northern regions of Bangladesh with clinical symptoms and suspected of having UTI and those who gave informed consent and fulfilled the inclusion and exclusion criteria were the subjects of the present study.

Research instruments of the study were firstly filling up a structured questionnaire at the time of collection of urine specimens which included medico-demographic and clinical details such as name, age, physiological age group marital status, pregnancy, diabetic status, blood pressure and symptoms of UTI etc. Secondly, clinical history taking, clinical examination of the patients and collection of urine samples for urinalysis were done by informed consent of the women and the permission to that effect was obtained from the ethical committee of the hospitals.

A total of 450 midstream urine (MSU) samples were taken from only female patients who had clinically suspected UTI .They were asked to collect a fresh sample of MSU in a sterile container after cleaning the genitals with soap and water. The sample was transported to the microbiology laboratory and processed by wet film microscopy (Routine urinary microscopy), Gram's stain and semi-quantitative urine culture in blood agar, CLED agar and MacConkey's agar. Biochemical testing was used to identify the organisms and antibiotic susceptibility testing was done by the Kirby-Bauer disc diffusion technique.

Results

Urinalyses of 450 female subjects for detection of UTI showed 151 patients had UTI (both symptomatic and asymptomatic) bring the prevalence rate of UTI 33.55% of the study population. Prevalence of symptomatic UTI was higher than asymptomatic UTI. (97(64.2%) vs 54 (35.76%). Most UTI sufferers were married females (62.91%) 95 subjects where as nearly half of the percentage (32.45%) observed in 49 single females.

In contrast, the incidence rate of both asymptomatic and symptomatic UTI among widow/divorced was found to be extremely low and was 7.41 % and 3.09 %, respectively.

Predominance of asymptomatic and symptomatic UTIs among pregnant women (88.89 vs. 70.10%) was noticed as compared to non-pregnant (29.63% vs. 29.90%). The prevalence of symptomatic and asymptomatic UTIs was found higher (nearly twice) in diabetic subjects (62.88% vs. 59.25%) as compared to non-diabetic subjects (37.11% vs. 40.74%). Symptomatic and asymptomatic UTIs were more common in hypertensive subjects (59.79% vs. 55.55%) than subjects with normal blood pressure (37.11% vs. 42.59%) and hypotension (3.09 % vs. 1.85%).

Age-wise incidence of UTI showed highest UTI sufferers 68 (44.44%) were the most sexually active women (26-35 years age group), while the least sufferers of UTI 37 (24.83%) were women of 15-25 years. Significant impact of socio-economic statues on UTI incidence was noticed and the highest UTI sufferers (49%) were from poor socio-economic class; whereas only 6 (3.98%) cases were from the rich socio-economic class.

Education seems to play a significant role in preventing the incidence of UTI and its incidence was extremely low 7 (4.64%) in patients having Master's degree; while very high 68 patients (45.03%) among the Illiterate. As far as profession is concerned UTIs was more prevalent among businesswomen constituting (48.88%) of the women with UTIs, followed by Artisans/ full housewives (44.79%), Women Traders (35.25%), Students (29.16%), teachers (19.11%) and the Civil Servants were the least UTI sufferers (11.42%.).

Results of incidence of UTI in relation to use and no use of commercial sanitary napkin during menstrual cycle of women shows use of commercial sanitary napkin plays a significant role in lowering incidence of UTI. Women using sanitary napkins regularly had lower incidence rate (20.53%) of UTI as compared to those not using sanitary napkin that had higher (49.00%) incidence of UTI. Results of prevalence of UTI based upon type of toilet use clearly demonstrated very high prevalence of UTI (51.0%) among women not using sanitary latrine at all. On the contrary, the incidence of UTI among sanitary latrine using women was found to be very low (17.88%).

The results of urine culture showed that of 450 urine samples, 151(33.55%) yielded significant growth of single organism and 12 (2.66%) yielded mixed growth. No growth was observed in 299 (66.44%) urine samples. *Escherichia coli* (42.38%) was the most common organism followed by *Pseudomonas aeruginosa* (12.58%). *E. coli* was highly sensitive to imipenem (91.2%), Amikacin (83.55%) and Gentamicin (78%) and was highly resistant to Azithromycin (85%), Nalidixic acid (77%) and co-trimoxazole (68%). Ciprofloxacin and gatifloxacin with (55.56%) and (48%) resistance respectively were moderately resistant.

Pseudomonas species were highly sensitive to imipenem (94.5%), gentamicin (78.72%) and Amikacin (77%) and moderately sensitive to Ciprofloxacin (55.32%). *Pseudomonas* showed highest resistance against cephradine (90%), followed by gatifloxacin (85%) and Azithromicin (85%), cefixime (82%), nalidixic acid (81.12%), cotrimoxazole (78.5%).

Klebsiella showed highest resistance to Azithromycin (82%), followed by Cefixime (78.5%), nalidixic acid (77.45%), gatifloxacin (77%), Ceftriaxone (75.95%), Ciprofloxacin (70%) and cotrimoxazole (60.55%). On the other hand, *Klebsiella* was found to be highly sensitive towards Imipenum (92.08%), Amikacin (91.5%) and moderately sensitive to Cephradine (65.5%).

Proteus showed highest resistance to nitrofurantoin (79.35%), followed by Azithromicin (78%), while *Proteus* showed moderate resistance of 55% to Nalidixic acid and cotrimoxazole (52.3%). On the other hand, *Proteus* was found to be highly sensitive to Amikacin (92.5%), Ceftriaxone (89.17%), Gentamicin (86.45%), gatifloxacin (75%), Ceftazidine (72.55%), Imipenum (70%), Cirprofloxacin a cefixime and cephradine (60%).

Staphylococcus saprophyticus showed highest resistance to Nalidixic acid (78%), Ceftazidine (77%), gatifloxacin (75.5%), cotrimoxazole (72%), ciprofloxacin (70%). Cephradine showed moderate resistance (55%). On the other hand, Staphylococcus *saprophyticus* was found to be highly sensitive to Imipenum (80%), followed by gentamicin (71.4%), Azithromycin (65.7%), Amikacin (64.3%). Ceftriaxone and Nirofurantoin both showed moderate sensitivity of 60%.

Staphylococcus aureus showed highest resistance to Ceftazidine (78%), followed by ciprofloxacin (77.5%), Cotrimaxazole and nalidixic acid (75%), Ceftriaxone (66.7 %). On

the contrary, *Staphylococcus aureus* showed highest sensitivity towards Imipenum (89%), followed by Azithromycin (78%), gentamicin (75%), Amikacin (71%) and gatifloxacin (70%) while Cephradine showed (65%) and cefixime (60%) sensitivity which can be considered as moderate sensitivity.

Conclusion: Overall, Antibiotic susceptibility testing of the major isolated uropathogen *E. coli.* and other uropathogens of the present study revealed that in general most uropathogens showed very higher resistance to commonly used antibiotics - Azithromycin, Nalidixic acid and Cotrimoxazole and these drugs have limited value for the treatment of UTI and should no longer be used. Moreover, this study concludes that *E. Coli* the major pathogen and other gram negative (as well as gram positive) isolates were more highly sensitive to Imipenum, Amikacin and Gentamicin as compared to other antibiotics tested and therefore these may be the drugs of choice for the treatment of complicated UTI caused by gram negative isolates in our region i.e. in the Northern region of Bangladesh.

Very alarming level of antibiotic resistance has been observed under the present study where Ciprofloxacin and even newer Gatifloxacin, broad spectrum antibiotics and major anti-pseudomonad weapons are becoming moderately sensitive to bacteria causing UTI. Ciprofloxacin, Gatifloxacin, Cephradine and cefixime (Except *Klebsiella* and *Pseudomonas* showing > 79 and 90% resistance, respectively) exhibited moderate to less moderate sensitivity in many cases under the study. One time blockbuster antibiotics such as Cephradine, and cefixime exhibited moderate resistance and reduced susceptibility. These findings are clearly alarming as our country could be running out of effective antibiotics if this trend continues. Since most of the organisms are showing resistance to routinely used antimicrobials in UTI, especially fluoroquinolones, no guidelines for empirical treatment of UTIs can be given. It is imperative to rationalize the use of fluoroquinolones in order to prevent the dissemination of resistant strains in the population.

For treatment of UTI caused by Gram-positive isolates *S. saprophyticus* and *S. aureus* the antibiotics - Imipenem, Azithromycin, Gentamicin and Amikacin to which they are found to be highly sensitive, should be the drug of choice in the Northern areas of Bangladesh. Cephradine and cefixime with moderate sensitivity can be considered as second line therapy, however only after performing a culture and sensitivity (CS) test of urine

specimens. On the other hand, Gram-positive isolates showed highest resistance towards Nalidixic acid, Ceftazidine, ciprofloxacin, gatifloxacin, cotrimoxazole, and Ceftriaxone and these antibiotics should no longer be prescribed for treating UTI caused by Gram-positive isolates in our region.

Under the above stated prevailing and changing antibiotic resistance pattern noticed among uropathogens under the present study in the northern region of Bangladesh, for the physicians to prescribe the drugs cautiously for the betterment of the patient's treatment of each and every UTI patients need to be individualized, if possible. It is recommended that, antibiotics should be used after doing a routine microscopy and culture/ sensitivity of urine in order to inhibit acquisition and spread of drug resistance by the bacteria.

The antimicrobial sensitivity testing is needed for selection of antibiotics for treatment of UTI patient's. Routine monitoring of drug resistance pattern will help to identify the resistance trends regionally. This will help in the empirical treatment of UTI to the clinicians and also for the preparation of antibiotic policy of the individual institute. This will avoid the indiscriminate use of antibiotics and prevent the further development of antimicrobial resistance. It is also urged that antimicrobial policy should be adopted at both the tertiary level hospital and the National level supervised by monitoring cell for taking necessary steps to minimize the drug resistance.

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LIST OF ABBREVIATIONS

ASB	- Asymptomatic bacteriuria
BSMMU	- Bangabandhu Sheikh Mujib Medical University
BPH	- Benign Prostatic Hyperplasia
CLSI	- Clinical and Laboratory Standard Institute
CLED	- Cystine lactose electrolyte deficient
CFU	- Colony forming unit
CDC	- Centre for disease control
ESBL	- Extended beta lactamase
°C	- Degree celsius
WBC	- White blood cell
RBC	- Red blood cell
RPM	- Revolution per minute
HPF	- High power field
UTI	- Urinary tract infection
MCA	- Mac Conkey Agar
NA	- Nutrient Agar
NB	- Nutrient Broth
MHA	- Mueller Hinton Agar
MHB	- Mueller Hinton Broth
OPDs	- Out door Patients Department
VUR	- Vesicoureteral Reflux

Chapter One
INTRODUCTION

The term “Urinary Tract Infection” (UTI) is used to describe either an infection of part or all part of the urinary system which includes - the urethra, urinary bladder, ureters and kidneys. UTI is defined as the presence of at least 100,000 i.e. ($>10^5$) organisms per milliliter of urine in an asymptomatic patient or as more than 100 organisms per milliliter of urine in a symptomatic patient with accompanying pyuria (>5 WBCs/mL) (Bloomberg *et al.* 2005). Particularly in asymptomatic patients, a diagnosis of UTI should be supported by a positive culture for an uropathogen (Emilie *et al.* 2011).

Urinary tract infections (UTI), which are caused by the presence and growth of microorganisms in the urinary tract, are perhaps the single commonest bacterial infections of mankind (Theodor 2007). Urinary tract infection is a most common infectious disease after respiratory tract infection in community practice (Hryniewicz *et al.* 2001). It remains a major public health problem in terms of morbidity and financial cost with an estimated 150 million cases per annum worldwide (Stamm and Norrby 2001, Fakhrossadat and Narges 2009, Gupta 2001), costing global economy in excess of 6 billion US dollars (Foxman 2003). Nearly 10% of people will experience a UTI during their lifetime (Hoberman *et al.* 1997, Delanghe *et al.* 2000).

Generally, Urinary tract infections (UTIs) are most common health problem for both sexes i.e. male and female (Kristen 2004). Although UTIs occur in all age groups including men and women, clinical studies suggest that the overall prevalence of UTI is higher in women. UTIs are most commonly found in women of childbearing age and rarely occur in men.

Females are more prone to UTIs as compared to males (Ibadin *et al.* 2002) probably because of the shortness of the urethra and its closeness to anus which facilitate

entrance of the faecal flora to urinary tract (Awaness *et al.* 2000, Ribeiro *et al.* 2002). Most infections are caused by retrograde ascent of bacteria from the faecal flora via the urethra to the bladder and kidney especially in the females who have a shorter and wider urethra and are more readily transfer by microorganisms (Jones *et al.* 2006).

The structure of the females urethra and vagina makes it susceptible to trauma during sexual intercourse as well as bacteria been massaged up the urethra and into the bladder during pregnancy and or child birth (El-Sweih *et al.* 2008, Kolawale *et al.* 2009). The behavioral factors are also associated with bacterial UTIs in women; such as sexual intercourse and use of contraceptive methods particularly diaphragm.

For women, the lifetime risk of having a UTI is greater than 50 percent (Griebling 2007). One woman in every five develops the Urinary Tract Infections during her life time. Infections are very common in women, especially sexually active women *i.e.* in women of child bearing age all over the world.

An estimated 50% of women experience at least one episode of UTI at some point of their lifetime and between 20% and 40% of women can have recurrent episodes within one year (Siiri *et al.* 2009, Vasquez and Hand 2004). One half of all women will experience a UTI in their lifetime, and one in three women will receive antimicrobial therapy for a UTI. In addition, the financial impact is enormous with costs exceeding $1.6 billion for community acquired UTI (Foxman 2003).

Infection rate for females approximate 1% of school-aged girls and 4% of women through childbearing years. Approximately 5.0-6.0% of girls have at least one episode of bacteriuria between first grade and their graduation from high school, and as many as 80.0% of these children experience recurrent infections (Kunin 1987). Bacteriuria occurs in 2.0-7.0% of pregnant women; of those who are not bacteriuric at initial screening, 1.0-2.0% will develop bacteriuria later in the pregnancy (Patterson and Andriole 1987, Norden and Kass 1968).

Urinary tract infections (UTIs) may involve urethra bladder, ureters and kidney (Al-Haddad 2005). Urinary tract infections can affect both lower urinary tract

(cystitis) as well as upper urinary tract i.e. pyelonephritis (Lane and Takhar 2011, Colgan and Williams 2011). The urinary tract infections may be asymptomatic, symptomatic, acute, chronic and complicated or uncomplicated and the clinical manifestations of UTI depend on the portion of the urinary tract involved, the etiologic organisms, the severity of the infection, and the patient's ability to mount an immune response to it. Acute urinary tract infection is an extremely common entity that affects almost half of women in globally (Foxman 2003).

The main symptoms of UTI include urgency, increased frequency, pain on urination and a foul odor of urine (Mims *et al.* 1995). Symptoms vary from painful urination to frequent urination along with fever and abdominal pain especially seen in case of pyelonephritis.

In most cases, urinary tract infections are annoyances that cause urinary discomfort and are often neglected. However, if left untreated, UTIs can develop into very serious and potentially life-threatening kidney infections (pyelonephritis) that can permanently scar or damage the kidneys. When the kidneys are involved, there is a risk of irreparable tissue damage with an increased risk of bacteremia (Hvidberg *et al.* 2000, Mims *et al.* 1995).

Recurrent UTI infections are common and can lead to irreversible damage of the kidneys, resulting in renal hypertension and renal failure in severe cases (New 1992). The infections may be symptomatic or asymptomatic, and either type of infection can result in serious sequelae if left untreated (Pezzlo 1988). It often results in serious complications like secondary bacteremia and sepsis leading to a rise in the hospital costs and mortality the infection may also spread into the bloodstream (called sepsis) and then elsewhere in the body.

UTIs in pregnant women pose serious health risks for both mother and child. UTIs that occur during pregnancy pose a higher than average risk of developing into kidney infections. Any pregnant woman who suspects she has a urinary tract infection should immediately contact her doctor. Many doctors recommend that

women receive periodic urine testing throughout their pregnancies to check for signs of bacterial infection.

Although several different microorganisms can cause UTI, including fungi and viruses, bacteria are the major causative organisms and are responsible for more than 95% of UTI cases (Bonadio *et al.* 2001). *Escherichia coli* are the most prevalent causative organism of UTI and are solely responsible for more than 80% of these infections. Details on the causative organisms of UTIs have been described in the Literature review chapter of this dissertation.

Antimicrobial therapy is seldom indicated for the asymptomatic UTI; but it is usually indicated for symptomatic UTIs (Nicoll 2003). UTIs are often treated with different broad-spectrum antibiotics, one with a narrow spectrum of activity may be inappropriate because of emerging concerns about infection with resistant organisms. The most common antibiotics often used to treat routine, uncomplicated UTIs are Trimethoprim (sulfonamides), Trimethoprim/ sulfamethoxazole, cephalosporins, floroquinolones (Ciprofloxacin, ofloxacin, norfloxacin, trovafloxacin), nitrofurantoin, Nalidixic acid, and fosfomycin (Prais *et al.* 2003).

Nowadays, increasing antimicrobial resistance in bacterial pathogens i.e. drug resistance of pathogens to antibiotics is a serious medical problem worldwide in treating infectious diseases like malaria, tuberculosis (TB), diarrheal diseases, urinary tract infections (UTIs) etc. As suggested by Goldman and Huskins (1997) the improper and uncontrolled or frequent misuse of antibiotics use of many antibiotics resulted in the occurrence of antimicrobial resistance, which became a major health problem world wide.

The emergence and spread of antibiotic resistance is a cause of increasing concern (Gupta 2001). Antibiotic resistance is the ability of a microorganism to withstand the effects of an antibiotic. It is one of the major causes of failure in the treatment of infectious diseases that results in increased morbidity, mortality, and costs of health care (Bouza & Cercenado 2002).

In the past decade, many kinds of resistant strains have been discovered. For example, methicillin resistant *Staphylococcus aureus* (MRSA) (Wagenlehner and Naber 2004), multidrug resistant *Pseudomonas aeruginosa* (Linuma 2007) and *Serratia marcescens* (Kim *et al*. 2006), vancomycin resistant enterococci (VRE) (Gold 2001) and extended spectrum beta lactamase (ESBL) resistant enterococci (Bhattacharya 2006). Microorganisms use varied mechanisms to acquire drug resistance viz. horizontal gene transfer (plasmids, transposons and bacteriophages), recombination of foreign DNA in bacterial chromosome and mutations in different chromosomal locus (Klemm *et al.* 2006).

Increasing rates of resistance among bacterial uropathogens has caused growing concern in both developed and developing countries (Gupta 2001). The prevalence of antimicrobial resistance among UTI agents is also increasing (Mathai *et al.* 2001, Karlowsky *et al.* 2002) and its treatment has become more complicated due to increasing resistance and empirical therapy leading to treatment failures mostly associated with gram-negative bacteria. In the last three decades, there have been a lot of reports globally in the scientific literature on the inappropriate use of antimicrobial agents and the spread of bacterial resistance among microorganisms causing urinary tract infections (Tenever and McGowan 1996, Hryniewicz *et al*. 2001, Kurutepe *et al.* 2005). The changing patterns in the etiological agents of urinary tract pathogens and their sensitivities to commonly prescribed antibiotics are reported (Hryniewicz *et al.* 2001, Kurutepe *et al*. 2005, Mordi and Erah 2006).

The emergence of antibiotic resistance in the management of Urinary tract infections (UTIs) is a serious public health issue, particularly in the developing world where apart from high level of poverty, ignorance and poor hygienic practices, there is also high prevalence of fake and spurious drugs of questionable quality in circulation. Malnutrition, poor hygiene, low socio-economic statuses are associated with urinary tract infections and these factors are rife in peripheral rural settings (Ahmed and Avasara 2008).

Indiscriminate use of antimicrobial by healthcare providers or by way of self-prescribing and over-the-counter availability are major risk factors for the development of high levels of antimicrobial resistance, which is common in rural Bangladesh and other developing countries. Other factors are overcrowding, poor hygienic practices prevalent in rural people of low socio-economic status, and an increasingly mobile population contributed to facilitate the dissemination of antibiotic resistance determinants among the pathogens (Spratt 1994). Some other factors contributing towards resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients, and the use of antibiotics as livestock food additives for growth promotion (Bouza & Cercenado 2002).

An accurate and prompt diagnosis of UTI is important in shortening the disease course and for preventing the ascent of the infection to the upper urinary tract and renal failure. Treatment of UTI cases is often started empirically. For appropriate treatment of UTIs, it is essential to isolate the infectious agent from the patient and then determine the sensitivity or the resistance to antimicrobial agents used in therapy. The choice of antibiotics for treatment of UTIs should be, therefore, based on antibiotic susceptibility data (Supriya *et al.* 2004).

Now much of the data is available on antibiotic susceptibility pattern are from community acquired infections. This may be different from that of hospital acquired infections. Since patterns of antibiotic resistance in a wide variety of pathogenic organisms may vary even over short periods and depend on site of isolation and on different environments, periodic evaluation of antibacterial activity is needed to update this information (Jones 1982, Fu and Neu 1978).

Sensitivity of bacteria to antibiotics shows a great geographical and historical variability due to different antibiotic treatments (Akinjogunla *et al.* 2009). The spectrums of etiologic agents causing UTIs and their antimicrobial resistance pattern have been continuously changing over the years, both in community and in hospitals (Kahlmeter 2003). The prevalence of antimicrobial resistance in both out

and hospital patients with UTI is increasing and can vary according to geographical and regional location in the same country (Mathai *et al.* 2001).

Studies from Nepal, India and Bangladesh have reported an increased resistance of the urinary pathogens to commonly- used antibiotics (Navaneeth 2002). Earlier reports in Bangladesh have shown on increased resistance of the urinary pathogens to commonly- used antibiotics (Khatun *et al.* 1985, Khaleque *et al.* 1990, Chowdhury *et.al* 1994, Bhowmick and Rashid 2004, Begum *et al*. 2006, Selimuzzaman *et al.* 2006, Abul Bashar *et al.* 2009, Arifuzzman 2011, Zinnat Shahina *et al.* 2011).

In the Northern region of Bangladesh there are four Governmental Tertiary Care hospitals namely - Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Medical College Rangpur and Dinajpur Medical College Hospital. A huge number of patients from different, social, cultural, educational and economical levels from the districts of Rajshahi, Bogra, Rangpur, Dinajpur and surrounding areas in the Northern region of Bangladesh attend to the respective OPDs or are admitted to the above tertiary level hospitals to receive treatment for different diseases including Urinary tract infection.

Due to rising antibiotic resistance among uropathogens it is important to have local hospital based knowledge of the organisms causing UTI and their antibiotic sensitivity patterns. This information would be relevant not only to the local hospital but would also be a vital regional database. So knowledge of the sensitivity pattern of common uropathogens according to local epidemiological studies is necessary for selection of appropriate antibiotics for empirical treatment. Area-specific monitoring studies aimed to gain knowledge about the type of pathogens responsible for UTIs and their susceptibility patterns may help the clinicians to choose the right empirical treatment.

Although earlier reports in Bangladesh on increased resistance of the urinary pathogens to commonly-used antibiotics are reported. Such information is not

available on the tertiary level care hospitals in the Northern parts of Bangladesh. Hence this study was undertaken with the view to find out the frequency of urinary tract infection in women of childbearing age, to isolate the causative microorganisms and determine the antibiotic susceptibility pattern of the uropathogens isolated from the urine samples from patients with UTIs in the Northern part of Bangladesh.

The information emerging from the present study is believed to be useful in understanding the etiological agents of UTIs and their sensitivities to available drugs would be of immense value to the rational selection and use of antimicrobial agents and to the development of appropriate prescribing policies.

Chapter Two
RATIONALE, HYPOTHESIS, AIM AND OBJECTIVES

2.1 Rationale

UTIs occur in all populations and ages, however, infection is most common in women, especially sexually active women *i.e.* in women of child bearing age all over the world. For women, the lifetime risk of having a UTI is greater than 50 percent (Griebling 2007). One woman in every five develops Urinary Tract Infections during her life time. About 20% of women experience a single episode of UTI during their lifetime, and 3% of women have more than one episode of UTI per year (Gebre-selassie 1998). In the women, 25-30% of women between 20 to 40 years of age will get Urinary Tract Infections (Wilma 2004).

As majority of, urinary tract infections are annoyances that cause urinary discomfort and are very often being neglected in our population. Untreated, UTIs often develop into very serious and potentially life-threatening kidney infections (pyelonephritis) that permanently scar or damage the kidneys. When the kidneys are involved, there is a risk of irreparable tissue damage with an increased risk of bacteremia (Hvidberg *et al.* 2000, Mims *et al.* 1995). Recurrent UTI infections in women are very common and lead to irreversible damage of the kidneys, resulting in renal hypertension and renal failure in severe cases (New 1992).

UTI is a very common problem in women of child bearing age of all over the world. In a developing country like Bangladesh a large number of women are reportedly suffering from this disease because of ignorance and not practicing health and hygiene factors properly. UTI is a significant source of morbidity rate in our country. UTIs in pregnant women pose serious health risks for both mother

and child. UTIs that occur during pregnancy poses a higher than average risk of developing into kidney infections. Any pregnant woman who suspects she has a urinary tract infection should immediately contact her doctor. Proper management and prevention of bacteriuria can reduce the incidence of the life-threatening consequences of urinary tract infections.

UTIs are often treated with different classes of antibiotics ranging from narrow spectrum to broad spectrum. However, despite the widespread availability of antimicrobials, now a day's treatment of UTI is most challenging because of increasing rates of resistance among bacterial uropathogens. The global prevalence of antimicrobial resistance among UTI agents is increasing (Mathai *et al.* 2001, Karlowsky *et al.* 2002) and its treatment has become more complicated due to increasing resistance and empirical therapy leading to treatment failures mostly associated with gram-negative bacteria.

Antibiotic resistance in UTI is a growing public health problem globally including Bangladesh. Earlier and recent reports in Bangladesh have shown on increased resistance of the urinary pathogens to commonly-used antibiotics. Add more information Antimicrobial resistance develops in urinary pathogen due to frequent misuse of antibiotics. Indiscriminate use of antimicrobial by healthcare providers or by way of self-prescribing and over-the-counter availability are major risk factors for the development of high levels of antimicrobial resistance, which is common in rural Bangladesh and other developing countries. Other factors are overcrowding, poor hygienic practices prevalent in rural people of low socio-economic status.

The prevalence of antimicrobial resistance in both out and hospital patients with UTI is increasing and can vary according to geographical and regional location in the same country (Mathai *et al.* 2001). Because of rising antibiotic resistance among uropathogens it is important to have local hospital based knowledge of the

organisms causing UTI and their antibiotic sensitivity patterns. So knowledge of the sensitivity pattern of common uropathogens according to local epidemiological studies is necessary for selection of appropriate antibiotics for empirical treatment.

In the Northern region of Bangladesh there are four Government owned Tertiary Level hospitals namely - Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Rangpur Medical College Rangpur and Dinajpur Medical College Hospital, Dinajpur. A huge number of female patients from different, social, cultural, educational and economical levels from the respective districts and surrounding areas attend to the respective OPDs or are admitted to the above tertiary level hospitals to receive treatment for different diseases including Urinary tract infection.

As far as our knowledge goes, no detailed study on the prevalence of UTI, isolation and identification of the uropathogens and the antibiotic susceptibility pattern of the isolates in providing basic guideline in treating UTIs have so far not been conducted on the tertiary care hospitals in the Northern parts of Bangladesh. Hence, the present study was undertaken with the view to fill this information gap.

The investigator selected this study because one woman in every five develops urinary tract infections (UTIs) during her lifetime and it is a significant cause of morbidity rate. Viewing the ascending trend of UTI prevalence in women of our country the present study was undertaken to provide a huge support to women of child bearing age. The information's emerging from the proposed study is believed to be helpful in the clinical management of UTI cases.

2.2 Research Hypothesis

Experimental hypothesis

H1: Urinary tract infection is most common in women of childbearing age.

H2: Antibiotic utility influences antibiotic sensitivity pattern of the micro- organisms.

H3: Drug-resistance is of common occurrence among the infecting micro-organisms.

2.3 Research Objectives

1. To find out the prevalence and observe the clinical presentation of UTI among women of child bearing age attending Hospitals of the study areas in the Northern regions of Bangladesh.
2. To study the prevalence of pathogens causing urinary tract infection and to isolate and identify the pathogens from urine in suspected cases.
3. To access the antibiotic sensitivity pattern of the isolates, so as to provide a basic guideline in treating UTIs.
4. To monitor drug resistance pattern of the isolated organisms.

Chapter Three
REVIEW OF LITERATURE

The purpose for review of literature is to obtain comprehensive knowledge base and in depth of information from previous studies. A detailed literature search in order to elicit known and unknown facts on Urinary tract infections (UTIs) relevant to the present study was conducted.

3.1 Background of the Problem of UTI in women

Urinary tract infection (UTI) is one of the most common infections encountered and treated worldwide (Theodore 2007). It affects all age group people including men, women and children worldwide. It is one of the most common bacterial infections encountered by clinicians in developing countries (Tessema *et al.* 2007). UTI remains a major public health problem in terms of morbidity and financial cost with an estimated 150 million cases per annum worldwide (Stamm & Norrby 2001, Fakhrossadat & Narges 2009, Gupta 2001), costing global economy in excess of 6 billion US dollars (Foxman 2003). Nearly 10% of people will experience a UTI during their lifetime (Hoberman & Wald, 1997, Delanghe *et al.* 2000). UTIs are much more common for women than men due to anatomical reasons. The relatively short urethra in women (about 1 to 1 1/2 inches long) makes it easy for bacteria introduced to the urethra to make their way up to the bladder. Some women may rarely or never experience a UTI in their lives, but others may have several.

In most cases episodes of UTIs are often overlooked as they appear not to be life threatening and do not cause any irreversible damage. However, when the kidneys are involved, there is a risk of irreparable tissue damage with an increased risk of bacteremia (Hvidberg *et al.* 2000, Mims *et al.* 1995). The UTI infections may be

symptomatic or asymptomatic, and either type of infection can result in serious sequelae if left untreated it often results in serious complications like secondary bacteremia and sepsis leading to a rise in the hospital costs and mortality (Pezzlo 1988).

Unrecognized UTI may progress into renal damage, hypertension and end stage renal disease (Ramadan 2003). Misdiagnosis, delay in diagnosis, and treatment of urinary tract infection appears to cause renal scarring and may produce hypertension and end-stage renal disease. It is very necessary to identify UTI and treat them as soon as possible to avoid any long term complications and to reduce the risk of any significant morbidity.

Antimicrobial therapy is seldom indicated for the asymptomatic UTI but it is usually indicated for symptomatic UTls (Nicoll 2003). For the treatment of UTI, floroquinolones, sulfonamides, cephalosporins, nitrofurantoin and fosfomycin are the most common antibiotics (Prais *et al.* 2003).

Despite the widespread availability of antibiotics, urinary tract infection (UTI) remains the most common bacterial infection in the human population (Sharma 1997). Antibiotics are usually given empirically before the laboratory results of urine cultures are available. To ensure appropriate therapy, current knowledge of the organisms that cause UTI and their antibiotic susceptibility is mandatory (Supriya *et al.* 2004).

Drug resistance of pathogens is a serious medical problem, because of very fast arise and spread of mutant strains that are insusceptible to medical treatment. The emergence of antibiotic resistance in the management of Urinary tract infections (UTIs) is a serious public health issue, particularly in the developing world including Bangladesh, where apart from high level of poverty, ignorance and poor hygienic practices, there is also high prevalence of fake and spurious drugs of

questionable quality in circulation. Studies aimed at gaining knowledge about the type of pathogens responsible for UTIs and their susceptibility patterns may help the clinicians to choose the right empirical treatment.

Due to rising antibiotic resistance among uropathogens, it is important to have local hospital based knowledge of the organisms causing UTI and their antibiotic sensitivity patterns. The spectrums of etiologic agents causing urinary tract infections and their antimicrobial resistance pattern have been continuously changing over the years, both in community and in hospitals (Kahlmeter 2003). The prevalence of antimicrobial resistance in both out and hospital patients with UTI is increasing and can vary according to geographical and regional location (Mathai *et al.* 2001).

Knowledge of etiological agents of UTIs and their sensitivities to available drugs is of immense value to the rational selection and use of antimicrobial agents and to the development of appropriate prescribing policies (El-Astal 2005). Therefore study is needed for gaining knowledge about the type of pathogens responsible for UTIs of particular regions and their susceptibility patterns may help the clinicians to choose the right empirical treatment. Keeping this in mind, the present research work was undertaken.

3.2 The Human Urinary system and urinary tract infection (UTI)

A urinary tract infection (UTI) is a condition where one or more parts of the urinary system (the kidneys, ureters, bladder, and urethra) become infected. UTIs are the most common of all bacterial infections and can occur at any time in the life of an individual. Almost 95% of cases of UTIs are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder. Much less often, bacteria spread to the kidney from the bloodstream.

The male and female urinary tracts are relatively the same except for the length of the urethra.

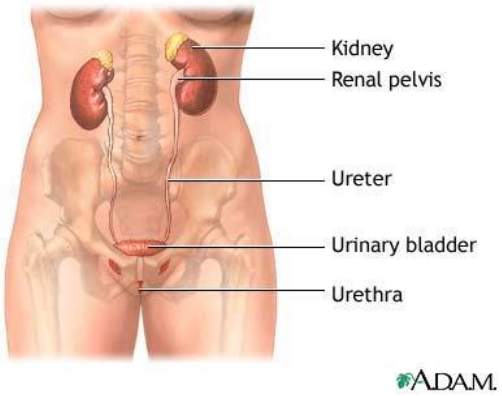


Figure 3.1
The Human (female) urinary system

***The Urinary System*.** The urinary system helps maintain proper water and salt balance throughout the body and also expels urine from the body. It is made up of the following organs and structures:

- The two kidneys, located on each side below the ribs and toward the middle of the back, play the major role in this process. They filter waste products, water, and salts from the blood to form urine.
- Urine passes from each kidney to the *bladder* through thin tubes called *ureters*.
- Ureters empty the urine into the bladder, which rests on top of the pelvic floor. The pelvic floor is a muscular structure similar to a sling running between the pubic bone in front to the base of the spine.
- The bladder stores the urine. When the bladder becomes filled, the muscles in the wall of the bladder squeeze, and the urine leaves the body via another tube called the *urethra*. In men the urethra is enclosed in the penis. In women, it leads directly out.)

Defense Systems against Bacteria: Infection does not always occur when bacteria are introduced into the bladder. A number of defense systems protect the urinary tract against infection-causing bacteria:

- Urine itself functions as an antiseptic, washing potentially harmful bacteria out of the body during normal urination. (Urine is normally sterile, that is, free of bacteria, viruses, and fungi.)

- The ureters join into the bladder in a manner designed to prevent urine from backing up into the kidney when the bladder squeezes urine out through the urethra.
- The prostate gland in men secretes infection-fighting substances.
- The immune system defenses and antibacterial substances in the mucous lining of the bladder eliminate many organisms.
- In healthy women, the vagina is colonized by lactobacilli, beneficial microorganisms that maintain a highly acidic environment (low pH) that is hostile to other bacteria. Lactobacilli also produce hydrogen peroxide, which helps eliminate bacteria and reduces the ability of *Escherichia coli* (*E. coli)* to adhere to vaginal cells. (*E. coli* is the major bacterial culprit in urinary tract infections.) Source: http://www.umm.edu/patiented/articles/what_a_urinary_tract_infection_000036_1.htm#ixzz2PqyEyvK3

3.3 Definition of UTI

A urinary tract infection (UTI) is a condition where one or more parts of the urinary system (the kidneys, ureters, bladder, and urethra) become infected. Urinary tract infection (UTI) is a term applied to a variety of clinical conditions ranging from asymptomatic presence of bacteria in the urine to severe infection of the kidney with resultant sepsis (Tanagho *et al.* 2004).

UTI is defined as the presence of at least 100,000 i.e. ($>10^5$) organisms per milliliter of urine in an asymptomatic patient or as more than 100 organisms per milliliter of urine in a symptomatic patient with accompanying pyuria (>5 WBCs/mL) (Bloomberg *et al.*, 2005). Particularly in asymptomatic patients, a diagnosis of UTI should be supported by a positive culture for an uropathogen (Emilie & Edward 2011).

UTIs are the most common of all bacterial infections and can occur at any time in the life of an individual. Almost 95% of cases of UTIs are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder. Much less often, bacteria spread to the kidney from the bloodstream.

3.4 Causative agents of UTI

UTIs may be caused by bacteria, viruses, fungi, and protozoa (Cheesbrough 2000).

3.4.1 Bacterial UTI

Bacteria usually originate from the bowel, vagina, or skin as normal flora of the host.

Gram-negative organisms causing UTIs: Nearly 90% of the total UTI cases are caused by gram-negative bacteria which include:

- *Escherichia coli* are the most common (75.5% to 87% of UTI cases including community-acquired infections) gram-negative bacteria responsible for UTI At least 80% of the uncomplicated cystitis and pyelonephritis are due to *Escherichia coli*. (Moore *et al.* 2002, Calbo *et al.* 2006, Roos *et al.* 2006, Garofalo *et al.* 2007), *Klebsiella species - Klebsiella pneumoniae, Klebsiella aerogenes* (Lavanya and Jogalakshmi 2002).
- *Proteus species- Proteus mirabilis* (Mohanty *et al.* 2003), *Proteus vulgaris* (Mohanty *et al.* 2003) and *Providencia* species.
- *Pseudomonas aeruginosa* (Shigpmura *et al.* 2006, Yetkin *et al.* 2006).
- *Enterobacter* and *Serratia marcescens* (Rodrigues *et al.* 2006).

Some less common organisms are *Acinetobocter* species (Mohanty *et al.* 2003). *Pseudomonas putida* (Yang *et al.* 1996), *Shigella sonnei* and *Erwinia persicinus* (Hara *et al.* 1998), *Morganella morganii* (Jones *et al.* 2006) and non-typhoidal Salmonella (Abbott *et al.* 1999). Among Grani-negative cocci. *Neisseria gonorrhoeae* also causes urinary tract infection (Tao *et al.* 1997).

3.4.2 Gram-positive organisms causing UTIs

Of the UTIs, 90% cases are caused by gram-negative bacteria while only 10% of the cases are caused by gram positive bacteria. Gram-positive bacteria causing UTI include -

- *Staphylococcus saprophyticus*, a gram-positive cocci, is a leading cause of cystitis in young women and accounts for causative organism in 5% to 15% of

UTIs (Raz *et al.* 2005). Another common and serious causative agent of UTI is *Staphylococcus aureus* (commonly a result of bacteremia, sometimes producing renal or perinephric abscesses in addition to bacteriuria) [Lavanya and Jogalakshmi 2002] and *Staphylococcus epidermidis* (Famurewa 1992).

- *Enterococcus faecalis* has also been isolated from urine samples (Moore *et al.* 2002, Mohanty *et al.* 2003, Taneja *et al.* 2004).

Rare causes

- *Salmonella* species
- *Mycobacterium tuberculosis*
- *Chlamydia trachomatis*
- *Candida* species (more common in immunocompromised patients, patients with diabetes, and patients who have recently received antibiotics)
- Multiple microbial organisms causing infection may be found in patients with renal calculi, chronic renal abscesses, indwelling urinary catheters, or a fistula between the bladder and either the bowel or the vagina

Serious causes

- Staphylococcus *aureus* (commonly a result of bacteremia, sometimes producing renal or perinephric abscesses in addition to bacteriuria)
- Candida species (found in critically ill, immunosuppressed, and chronically catheterized patients)

Source: https://www.clinicalkey.com/topics/urology/urinary-tract-infection.html

3.4.3 Fungal and Viral UTI

(www.urology.wisc.edu/education/module_7_pediatric_uti.pdf).

Urinary tract infection may be caused by viruses and Fungi. Fungi, such as Candida, is the second most cause of Nosocomial UTI in children it can be spread systemically and can be life threatening

Fungi infections are seen in infants and children who are on long-term antibiotics, patients who are Immuno-compromised, or patients using invasive devices like

IVs, grains and catheters (Dulczak & Kirk 2005). Candida Fungi infections are more prevalent in children with Urinary tract anomaly (Yildiz *et al.* 2007); it is associated with infections after instrumentation of the urinary tract (Schlager 2001).The prevalence of UTI due to Candida increased gradually by the duration of hospitalization, with a prevalence rate 27.2% (Parlak *et al.* 2007). Treatment of Candiduria includes stopping antibiotics, removing or changing indwelling catheters, and starting antifungal therapy with antifungal agents like oral fluconazole, parental or intravesical amphotercin B. Viral UTI can be caused by Adenoviruses types 11 and 21, polyomavirus BK, and herpes simplex viruses

Source: www.urology.wisc.edu/education/module_7_pediatric_uti.pdf.

3.5 Risk factors of UTI

http://www.umm.edu/patiented/articles/what_risk_factors_urinary_tract_infections__000036_4.htm

After the flu and common cold, urinary tract infections (UTIs) are the most common medical complaint among women in their reproductive years. UTIs are far more common among women than among men. Most women will develop a UTI at some time in their lives, and many will have recurrences.

3.5.1 Specific Risk Factors in Women

Structure of the Female Urinary Tract. In general, the higher risk in women is mostly due to the shortness of the female urethra, which is 1.5 inches compared to 8 inches in men. Bacteria from fecal matter at the anal opening can be easily transferred to the opening of the urethra. The female and male urinary tracts are relatively the same except for the length of the urethra.

Sexual Behavior. Frequent or recent sexual activity is the most important risk factor for urinary tract infection in young women. Nearly 80% of all urinary tract infections in pre-menopausal women occur within 24 hours of intercourse. UTIs are very rare in celibate women. However, UTIs are NOT sexually transmitted infections.

In general, it is the physical act of intercourse itself that produces conditions that increase susceptibility to the UTI bacteria, with some factors increasing the risk:

- Women having sex for the first time or who have intense and frequent sex after periods of abstinence are at risk for a condition called "honeymoon cystitis."
- Sexual position (such as the woman on top) may contribute to the risk.

Certain types of contraceptives can also increase the risk of UTIs. In particular, women who use diaphragms tend to develop UTIs. The spring-rim of the diaphragm can bruise the area near the bladder, making it susceptible to bacteria. Spermicidal foam or gel used with diaphragms, and spermicidal-coated condoms, also increase susceptibility to UTIs. Most spermicides contain nonoxynol-9, a chemical that is associated with increased UTI risk.

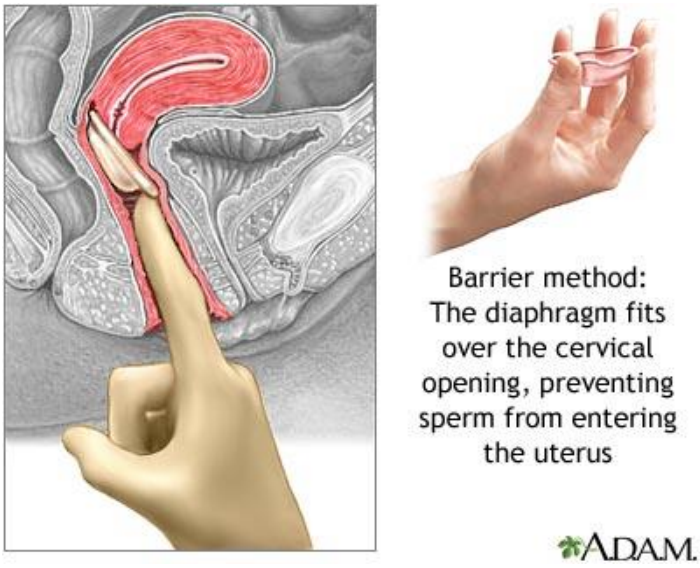


Figure 3.2
A diaphragm (Barrier method of contraception)

Pregnancy. Although pregnancy does not increase the rates of asymptomatic bacteriuria, it does increase the risk that it will progress to a full-blown kidney infection, which can cause early labor and other serious pregnancy complications. (However in early pregnancy, frequent urination -- a common symptom of UTI -- is most likely due to pressure on the bladder.) For this reason, pregnant women should be screened and treated for asymptomatic bacteriuria.

Menopause. The risk for UTIs, both symptomatic and asymptomatic, is highest in women after menopause. This is primarily due to estrogen loss, which thins the walls of the urinary tract and reduces its ability to resist bacteria. Estrogen loss can also reduce certain immune factors in the vagina that help block *E. coli* from adhering to vaginal cells.

Other aging-related urinary conditions, such as urinary incontinence, can increase the risk for recurrent urinary tract infections.

Allergies. Women who have skin allergies to ingredients in soaps, vaginal creams, bubble baths, or other chemicals that are used in the genital area are at increased risk for UTIs. In such cases, the allergies may cause small injuries that can introduce bacteria.

Antibiotic Use. Antibiotics often eliminate lactobacilli, the protective bacteria, along with harmful bacteria. This can cause an overgrowth of *E. coli* in the vagina.

3.5.2 Specific Risk Factors in Men

Benign Prostatic Hyperplasia (BPH)

Source: http://www.umm.edu/patiented/articles/benign_prostatic_hyperplasia_000071.htm#ixzz2PqviCUQn

Men become more susceptible to UTIs after 50 years of age, when they begin to develop prostate problems. Benign prostatic hyperplasia (BPH), enlargement of the prostate gland, can produce obstruction in the urinary tract and increase the risk for infection. In men, recurrent urinary tract infections are also associated with prostatitis, an infection of the prostate gland. Although only about 20% of UTIs occur in men, these infections can cause more serious problems than they do in women. Men with UTIs are far more likely to be hospitalized than women.

Benign prostatic hyperplasia (BPH) is a condition in which the prostate gland becomes enlarged. However, the actual size of the gland does not always predict symptom severity. Some men with minimally enlarged prostate glands may experience symptoms while other men with much larger glands may have few

symptoms. BPH is very common among older men, affecting about 60% of men over age 60 and 80% of men over age 80.

BPH Symptoms

The symptoms associated with BPH are collectively called lower urinary tract symptoms (LUTS). These are generally classified as either *voiding* (obstructive) symptoms or *storage* (irritative) symptoms.

Common symptoms of BPH include:

- An urgent need to urinate and difficulty postponing urination
- A hesitation before urine flow starts despite the urgency to urinate
- Straining when urinating
- Weak or intermittent urinary stream
- A sense that the bladder has not emptied completely
- Dribbling at the end of urination or leakage afterward
- An increased frequency of urination (every few hours), particularly at night

Urinary retention (inability to void) is a serious symptom of severe BPH that requires immediate medical attention

Treatment

BPH is not a cancerous or precancerous condition. It rarely causes serious complications, and men usually have a choice whether to treat it immediately or delay treatment. Treatment options include medications and surgery.

3.5.3 Specific Risk Factors in Children

Each year, about 3% of American children develop urinary tract infections. During the first few months of life, UTIs are more common in boys than in girls. Boys who are uncircumcised are about 10 - 12 times more likely than circumcised boys to develop UTIs by the time they are 1 year old. After the age of 2 years, UTIs are far more common in girls. Throughout childhood, the risk of UTIs is about 2% for boys and 8% for girls. As with adults, *E. coli* is the most common cause of UTIs in children.

Vesicoureteral Reflux (VUR). Vesicoureteral reflux (VUR) affects about 10% of all children and is the cause of up to 50% of urinary tract infections during childhood. VUR also puts children at risk for UTI recurrence.

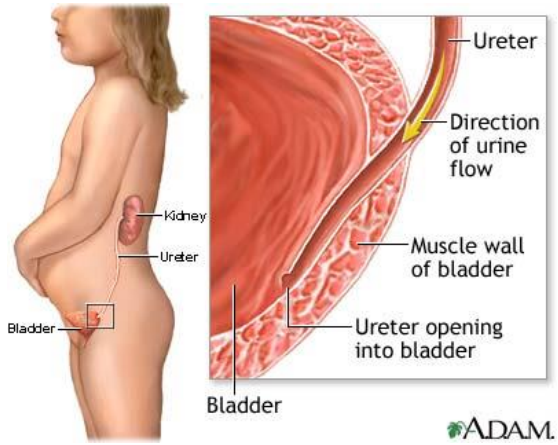


Figure 3.3
Vesicoureteral reflux

Normally, when the bladder becomes filled, the muscles in the wall of the bladder squeeze, and the urine leaves the body via another tube called the urethra. There is a valve-like mechanism where the ureter joins the bladder. This valve's job is to keep urine from flowing backward towards the kidneys when the bladder squeezes. If the valve does not work well, urine may remain in the bladder where bacteria can grow. The back flow of urine may also carry any infection from the bladder up into the kidneys.

3.5.4 Institutionalization, Catheterization, and UTI Risk

Hospitalizations. About 40% of all infections that develop in patients while in the hospital are in the urinary tract. The organisms that cause infections in hospitals (called nosocomial infections) are often different from those that commonly cause UTIs. They are also more likely to be resistant to standard antibiotics. Hospitalized patients at highest risk for such infections are those with in-dwelling urinary catheters, patients undergoing urinary procedures, long-stay elderly men, and patients with severe medical conditions.

Catheters. About 80% of UTIs in the hospital are due to catheters. The longer any urinary catheter is in place, the higher the risk for growth of bacteria and an

infection. In most cases of catheter-induced UTIs, there are no symptoms. Because of the risk for wider infection, however, anyone requiring a catheter should be screened for infection. Catheters should be used only when necessary and should be removed as soon as possible.

Nursing Homes. All older adults who are immobilized, catheterized, or dehydrated are at increased risk for UTIs. Nursing home residents, particularly those who are incontinent, are at very high risk. Symptoms of urinary tract infection in patients and nursing home residents are often subtle.

3.5.5 Medical Conditions that Increase the Risk of UTIs

Diabetes. Diabetes puts women at significantly higher risk for asymptomatic bacteriuria. The longer a woman has diabetes, the higher the risk. (Control of blood sugar has no effect on this condition.) The risk for UTI complications, and fungal-related UTIs, is also higher in people with diabetes.

Kidney Problems. Nearly any kidney disorder, including kidney stones, increases the risk for complicated UTIs.

Neurogenic Bladder. A number of brain and nerve disorders can affect the nerves of the bladder and cause problems with the ability to empty the bladder and control urine leakage. Multiple sclerosis, stroke, spinal cord injury, and diabetic neuropathy are common examples.

Sickle-Cell Anemia. Patients with sickle-cell anemia are particularly susceptible to kidney damage from their disease, and UTIs put them at even greater risk.

Immune System Problems. People with immunocompromised systems, (such as those who have HIV/AIDS or who are undergoing treatment for cancer), are at increased risk for all types of infections, including UTIs and pyelonephritis.

Urinary Tract Abnormalities. Some people have structural abnormalities of the urinary tract that cause urine to stagnate or flow backward into the upper urinary tract. A prolapsed bladder (cystocele) can result in incomplete urination so that

urine collects, creating a breeding ground for bacteria. Tiny pockets called diverticula sometimes develop inside the urethral wall and can collect urine and debris, further increasing the risk for infection.

3.6 Classification (Types) of UTI

Urinary tract infections (UTIs) can be classified in deferent ways

3.6.1 Classification of UTI on the basis of anatomic site of involvement

UTIs can be classified on the basis of anatomic site of involvement, complication of UTIs, environment and presence or absence of specific symptoms of UTI.

On the basis of anatomic site of infection, UTIs are grouped into lower and upper UTIs. Infections of the lower urinary tract include cystitis and urethritis. The main symptoms of the lower UTIs include urgency (urgent desire to urinate), increased frequency, dysuria (pain on urination), bladder pressure and a foul odor of urine. The urine may be bloody and cloudy (Wilks *et al.* 1995). There may also be a feeling of fullness in the lower abdomen or pain above the symphysis pubis (Inglis, 1996),

The upper urinary tract infections include pyelonephritis (Mims *et al.*, 1995). Upper UTI is characterized by flank pain or tenderness just below ribs (costo-vertebral or Loin pain), fever and chills (Mims *et al.*, 1995).

3.6.2 Classification of UTI on the basis of complications

On the basis of complications, UTIs can be divided into two major categories, uncomplicated and complicated UTI (Wagenlehner *et al.* 2006).

a).Uncomplicated Urinary Tract Infections (UTIs)

Uncomplicated UTIs are due to a bacterial infection, most often *E. coli*. They affect women much more often than men.

Cystitis. Cystitis, or bladder infection, is the most common urinary tract infection. It occurs in the lower urinary tract (the bladder and urethra) and nearly always in women. In most cases, the infection is brief and acute and only the surface of the

bladder is infected. Deeper layers of the bladder may be harmed if the infection becomes persistent, or chronic, or if the urinary tract is structurally abnormal.

Pyelonephritis (Kidney Infection). Sometimes the infection spreads to the upper tract (the ureters and kidneys). This is called *pyelonephritis*, or more commonly, a kidney infection.

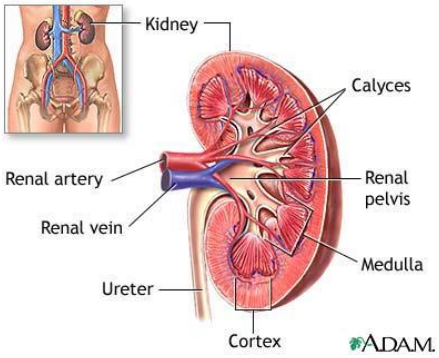


Figure 3.4
Kidney anatomy

b). Complicated Urinary Tract Infections

Complicated infections, which occur in men and women of any age, are also caused by bacteria but they tend to be more severe, more difficult to treat, and recurrent. They are often the result of:

- Some anatomical or structural abnormality that impairs the ability of the urinary tract to clear out urine and therefore bacteria.
- Catheter use in the hospital setting or chronic indwelling catheter in the outpatient setting,
- Bladder and kidney dysfunction, or kidney transplant (especially in the first 3 months after transplant).

Recurrences occur in up to 50 - 60% of patients with complicated UTI if the underlying structural or anatomical abnormalities are not corrected.

Recurrent Urinary Tract Infections

Most women who have had an uncomplicated UTI have occasional recurrences. About 25 - 50% of these women can expect another infection within a year of the

previous one. Between 3 - 5% of women have ongoing, recurrent urinary tract infections, which follow the resolution of a previous treated or untreated episode.

Recurrence is often categorized as either *reinfection* or *relapse*:

- *Reinfection.* About 80% of recurring UTIs are reinfections. A reinfection occurs several weeks after antibiotic treatment has cleared up the initial episode and can be caused by the same bacterial strain that caused the original episode or a different one. The infecting organism is usually introduced through fecal bacteria and moves up through the urinary tract.

- *Relapse.* Relapse is the less common form of recurrent urinary tract infection. It is diagnosed when a UTI recurs within 2 weeks of treatment of the first episode and is due to treatment failure. Relapse usually occurs in kidney infection (pyelonephritis) or is associated with obstructions such as kidney stones, structural abnormalities or, in men, chronic prostatitis.

3.6.3 Classification of UTI on the basis of environment

When environment is the basis of categorization, UTIs may be community-acquired (inpatients) or hospital-acquired (nosocomial/ outpatients). Community acquired UTIs are usually from ascending infection following colonization of the vagina, periurethral area and anterior urethra by uropathogenic bacteria (Wilks *et al.* 1995).

3.6.4 Classification of UTI on the basis of symptoms

On the basis of symptoms, there are two clinical features of UTI, symptomatic and asymptomatic infection. Symptomatic infection is associated with significant bacteriuria ($>10^5$ CFU/ml of urine) with symptoms of UTI. Asymptomatic infection (silent infection or covert bacteriuria) is defined as the presence of significant bacteriuria with no symptoms of UTIs. Asymptomatic infection is several-fold more common among women than men (Ronald and Ludwig, 2001). It is usually incidentally detected during screening of apparently healthy individuals

(Nagoba and Pichare, 2007) and rarely requires treatment and is not associated with increased morbidity in elderly patients.

Source: http://www.umm.edu/patiented/articles/what_a_urinary_tract_infection_000036_1.htm#ixzz2PrDxGMAd

Screening for asymptomatic bacteriuria is not necessary during most routine medical examinations, with the following exceptions:

- Pregnant women. Pregnant women with asymptomatic bacteriuria have an increased risk of acute pyelonephritis in their second or third trimester. Therefore, they need screening and treatment for this condition. Guidelines recommend that pregnant women be screened for asymptomatic bacteriuria at 12 - 16 weeks gestation or at the first pre-natal visit, if later.

- People undergoing urologic surgery (such as prostate surgery in men). The presence of an infection during surgery can lead to serious consequences. Source: http://www.umm.edu/patiented/articles/what_a_urinary_tract_infection_000036_1.htm#ixzz2PrCS6Iqy

3.7 Epidemiology of UTI

UTI spans all age groups from neonates to elderly. It is much more common in boys during first 3 months, often in association with urologic abnormalities. During pre-school years it is common in girls than boys. Presence of bacteriuria in childhood defines a population at higher risk for development of bacteriuria in adulthood (Sobel and Kaye 2005). Once adulthood is reached, prevalence of asymptomatic bacteriuria increases in the female population. Up to 40%–50% of female population will experience asymptomatic UTI at some time during their life (Foxman 2002). The prevalence of bacteriuria in adult men is low, until later years, when it rises. In young men lack of circumcision increases the risk for UTI caused by uropathogenic strains of *Escherichia coli* including the development of symptomatic urethritis (Spach *et al*. 1992).

Among young adults bacteriuria is 30 times more frequent in women than men. However in those older than 65 years of age, the ratio alters dramatically with progressive decrease in female-to-male ratio (Nicolle 2001, Baldassare & Kaye 1991). Obstructive uropathy due to enlarged prostate and loss of bactericidal activity of prostatic secretions in men and poor emptying of bladder due to prolapse of uterus in women are the possible reasons (Baldassare & Kaye 1991).

As a result of anatomic and hormonal changes that favour development of UTIs, the incidence of bacteriuria increases during pregnancy. UTIs are important complications of diabetes, renal disease, renal transplantation and structural abnormalities that interfere with urine flow (Forbes *et al.* 2007).

Urinary tract infections are the most frequent bacterial infection in women (Colgan and Williams 2011). They occur most frequently between the ages of 16 and 35 years, with 10% of women getting an infection yearly and 60% having an infection at some point in their lives (Nicolle 2008, Salvatore *et al*. 2011).

Recurrences are common, with nearly half of people getting a second infection within a year. Urinary tract infections occur four times more frequently in females than males (Salvatore *et al*. 2011). Pyelonephritis occurs between 20–30 times less frequently (Nicolle 2008). They are the most common cause of hospital acquired infections accounting for approximately 40% (Brunner & Suddarth's Textbook 2010). Rates of asymptomatic bacteria in the urine increase with age from two to seven percent in women of child bearing age to as high as 50% in elderly women in care homes (Dielubanza & Schaeffer 2011). Rates of asymptomatic bacteria in the urine among men over 75 are between 7-10% (Woodford and George 2011).

Urinary tract infections may affect 10% of people during childhood (Salvatore *et al*. 2011). Among children urinary tract infections are the most common in uncircumcised males less than three months of age, followed by females less than one year (Bhat *et al.* 2011). Estimates of frequency among children however vary widely. In a group of children with a fever, ranging in age between birth and two years, two to 20% were diagnosed with a UTI (Bhat *et al.* 2011).

3.8 Modes of bacterial entry (Routes of infection)

There are two major routes by which bacteria can invade and spread within the urinary tract. These are - the ascending route and the hematogenous routes.

3.8.1 The ascending route:

Most cases of pyelonephritis are caused by the ascent of bacteria from the bladder, through the ureters and into the renal parenchyma. Most cases of UTIs are caused by bacteria ascending from the perineum (Tanagho *et al.* 2004). Urinary tract infection is much more common in women. The female urethra is short and is in proximity to the warm moist vulvar and perirectal areas, making contamination likely. Organisms that cause urinary tract infection in women colonize the vaginal introitus and the periurethral area before urinary infection results. Once within the bladder, bacteria may multiply and then pass up by the ureters, especially if vesicourethral reflex is present, to the renal pelvis and parenchyma.

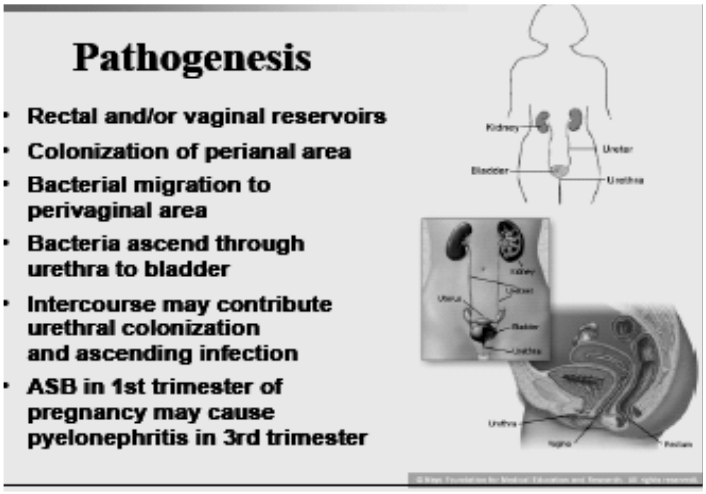
This ascent however is greatly increased if bacteria have special adhesions (i.e., *P.* pili) or if any process interferes with the normal urethral peristaltic function. Gram-negative bacteria and their endotoxins as well as pregnancy have a marked anti- peristaltic effect

3.8.2 Hematogenous route

This type usually occurs in neonates and immunocompromised patients (Tanagho *et al.,* 2004). At the first 8 to 12 weeks of life urinary tract infection may be secondary to hematogenous source. Because of that, the diagnosis of UTI in young children is very important as it is considered a marker for urinary tract abnormalities in the newborns. UTI from hematogenous source may be associated with bacteraemia. *Staphylococcus aureus*, *Candida* species, and *Mycobacterium tuberculosis* are common pathogens travel through the blood to infect the urinary tract (Tanagho *et al.* 2004).

3.9 Pathogenesis of UTI

Bacteria gain access to the urinary tract by the ascending route, the hematogenous route and lymphatic pathways. Usually UTIs are acquired via the ascending route. Once established in the bladder, bacteria may ascend the ureters, probably aided in many cases by vesicoureteral reflux or by peristaltic dilated ureters caused by intraluminal infection, an inflammation of the genitourinary tract musculature.



Infection of the renal parenchyma by many species of gram-positive bacteria, following staphylococcal bacterimia or endocarditis, mycobacterial infection an candidial infection occurs by haematogenous route. Gram-negative infections rarely occur by haematogenous route (Sobel & Kaye 2005). Evidence for a significant role for renal lymphatics in the pathogenesis of pyelonephritis is unimpressive (Alonto 2007).

3.10 Diagnosis of UTI

Source: http://www.umm.edu/patiented/articles/which_tests_will_confirm_diagnosis_of_urinary_tract_infections_000036_6.htm

3.10.1 Urinalysis.

Urinalysis is also known as also known as R&M (Routine and Microscopy) performed by using urine test strips or light microscopy of urine samples to detect the cause of infection. A urinalysis is an evaluation of various components of a urine sample and includes three types of Examinations- Visual, Chemical and

Microscopic examination. It involves looking at the urine color and clarity, using a special dipstick to do different chemical testing, and possibly inspecting some of the urine underneath a microscope. A urinalysis usually provides enough information for a doctor or nurse to start treatment. Diagnosis of uncomplicated cystitis can be inferred from history and physical, and confirmed by Urinalysis

3.10.2 The Visual Examination

Source: *http://labtestsonline.org/understanding/analytes/urinalysis/ui-exams/*

During the visual examination of the urine, the laboratorian observes the urine's color, clarity, and concentration. Urine can be a variety of colors, most often shades of yellow, from very pale or colorless to very dark or amber.

Unusual or abnormal urine colors can be the result of a disease process, some medications, or the result of eating certain foods. For example, some people excrete red-colored urine after eating beets. The color is from the natural pigment of beets and is not a cause for worry. However, red-colored urine can also occur when blood is present in the urine and can be an indicator of disease or damage to some part of the urinary system.

Blood can also be a contaminant that gets into the urine unintentionally during collection, such as from hemorrhoids or from a woman's menstruation. Once this contaminating blood is in the urine, it will be detected during the chemical phase of a urinalysis, and the doctor will initially assume that it came from the urinary tract. The importance of blood in urine is discussed further in the chemical and microscopic examination sections.

The depth of urine color is also a crude indicator of urine concentration:

- Pale yellow or colorless urine indicates a dilute urine where lots of water is being excreted.
- Dark yellow urine indicates concentrated urine and the excretion of waste products in a smaller quantity of water, such as is seen with the first morning urine, with dehydration, and during a fever.

Urine clarity refers to how clear the urine is. Usually, laboratories report the clarity of the urine using one of the following terms: clear, slightly cloudy, cloudy, or turbid. "Normal" urine can be clear or cloudy. Substances that cause cloudiness but that are not considered unhealthy include mucus, sperm and prostatic fluid, cells from the skin, normal urine crystals, and contaminants such as body lotions and powders. Other substances that can make urine cloudy, like red blood cells, white blood cells, or bacteria, indicate a condition that requires attention.

Urine color and clarity can be a sign of what substances may be present in urine. However, confirmation of suspected substances is obtained during the chemical and microscopic examinations.

3.10.3 The Chemical Examination

http://labtestsonline.org/understanding/analytes/urinalysis/ui-exams/

To perform the chemical examination, most clinical laboratories use commercially prepared test strips. These are narrow plastic strips that hold small squares of paper called test pads, arranged in a row. The test pads have chemicals impregnated into them. When a strip is briefly, but completely, dipped into urine, the test pads absorb the urine and a chemical reaction changes the color of the pad within seconds to minutes.

The laboratorian compares the color change for each reaction pad to a color chart provided with the test strips to determine the result for each test. Each reaction pad must be evaluated at the appropriate time for that chemical. If too little time or too much time has passed since the reaction, the laboratorian may get incorrect results. To reduce timing errors and eliminate variations in color interpretation, automated instruments are frequently used to “read” the reaction color on each test pad.

The degree of color change on a test pad can also give an approximation of the amount of substance present. For example, a slight color change in the test pad for protein may indicate a small amount of protein present in the urine whereas a deep color change may indicate a large amount.

The most frequently performed chemical tests using reagent test strips are:

- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Leukocyte esterase
- Nitrite
- Bilirubin
- Urobilinogen

Specific Gravity (SG)

The first test, specific gravity, is actually a physical characteristic of the urine, a measure of urine concentration that can be determined using a chemical test.

There are no "abnormal" specific gravity values. This test simply indicates how concentrated the urine is. Specific gravity measurements are actually a comparison of the amount of solutes (substances dissolved) in urine as compared to pure water. If there were no solutes present, the SG of urine would be 1.000 – the same as pure water. Since all urine has some solutes a urine SG of 1.000 is not possible. If a person drinks excessive quantities of water in a short period of time or gets an intravenous (IV) infusion of large volumes of fluid, then the urine SG may be as low as 1.002. The upper limit of the test pad, an SG of 1.035, indicates a concentrated urine, one with many solutes in a limited amount of water.

Knowing the urine concentration helps health care providers decide if the urine specimen they are evaluating is the best one to detect a particular substance. For example, if they are looking for very small amounts of protein, a concentrated morning urine specimen would be the best sample.

pH

As with specific gravity, there are typical but not "abnormal" pH values. The kidneys play an important role in maintaining the acid-base balance of the body.

Therefore, any condition that produces acids or bases in the body such as acidosis or alkalosis, or the ingestion of acidic or basic foods, can directly affect urine pH.

Diet can be used to modify urine pH. A high-protein diet or consuming cranberries will make the urine more acidic. A vegetarian diet, a low-carbohydrate diet, or the ingestion of citrus fruits will tend to make the urine more alkaline.

Some of the substances dissolved in urine will precipitate out to form crystals when the urine is acidic; others will form crystals when the urine is basic. If crystals form while the urine is being produced in the kidneys, a kidney stone or "calculus" can develop. By modifying urine pH through diet or medications, the formation of these crystals can be reduced or eliminated.

Protein

The protein test pad measures the amount of albumin in the urine. Normally, there will not be detectable quantities. When urine protein is elevated, a person has a condition called proteinuria; this can be an early sign of kidney disease. Albumin is smaller than most other proteins and is typically the first protein that is seen in the urine when kidney dysfunction begins to develop. Other proteins are not detected by the test pad but may be measured with a separate urine protein test. Other conditions that can produce proteinuria include:

- Disorders that produce high amounts of proteins in the blood, such as multiple myeloma
- Conditions that destroy red blood cells
- Inflammation, malignancies (cancer), or injury of the urinary tract - for example, the bladder, prostate, or urethra
- Vaginal secretions that get into urine

Glucose

Glucose is normally not present in urine. When glucose is present, the condition is called glucosuria. It results from either:

1. An excessively high glucose concentration in the blood, such as may be seen with people who have uncontrolled diabetes mellitus
2. A reduction in the "renal threshold." When blood glucose levels reach a certain concentration, the kidneys begin to excrete glucose into the urine to decrease blood concentrations. Sometimes the threshold concentration is reduced and glucose enters the urine sooner, at a lower blood glucose concentration.

Some other conditions that can cause glucosuria include hormonal disorders, liver disease, medications, and pregnancy. When glucosuria occurs, other tests such as blood glucose are usually performed to further identify the specific cause.

Ketones

Ketones are not normally found in the urine. They are intermediate products of fat metabolism. They can form when a person does not eat enough carbohydrates (for example, in cases of starvation or high-protein diets) or when a person's body cannot use carbohydrates properly. When carbohydrates are not available, the body metabolizes fat instead to get the energy it needs to keep functioning.

Ketones in urine can give an early indication of insufficient insulin in a person who has diabetes. Severe exercise, exposure to cold, and loss of carbohydrates, such as with frequent vomiting, can also increase fat metabolism, resulting in ketonuria.

Blood (Hemoglobin)

This test is used to detect hemoglobin in the urine (hemoglobinuria). Hemoglobin is an oxygen-transporting protein found inside red blood cells (RBCs). Its presence in the urine indicates blood in the urine (known as hematuria). The small number of RBCs normally present in urine usually result in a "negative" test. However, when the number of RBCs increases, they are detected as a "positive" test result.

Even small increases in the amount of RBCs in urine can be significant. Numerous diseases of the kidney and urinary tract, as well as trauma, medications, smoking, or strenuous exercise can cause hematuria or hemoglobinuria.

This test cannot determine the severity of disease nor be used to identify where the blood is coming from. For instance, contamination of urine with blood from hemorrhoids or vaginal bleeding cannot be distinguished from a bleed in the urinary tract. This is why it is important to collect a urine specimen correctly and for women to tell their health care provider that they are menstruating when asked to collect a urine specimen.

Sometimes a chemical test for blood in the urine is negative, but the Microscopic Exam shows increased numbers of RBCs. When this happens, the laboratorian may test the sample for ascorbic acid (vitamin C), because vitamin C has been known to interfere with the accuracy of urine blood test results, causing them to be falsely low or falsely negative.

Leukocyte Esterase

Leukocyte esterase is an enzyme present in most white blood cells (WBCs). Normally, a few white blood cells are present in urine and this test is negative. When the number of WBCs in urine increases significantly, this screening test will become positive.

When the WBC count in urine is high, it means that there is inflammation in the urinary tract or kidneys. The most common cause for WBCs in urine (leukocyturia) is a bacterial urinary tract infection (UTI), such as a bladder or kidney infection.

Nitrite

This test detects nitrite and is based upon the fact that many bacteria can convert nitrate to nitrite in the urine. Normally the urinary tract and urine are free of bacteria. When bacteria find their way into the urinary tract, they can cause a urinary tract infection (UTI). A positive nitrite test result can indicate a UTI. However, since not all bacteria are capable of converting nitrate to nitrite, someone can still have a UTI despite a negative nitrite test.

Bilirubin

Bilirubin is not present in the urine of normal, healthy individuals. Bilirubin is a waste product that is produced by the liver from the hemoglobin of RBCs that are removed from circulation. It becomes a component of bile, a fluid that is secreted into the intestines to aid in food digestion.

In certain liver diseases, such as biliary obstruction or hepatitis, bilirubin leaks back into the blood stream and is excreted in urine. The presence of bilirubin in urine is an early indicator of liver disease and can occur before clinical symptoms such as jaundice develop.

Urobilinogen

Urobilinogen is normally present in urine in low concentrations. It is formed in the intestine from bilirubin, and a portion of it is absorbed back into the bloodstream. Positive test results help detect liver diseases such as hepatitis and cirrhosis and conditions associated with increased RBC destruction (hemolytic anemia). When urine urobilinogen is low or absent in a person with urine bilirubin and/or signs of liver dysfunction, it can indicate the presence of hepatic or biliary obstruction.

3.10.4 The Microscopic Examination

http://labtestsonline.org/understanding/analytes/urinalysis/ui-exams/

A microscopic examination may or may not be performed as part of a routine urinalysis. It will typically be done when there are abnormal findings on the physical or chemical examination. It is performed on urine sediment – urine that has been centrifuged to concentrate the substances in it at the bottom of a tube. The fluid at the top of the tube is then discarded and the drops of fluid remaining are examined under a microscope. Cells, crystals, and other substances are counted and reported either as the number observed "per low power field" (LPF) or "per high power field" (HPF). In addition, some entities, if present, are estimated as "few," "moderate," or "many," such as epithelial cells, bacteria, and crystals.

Red Blood Cells (RBCs)

Normally, a few RBCs are present in urine sediment. Inflammation, injury, or disease in the kidneys or elsewhere in the urinary tract, for example, in the bladder or urethra, can cause RBCs to leak out of the blood vessels into the urine. RBCs can also be a contaminant due to an improper sample collection and blood from hemorrhoids or menstruation.

White Blood Cells (WBCs)

The number of WBCs in urine sediment is normally low. When the number is high, it indicates an infection or inflammation somewhere in the urinary tract. WBCs can also be a contaminant, such as those from vaginal secretions.

Epithelial Cells

Normally in men and women, a few epithelial cells from the bladder (transitional epithelial cells) or from the external urethra (squamous epithelial cells) can be found in the urine sediment. Cells from the kidney (kidney cells) are less common. In urinary tract conditions such as infections, inflammation, and malignancies, more epithelial cells are present. Determining the kinds of cells present helps the health care provider pinpoint where the condition is located. For example, a bladder infection may result in large numbers of transitional epithelial cells in urine sediment. Epithelial cells are usually reported as "few," "moderate," or "many" present per low power field (LPF).

Microorganisms (bacteria, trichomonads, yeast)

In health, the urinary tract is sterile; there will be no microorganisms seen in the urine sediment. Microorganisms are usually reported as "none," "few," "moderate," or "many" present per high power field (HPF). Bacteria from the surrounding skin can enter the urinary tract at the urethra and move up to the bladder, causing a urinary tract infection (UTI). If the infection is not treated, it can eventually move to the kidneys and cause pyelonephritis. Less frequently, bacteria from a blood infection (septicemia) may move into the urinary tract. This

also results in a UTI. Special care must be taken during specimen collection, particularly in women, to prevent bacteria that normally live on the skin or in vaginal secretions from contaminating the urine. A urine culture may be performed if a UTI is suspected.

In women (and rarely in men), yeast can also be present in urine. They are most often present in women who have a vaginal yeast infection, because the urine has been contaminated with vaginal secretions during collection. If yeast is observed in urine, then tests for a yeast (fungal) infection may be performed on vaginal secretions.

Trichomonads

Trichomonads are parasites that may be found in the urine of women or men (rarely). As with yeast, the trichomonads are actually infecting the vaginal canal and their presence in urine is due to contamination. If these are found during a urinalysis, then follow-up testing for *Trichomonas vaginalis* may be performed to look for a vaginal infection.

Casts

Casts are cylindrical particles sometimes found in urine that are formed from coagulated protein secreted by kidney cells. They are formed in the long, thin, hollow tubes of the kidneys known as tubules and usually take the shape of the tubule (hence the name). Under the microscope, they often look like the shape of a "hot dog" and in healthy people they appear nearly clear. This type of cast is called a "hyaline" cast.

When a disease process is present in the kidney, other things such as RBCs or WBCs can become trapped in the protein as the cast is formed. When this happens, the cast is identified by the substances inside it, for example, as a red blood cell cast or white blood cell cast. Different types of casts are associated with different kidney diseases, and the type of casts found in the urine may give clues as to which disorder is affecting the kidney. Some other examples of types of casts include granular casts, fatty casts, and waxy casts.

Normally, healthy people may have a few (0–5) hyaline casts per low power field (LPF). After strenuous exercise, more hyaline casts may be detected. Cellular casts, such as RBC and WBC casts, indicate a kidney disorder.

Crystals

Urine contains many dissolved substances (solutes) – waste chemicals that the body needs to eliminate. These solutes can form crystals, solid forms of a particular substance, in the urine if:

1. The urine pH is increasingly acidic or basic;
2. The concentration of dissolved substances is increased; and
3. The urine temperature promotes their formation.

Crystals are identified by their shape, color, and by the urine pH. They may be small, sand-like particles with no specific shape (amorphous) or have specific shapes, such as needle-like. Crystals are considered "normal" if they are from solutes that are typically found in the urine. Some examples of crystals that can be found in the urine of healthy individuals include:

- Amorphous urates
- Crystalline uric acid
- Calcium oxalates
- Amorphous phosphates
- Calcium carbonate

If the crystals are from solutes that are not normally in the urine, they are considered "abnormal." Abnormal crystals may indicate an abnormal metabolic process. Some of these include:

- Cystine
- Tyrosine
- Leucine

When crystals form as urine is being made in the kidney, they may group together to form kidney "stones" or calculi. These stones can become lodged in the kidney

itself or in the ureters, tubes that pass the urine from kidney to the bladder, causing extreme pain.

Medications, drugs, and x-ray dye can also crystallize in urine. Therefore, the laboratorian must be familiar with and trained in the identification of urine crystals.

3.10.5 Urine Culture

If necessary, the doctor may order a urine culture, which involves incubating and growing the bacteria contained in the urine. A urine culture can help identify the specific bacteria causing the infection, and determine which type of antibiotics to use for treatment. A urine culture may be ordered if the urinalysis does not show signs of infection but the doctor still suspects a UTI is causing the symptoms. It may also be ordered if the doctor suspects complications from the infection.

3.10.6 Prevention of UTI

http://www.mayoclinic.com/health/urinary-tract- infection/DS00286/DSECTION=prevention

To reduce risk of developing a urinary tract infection (UTI) the following steps can be taken:

1. **Staying Hydrated:** Urinary tract infections (UTIs) are less likely to occur in someone who is drinking enough water to promote regular urination, so it is very important to stay hydrated in order to help flush out bacteria from the urinary tract.
2. **Wiping from front to back (In case of women)** Doing so after urinating and after a bowel movement helps prevent bacteria in the anal region from spreading to the vagina and urethra.
3. **Responding to "Nature's Call":** It is always a good idea to urinate as soon as one feels the need. While "holding it in" does not directly cause an infection, it can cause over distension that can damage the lining of the bladder, making it more vulnerable to bacteria.

4. **Emptying bladder soon after intercourse-** Also, a full glass of water is to be drunk to help flush bacteria.
5. **Avoiding potentially irritating feminine products.** Using deodorant sprays or other feminine products, such as douches and powders, in the genital area can irritate the urethra.
6. **Removing Tampons before Going:** Remember to always take out tampons before urinating, and change tampons often. Leaving tampons in place can actually affect the stream of urine.
7. **Practicing Proper Bathroom Hygiene:** To keep bacteria near the urethral opening to a minimum, it is important to practice proper wiping techniques (i.e. front to back wiping) to help prevent rectal bacteria from entering the uretro-genital area. Another good way to help keep bacteria away from the urethral opening is the "two-paper rule" - use one piece of toilet paper to wipe urine and a second, separate piece to wipe everything else.
8. **Taking a Vitamin C Supplement:** About 1,000 milligrams of vitamin C taken daily can help inhibit the growth of some bacteria by acidifying the urine.
9. **Maintaining Control with Cranberries:** Cranberries contain hippuronic acid, which is a natural antiseptic that may help prevent the adherence of bacteria to the bladder lining. Drinking 100% pure cranberry juice may help to prevent an infection. However, it is important to note that cranberry juices/supplements are not helpful once a urinary tract infection (UTI) is present, as they are unable to destroy the overabundance of bacteria and can actually cause discomfort and pain while urinating.
10. **Paying attention to ones Pee:** Urine can change color for a variety of reasons, including from the medications one takes, so paying close attention to it to monitor ones overall health. One key thing to note is that if urine is typically a darker yellow, body is dehydrated; one needs to step up water intake.

Source: http://www.cystex.com/Pages/UTI%20Prevention

3.10.7 Treatment of UTI

Treatment for a UTI should be designed for each patient individually and is usually based on the patient's underlying medical conditions, what pathogen(s) are causing the infection, and the susceptibility of the pathogen(s) to treatments. Patients who are very ill usually require intravenous (IV) antibiotics and admission to a hospital; they usually have a kidney infection (pyelonephritis) that may be spreading to the bloodstream. Other people may have a milder infection (cystitis) and may get well quickly with oral antibiotics.

Still others may have a UTI caused by pathogens that cause STDs and may require more than a single oral antibiotic. The caregivers often begin treatment before the pathogenic agent and its antibiotic susceptibilities are known, so in some individuals, the antibiotic treatment may need to be changed. In addition, pediatric patients and pregnant patients should not use certain antibiotics that are commonly used in adults. For example,ciprofloxacin (Cipro) and other related quinolones should not be used in children or pregnant patients due to side effects. However, penicillins and cephalosporins are usually considered safe for both groups if the individuals are not allergic to the antibiotics. Patients with STD-related UTIs usually require two antibiotics to eliminate STD pathogens. The less frequent or rare fungal and parasitic pathogens require specific antifungal or antiparasitic medications; these more complicated UTIs should often be treated in consultation with an infectious disease expert. All antibiotics prescribed should be taken even if the person's symptoms disappear early. Reoccurrence of the UTI and evenantibiotic resistance of the pathogen may happen in individuals who are not adequately treated.

Although treatment for a UTI should be designed for each patient individually and is usually based on the patient's underlying medical conditions, what pathogen(s) are causing the infection, and the susceptibility of the pathogen(s) to treatments. However, below is a general guideline for the treatment of UTI from GlobalRph. http://www.globalrph.com/uti.htm

General guideline for UTI treatment

Type of UTI	**Possible therapeutics**
UTI: Uncomplicated cystitis - urethritis	Bactrim DS orally twice daily for 3 days or Ciprofloxacin 250mg orally twice daily for 3 days or Norfloxacin 400mg orally twice daily for 3 days or Ofloxacin 200mg orally twice daily for 3 days or Levofloxacin 250mg orally once daily for 3 days. or Augmentin 875mg orally twice daily or 500mg po tid.
Recurrent cystitis (> 3 episodes per/yr)	Treat infection with one of the regimens above, then start long term maintenance therapy with Bactrim single-strength one tablet once daily
Complicated UTI: catheter in place, obstruction etc.	[Ampicillin 1 gram IV every 6 hours +Gentamicin IV] or Ciprofloxacin 200-400mg IV every 12 hours orLevofloxacin 250 to 500mg IV qd or Piperacillin-tazobactam 3.375 grams IV every 6 hours or Imipenem 500mg IV q6h
Gonococcal urethritis ***Neisseria gonorrhoeae***	Cefixime 400 mg PO x 1 PLUS [Azithromycin1 g PO x 1 OR Doxycycline 100 mg PO bid x 7 d if chlamydia infection has not been ruled out] Ceftriaxone 125 mg IM x 1 PLUS [Azithromycin 1 g PO x 1 OR Doxycycline 100 mg PO bid x 7 d if chlamydia infection has not been ruled out]
Non-gonococcal urethritis ***Chlamydia trachomatis***	Azithromycin 1 g PO x 1 Doxycycline 100 mg PO bid x 7d
Recurrent or persistent urethritis	Metronidazole 2 grams po once +Erythromycin base 500 mg PO qid x 7 days

Chapter Four
MATERIALS AND METHODS

This chapter describes the type of the study, the study population, sample size, setting, ethical considerations, instruments, data collection, and experimental work.

4.1 Type, place and period of study:

The present study was a prospective one and was carried out in the Molecular Biology Laboratory, Institute of Biological Sciences, University of Rajshahi, Bangladesh during the period of July 2008 to June 2011, availing also some of the laboratory facilities of the Departments of Microbiology, Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Combined Military Hospital, Bogra, Bangladesh, Rangpur Medical College Rangpur and Dinajpur Medical College Hospital, Dinajpur.

4.2 Study population

The study population comprised of four hundred fifty (450) female patients clinically **s**uspected of having UTI aged between 15-45 years attending the OPDs or admitted to Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Combined Military Hospital (CMH), Bogra, Bangladesh, Rangpur Medical College, Rangpur, Dinajpur Medical College, Dinajpur in the Northern regions of Bangladesh. Selection of the participants of the study population was done on the basis of some inclusion and exclusion criteria mentioned below.

4.3 Sample size

We collected data from 450 patients with suspected UTI during the study. In the planning phase we estimated a total sample size of 750 cases. But in place due to shorter period of time and limited logistic support we could not reach up to that many samples.

4.4 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were set to meticulously select participants of the study population.

4.4.1 Inclusion criteria

1. Married and unmarried women of reproductive (child bearing age) *i.e.* 18-45 years of age.

2. Women having clinically suspected UTI. Clinical diagnostic criteria- dysuria, frequency, urgency and fever.

3. Women who are willing to participate in the study

4.4.2 Exclusion criteria:

1. Women below 18 and above 45 years of age and menopausal women.

2. Patients currently on antibiotic therapy or having history of receiving antibiotics within two weeks prior to enrolment in the study.

3. Women who are not willing to participate.

4. Patients on continuous indwelling catheter.

5. Women with severe concomitant diseases besides symptoms of UTI.

4.5 Categorization of the subjects

The subjects were grouped into two on the basis of symptoms suggesting UTI noted at the time of completion of subject information questionnaire like urgency, frequency, dysuria, nocturia, flank pain and a foul odor of urine etc.

Group I: (Symptomatic) included subjects having at least one of the symptoms suggesting UTI.

Group II: (Asymptomatic) included subjects having no symptom suggesting UTI.

Age: The subjects were categorized into age groups of 15-25 years- **Group-A**, 26-35 years **Group-B**, and 36-45 years **Group-C**.

Marital status: The subjects were classified into three groups: single, married, widow/divorced,

Pregnancy: For the categorization on the basis of pregnancy, only married female were included and grouped as pregnant and non- pregnant.

Diabetes: All the subjects were grouped into diabetic (patients having history of diabetes) and non-diabetic.

Blood pressure: On the basis of history of blood pressure, the subjects were classified into three groups; hypotensive subjects, hypertensive subjects and subjects with normal blood pressure.

4.6 Sampling procedure

We underwent consecutive sampling for selection of cases for this study. Four hundred seventy three (473) women who fulfilled inclusion criteria were asked to take part in the study. Among them 23 refused to participate. The rest 450 women with suspected UTI willing to participate were selected as cases for the study.

4.7 Ethical issues

Approval to carry out the present study was sought from the Human Research Ethics Committee, of the Institute of Biological Sciences, University of Rajshahi, Rajshahi, Bangladesh. Before the commencement of the study, the purpose, objectives of the study and possible benefits of the study were explained to the relevant authorities at Rajshahi Medical Collage Hospital, Rajshahi, Bangladesh and all other hospitals of the Northern regions of Bangladesh stated previously from where urine samples were collected.

In order to have access to patients' information and to use patient materials and laboratory medical records for this study; permission was sought from the Director of Rajshahi Medical Collage Hospital, Rajshahi, Bangladesh and the other Hospitals.

Prior to interview, the purpose and objectives of the study was explained to the prospective participants. Decision to join in the study was made on the basis of

informed consent. Written consent to take part in this study was sought prior to their inclusion to this study in presence of a witness (Appendix-II, page no. 114 in Appendix chapter 9). Participation in this study had been voluntary and participants had the right to withdraw at any period of the investigation. No penalty was attached to such decisions. The findings were treated with highest possible degree of confidentiality. Each participant was given a separate identity number.

4.8 Instruments of the Research

The present study utilized two main instruments:

4.8.1 Collection of history through questionnaire

At the time of collection of urine specimens, all the subjects were interviewed and a specially designed questionnaire (Appendix-I, page 111, Chapter 9) was completed. The questionnaire included medico-demographic and clinical details such as name, age, physiological age group marital status, pregnancy, diabetic status, blood pressure and symptoms of UTI etc.

Clinical history taking, clinical examination of the patients and collection of urine samples were done by informed consent of the women and the permission to that effect was obtained from the ethical committee of the hospitals and clinics.

4.8.2 Laboratory examination of the urine samples (urinalysis)

Methods and Materials used in urine testing:

Sterilization of media and materials

The media the used were Nutrient Agar (NA) from Mast Diagnostics Limited, while Nutrient Broth (NB), MacConkey agar (MCA), Blood Agar (BA) and Cystein Lactose Electrolyte Deficient (CLED) Agar was the product of Oxoid Limited. All glassware were washed with detergent, rinsed with water and then allowed to dry. The glassware were later wrapped in aluminum foil and sterilized in a hot air oven at 160 °C for 3 h. Media were prepared according to the manufacturer's specifications and sterilized by autoclaving at 121 Ib/g for 15 min.

4.8.3 Collection of the urine samples

Early morning mid-stream urine samples were collected in sterile, dry test tube as described by Karlowsky *et al.* (2006) and Solberg *et al.* (2006). Before collection of the urine specimen, the subjects were instructed to clean the genital area carefully with non-antiseptic soap and water. Then, freshly voided midstream (10-20 ml) urine specimen was collected with the labia held apart in sterile, dry test tubes. The test tube containing urine sample was properly labeled with the date, the name, age, number of the patient age and time of collection.

4.8.3.1 Specimen transportation

Urine specimens were immediately transported to the Molecular Biology Laboratory, Institute of Biological Sciences or Department of Microbiology, Rajshahi Medical College, Rajshahi University of Rajshahi, Rajshahi, Bangladesh to be processed within one hour of collection. When immediate delivery to the laboratory was not possible, the urine was refrigerated at 4-6°C. When a delay in delivery of more than 2 hours was suspected, the preservative boric acid (0.lg/10 ml of urine) was added to prevent multiplication of bacteria and the specimens containing boric acid need not to be refrigerated (Cheesbrough 2000).

4.8.3.2 Analyses of the specimens

All the urine specimens were subjected to urinalysis, culture for quantitation and qualitative assessment of bacteria.

4.8.3.3 Microscopic examination of the urine specimens

Urine was examined microscopically as wet preparation for the detection of -

- Significant pyuria, i.e. WBCs (pus cells) in excess of 10 cells/µl (10^6/1) of urine
- Red cells (Erythrocytes)
- Casts/ Pus cells
- Yeast cells
- Bacteria (From freshly collected urine)

The urine samples were thoroughly mixed and 10 ml of urine was transferred to a conical centrifuged tube and centrifuged at 5000 rpm for 5 min. After centrifugation supernatant was discarded with a single smooth action and sediment was resuspended in remaining drop of supernatant with several firm finger strokes. A drop of the urine samples were applied to a glass microscope slide, allowed to air dry, stained with gram stain, overlaid with cover slip and the deposits were examined microscopically using both 10X and 40X objectives (Kolawole *et al,* 2009). Bacterial isolates were identified generally using a battery of tests (Cheesbrough 2004, Prescott *et al.* 2008).

Several fields were examined immediately before evaporation for search of erythrocytes, pus cells, epithelial cells, cast, crystals etc. If pus cells, erythrocytes or casts were found, the count was performed in several fields. For pus cells and erythrocytes, the count was recorded as per high power field (HPF) and for casts as per low power field (LPF) (Prescott *et al*. 2008 Sonnerwirth 1980).

White cells (pus cells): are round, 10–15 µm in diameter. In urinary infections they are often found in clumps. In urine sediments, white blood cells (WBC) are usually reported as: (Cheesbrough 2004).

Few: Up to 10 WBCs/HPF (high power field, i.e. using 40 X objectives)

Moderate: 11–40/HPF

Plenty: More than 40 WBC/HPF

4.8.3.4 Examination of Gram stained smear

Gram stained smears of urine samples were prepared when bacteria and, or white cells were seen in the wet preparations. A drop of the urine sediment from centrifuged urine was transferred to a slide and spread it to make a thin smear and allowed to air-dry. The smear slide was heat fixed or methanol fix and stained it by the Gram technique as described by Cheesbrough (2000). Then the smear was first examined with the 40 x objective to see the distribution of material, and then with the oil immersion objective to look especially for bacteria associated with urinary

infections, especially Gram negative rods. Occasionally Gram positive cocci and streptococci may be seen. The presence of bacteria (s) and cells were reported after microscopical examination.

4.8.3.5 Urine culture

Media

Nutrient Agar (NA) from Mast Diagnostics Limited, while Nutrient Broth (NB), MacConkey agar (MCA), Blood Agar (BA) and Cystein Lactose Electrolyte Deficient (CLED) Agar was the product of Oxoid Limited. MacConkey's agar (Oxoid) and Blood agar media were used for quantitation and primary isolation of microorganisms. Blood agar base (Oxoid) was used for the preparation of blood agar medium. All the plates were incubated at 35°-37°C for l8-24 hours to check the sterility.

Culture of urine samples

This was carried out as described by Cheesbrough (2002, 2004). Ten-fold serial dilutions were made by transferring 1.0 ml of the sample in 9.0 ml of sterile physiological saline. One ml was then poured into molten nutrient agar in Petri dishes and rotated gently for proper homogenization. The contents were allowed to set and the plates were then incubated at 37 °C for 24 h. Bacterial colonies appearing on the plates after the incubation period were enumerated to determine urine samples with significant bacteriuria. A loopful of each urine sample was also streaked on Mac Conkey agar and Blood agar plate for the isolation of the bacteria present in the urine. After incubation, plates with growth were selected, the colonies were isolated using inoculating loop and subsequently sub-cultured on agar slants for use in further tests.

4.8.3.6 Quantitation for significant bacteriuria

Quantitation was performed by standard calibrated loop method. A calibrated sterile platinum wire loop for the semi-quantitative method was used for the plating and it has a 4.0 mm diameter designed to deliver 0.01 ml. It was

dipped vertically into the urine and a loop full of the well mixed urine sample was spread onto the surface of blood agar medium plate for total count and MacConkey agar medium plate for count of Gram-negative bacteria (duplicate plates of Blood and Mac-Conkey agar were used). After incubation at 35-37°C for 18-24 hours, plates were examined macroscopically and microscopically for bacterial growth and colonies were counted. The bacterial colonies were counted and multiplied by 100 to give an estimate of the number of bacteria present per milliliter of urine. A significant bacterial count was taken as any count equal to or in excess of 10,000 cfu /ml (Stamm *et al.* 1982, Stark and Maki 1984).

4.8.3.7 Qualitative assessment

Different types of isolated colonies were picked and streaked on fresh media plates. All plates were incubated at 35-37°C for 18-24 hours. After incubation, the isolated colonies were transferred to nutrient agar slants or blood agar slants to get pure cultures for storage in refrigerator at 4°'C. All the pure cultures were subjected to characterization by using different tests conforming to required standard diagnostic criteria (Baron *et al.* 1994, Cheesbrough 2002). The criteria included study of morphological, cultural, biochemical and physiological characteristics.

Cystine lactose electrolyte-deficient (CLED) agar

– The urine was mixed (freshly collected clean-catch specimen) by rotating the container.
– Using a sterile calibrated wire loop, e.g. one that holds ml (0.002 ml), a loopful of urine was inoculated on a quarter plate of CLED agar . If microscopy showed many bacteria, a half plate of medium was used.
– The plate was incubated aerobically at 35–37 °C overnight.

Cystine lactose electrolyte-deficient (CLED) agar is widely used by 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 of *Proteus* species.

Appearance of some urinary pathogens on CLED agar:

- *E. coli*: Yellow (lactose-fermenting) opaque colonies often with slightly deeper coloured centre.
- *Klebsiella* species: Large mucoid yellow or yellow-white colonies.
- *Proteus* species: Transluscent blue-grey colonies.
- *P. aeruginosa*: Green colonies with rough periphery (characteristic colour).
- *E. faecalis*: Small yellow colonies.
- *S. aureus*: Deep yellow colonies of uniform colour.
- *S. saprophyticus* and other coagulase negative staphylococci: Yellow to white colonies.

4.8.3.8 Identification of the isolates

The methods used in the identification and characterizations of isolated bacteria included Gram stain followed by microscopic examination, motility test and biochemical tests according to Cheesbrough (2002; 2004). The isolates were identified by Bergey's Manual for Determinative Bacteriology (Buchanan and Gribbons, 1974).

4.8.3.9 Determination of antibiotic susceptibilities

Antibiotic susceptibility testing of the isolated uropathogens was performed using disc diffusion method as described by National Committee for Clinical Laboratory Standards (Presently called as Clinical Laboratory Standards Institute) (Cheesbrough, 2000). This is basically the agar disc diffusion technique as described by Bauer *et al.* (1996).

Media

Mueller Hinton Agar (MHA) from Oxoid UK was employed for determination of antimicrobial susceptibility lest and Mueller Hinton Broth (MHB) from Oxoid UK was used for preparation of inoculum.

Preparation of plates for antimicrobial susceptibility

MHA was poured into sterile petri plates to get a depth of 4-6 mm. These plates were incubated at 35-37°C for 18-24 hours to check the sterility of plates. The plates were stored at 4°'C and were used within two weeks. Prior to use, plates were dried in an incubator to facilitate the removal of excess surface water.

Antibiotic discs used

The following twelve commercially prepared antibiotic disks (Oxoid, UK) were used: Cephradine (30 µg), Ciprofloxacin (5 µg), Cefixime (5µg), Gatifloxacin (5 µg), Ceftazidime (30µg), Nalidixic Acid (30µg), Nitrofuration (300µg), Azithromycin (15 µg), Ceftriaxone (30µg), Cotrimoxazole (23.75µg), Amikacin (30µg), Imipenem (10µg) and Gentamicin (10 µg) were used in antibiotic susceptibility testing.

Preparation of turbidity standard

McFarland Nephlometer standard tube number 0.5 was used to standardize the turbidity of test inoculums. Since inoculums was prepared in MHB, 1% (v/v) sulphuric acid in MHB and 1.175% (w/v) aqueous solution of barium chloride ($BaCl_2.2H_20$) were prepared in order to estimate bacterial cell density (Sonnenwirth and Jerett 1980, Baron *et al.* 1994). For the preparation of turbidity standard 0.05 ml 1.175% barium chloride solution was added to 9.95 ml 1% sulphuric acid solution slowly and with constant agitation. The tube was scaled and stored in dark at room temperature (Baron *et al.* 1994).

Inoculum

A loop full from pure growth of organisms was transferred to 5 ml of MHB. The broth was incubated at 35-25°C for 18-24 hours. After incubation, the turbidity of the culture was compared with O.5 McFarland Nephlometer Standard to get approximate cell density 150 x 10^6 CFU/ml. The standardized inoculum suspension was inoculated within 15-20 minutes.

Inoculation of medium

A sterile cotton swab was immersed into the standardized inoculum suspension. Excess broth was drained by pressing and rotating the swab against the inside of the suspension tube. Then, it was streaked evenly in three directions on the surface of agar plates. A final circular motion was made around the agar rim with the cotton swab. These plates were allowed to dry for 3-5 minutes.

Disc placement

Antibiotic susceptibility discs were placed on the surface of inoculated MHA plates by using a sterile forcep. The appropriate multi-disc depending on whether the test organism plated was a gram negative or gram-positive organism was then placed firmly onto the surface of the dried plates, using sterile forceps. After placement the discs were pressed gently to the agar surface. The plates were left at room temperature for one hour to allow diffusion of the different antibiotics from the disc into the medium

Incubation

The inoculated plates were incubated at 35-37°'C for 18-24 hours.

Interpretation

Interpretative criteria for each antibiotic tested were those recommended by the NCCLS (Cheesbrough, 2000). Inhibition zone diameters were measured with a ruler under reflected light. Interpretation of results was done using the zone sizes. Zone of inhibition of greater than 10 mm were considered sensitive, 5-10mm moderate sensitive and no zone of inhibition resistant (Vandepitte *et al.* 1991).

4.8.3.10 Data handling and analysis

Individual case was given a case number to avoid mixing up of data. In the field data were entered into Microsoft Access 98 according to pre-coded categories. The data were checked by going through each and every questionnaire.

Chapter Five
OBSERVATIONS AND RESULTS

In the present study, a total of 450 midstream urine samples were collected from female patients suspected of having UTI attending the OPDs or admitted to Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Combined Military Hospital (CMH) Bogra, Rangpur Medical College, Rangpur and Dinajpur Medical College, Dinajpur, Bangladesh in the Northern regions of Bangladesh and were subjected to urinalysis.

5.1 Prevalence rate of UTI of the study population

Of the 450 patients screened for the presence of UTI, in the present study, one hundred fifty one (151) patients were diagnosed of having UTI (both symptomatic and asymptomatic). The prevalence rate of urinary tract infection (UTI) of the present study population was therefore 33.55%, as shown in Table 5.1.

As shown in Table 5.1, among the 151 confirmly diagnosed UTI patients, asymptomatic UTI (Group A) was diagnosed in 54 women whereas, significant bacteriuria i.e. symptomatic UTI (Group B) was found in 97 patients (Table 5.1). The prevalence of symptomatic UTI was therefore higher than asymptomatic UTI.

The distribution of asymptomatic UTI (Group A) and symptomatic UTI (Group B) subjects with respect to medico-demographic characteristics *i.e.* marital status (single, married, widow/divorced), pregnancy (pregnant, non pregnant), diabetes (diabetic, non-diabetic), and blood pressure (hypotension, hypertension, normal blood pressure) has been presented in Table 5.1. The incidence rate of UTI in relation to marital status, occurrence of pregnancy, presence of diabetes and high blood pressure has been graphically represented in the Figures 5a – 5d.

In the current study, only married women were considered for the pregnancy group and unmarried pregnant women were ruled out of the study because in our society

there is no concept of such unmarried pregnant women and such cases, if exist, are not disclosed and thus are not available.

Table 5.1
Distribution of asymptomatic UTI (Group A) and symptomatic UTI Group-B) subjects with respect to medico-demographic characteristics (n= 151).

Characteristics	**Group A (Asymptomatic UTI)**		**Group B (Symptomatic UTI)**		**Total**	
	No.	%	No.	%	No.	%
Marital status						
Single	12	22.22	37	38.14	49	32.45
Married	38	70.37	57	58.76	95	62.91
Widow/divorced	04	7.41	03	3.09	07	4.64
Total	54	100	97	100	151	100
Pregnancy						
Non-pregnant (married)	16	29.63	29	29.90	45	29.80
Pregnant	48	88.89	68	70.10	116	76.82
Total	54	100	97	100	151	100
Diabetes						
Non-diabetic	22	40.74	36	37.11	58	38.41
Diabetic	32	59.25	61	62.88	93	61.58
Total	54	100	97	100	151	100
Blood Pressure (BP)						
Hypotension	1	1.85	3	3.09	4	2.64
Hypertension	30	55.55	58	59.79	88	58.27
Normal BP	23	42.59	36	37.11	59	39.07
Total	54	100	97	100	151	100

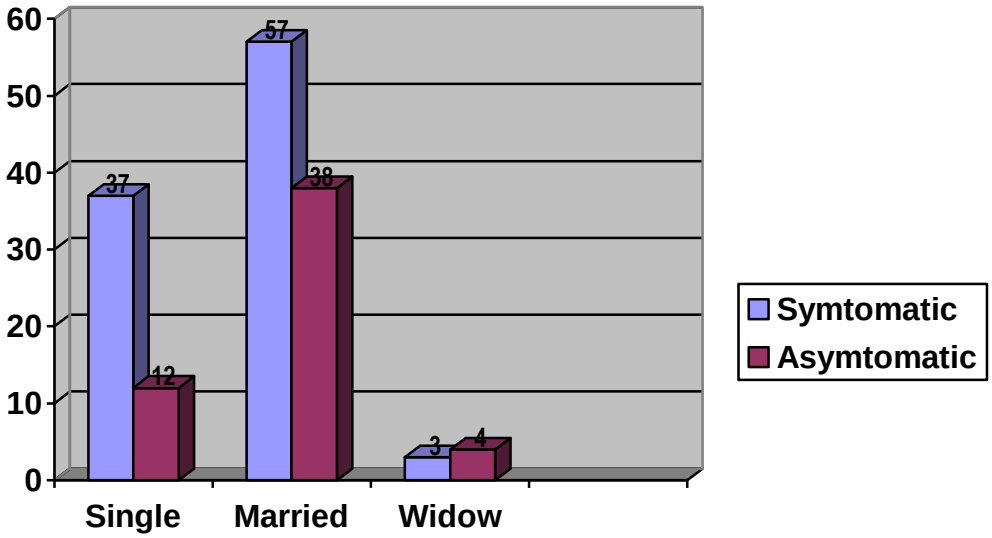


Figure 5.1
Incidence of UTI based on marital status.

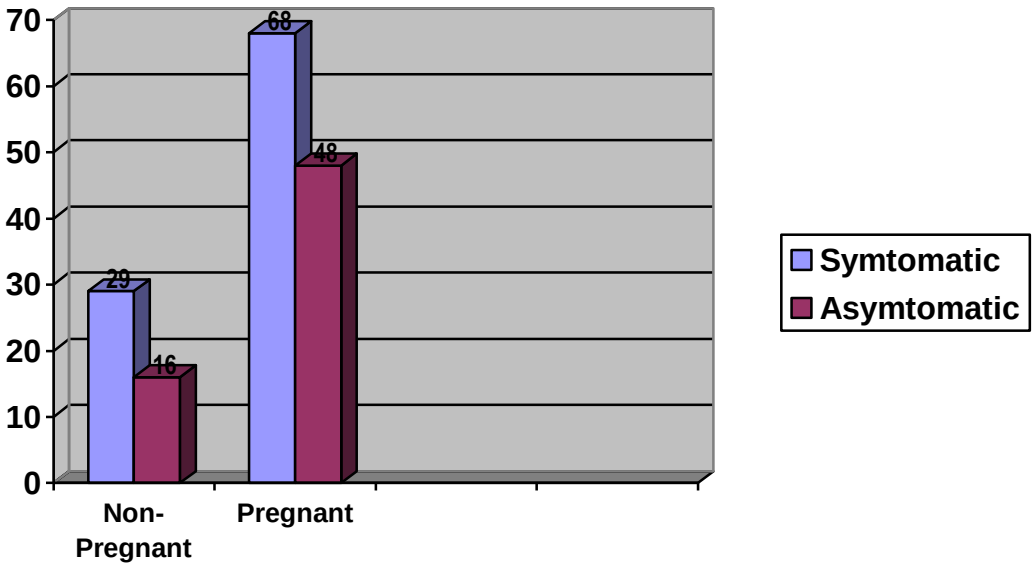


Figure 5.2
Incidence of UTI based on Pregnancy.

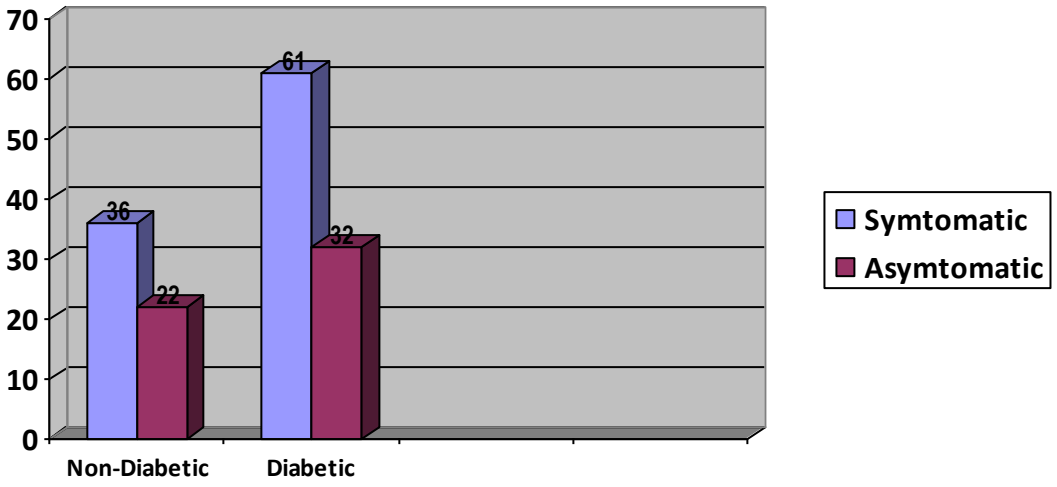


Figure 5.3
Incidence of UTI based on presence and absence of Diabetes.

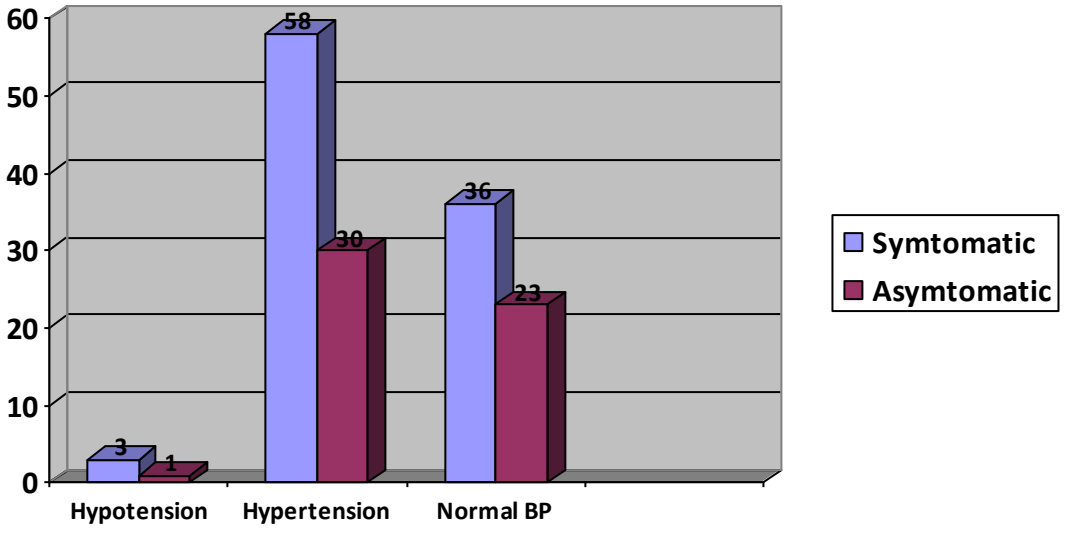


Figure 5.4
Incidence of UTI based on Blood Pressure levels.

Data presented in Table 5.1 shows that majority of the UTI incidence was discovered in married female 95 (62.91%) of the total UTIs cases, where as nearly half of the percentage (32.45%) observed in 49 single females.

As shown in Table 5.1, the incidence of UTIs with respect to marital status revealed higher prevalence of both asymptomatic UTI (70.37%) and symptomatic UTI (58.76%) in married subjects as compared to singles where the incidence rate of asymptomatic UTI was (22.22%) and symptomatic UTI was (38.14%). In contrast, the incidence rate of both asymptomatic UTI and symptomatic UTI among widow/divorced was found to be very low and was 7.41 % and 3.09 %, respectively (Table 5.1).

The predominance of asymptomatic and symptomatic UTIs among pregnant women (88.89 vs. 70.10%) was also noticed as compared to non-pregnant (29.63% vs. 29.90%) as shown in Table 5.1.

The prevalence of symptomatic and asymptomatic UTIs was observed to be higher (nearly twice) in diabetic subjects (62.88% vs. 59.25%) as compared to non-diabetic subjects (37.11% vs. 40.74%). It has also been observed that symptomatic and asymptomatic UTIs were more common in hypertensive subjects (59.79% vs. 55.55%) than subjects with normal blood pressure (37.11% vs. 42.59%) and hypotension (3.09 % vs. 1.85%).

5.2 Age-wise distribution of patients of the study population

The prevalence of UTI in relation to age of the subjects of the present study has been shown in Table 5.2. The highest UTI patients 68 (44.44%) were women within the 26-35 years age group (i.e. group-B women) followed by Group-C 46 (31.08%) whose ages are within 36-45 years, while the Group-A women (15-25 years of age) were the least sufferers of UTI (24.83%) i.e. 37 patients.

Table 5.2
Age-wise distribution of women of the study population (n=450).

Age group (yrs)	No. tested (%)	No. Positive (%)	No. Negative (%)
15-25 Group-A	149 (33.11)	37 (24.83)	112 (75.16)
26-35 Group-B	153 (34)	68 (44.44)	85 (55.55)
36-45 Group-C	148 (32.89)	46 (31.08)	102 (68.92)
Total	**450 (100.0)**	**151(33.55)**	**299 (66.45)**

Graphical representation of the above table is given below:

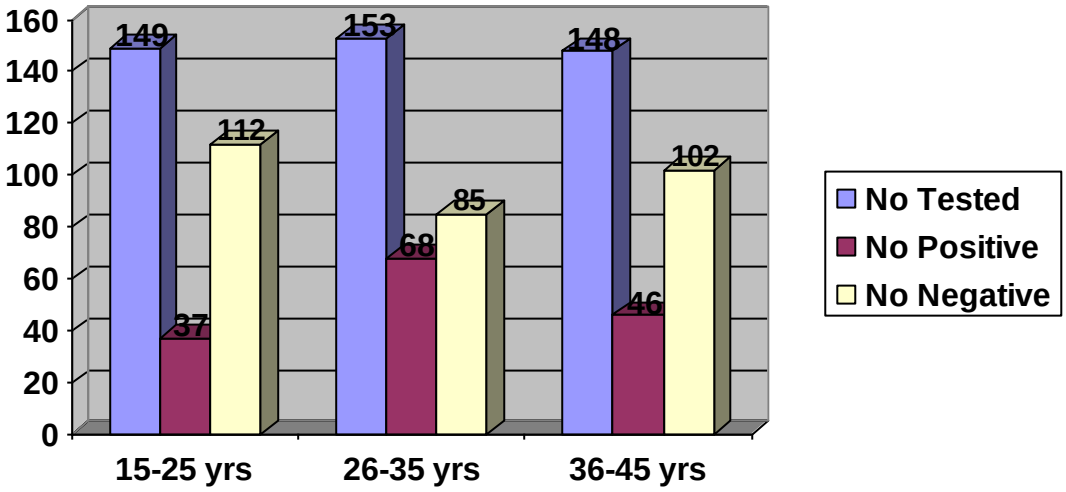


Figure 5.5
Age-wise distribution of women of the study population (n=450).

5.3 Socio - economic statues of the respondents

The Socio-economic statues of the respondents of the current study have been presented in Table 5.3. Socio-economic classes was assessed based on monthly income of the subject's husband's or Father's or own income (where applicable) as mentioned below the Table 5.3 and was divided into four different groups – Rich, Upper middle class, Lower middle class and poor.

Socio - economic statues seems to play an important impact on the incidence of UTI in the present study population as the highest 74 (49%) UTI sufferers belonged to the poor socio-economic group; while only 6 (3.98%) cases of UTI were recorded from the rich socio-economic group as shown in Table 5.3.

Table 5.3
Socio Economic Status of the Respondents (n=151).

Class	UTI positive cases	Percentage
Poor	74	49.00
Lower middle	49	32.45
Upper middle	22	14.57
Rich	6	3.98
Total	151	100.0

Socioeconomic status was divided into four categories:

(Poor class < Tk. 5000/monthly income; Lower middle class from Tk. 5000 to 12,000/month income; Upper middle class Tk. 12,000 to 20,000/month income and Rich > Tk. 20,000 and above per month.

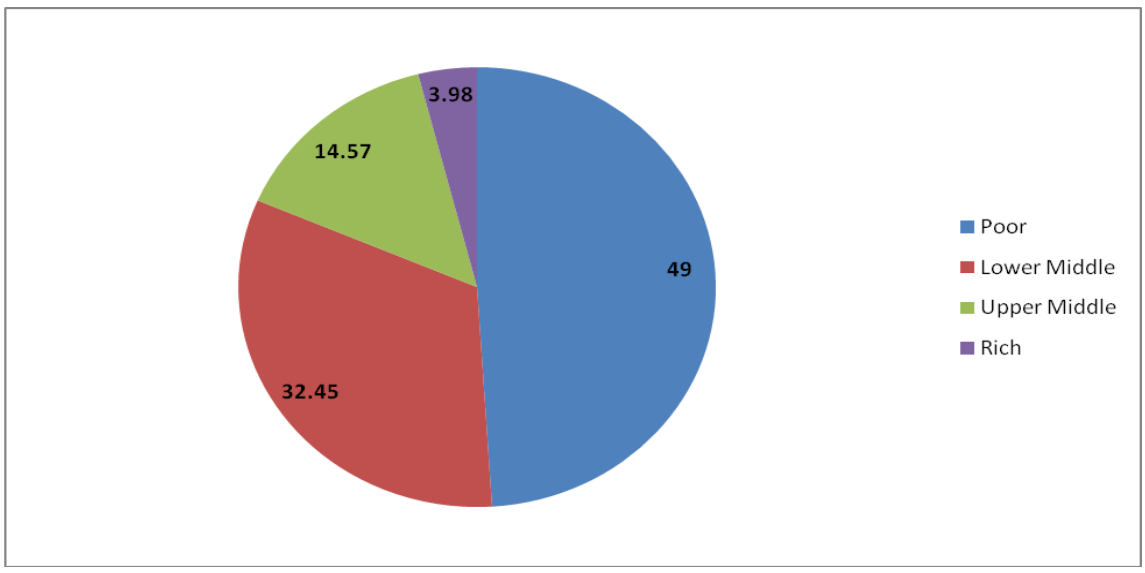


Figure 5.6
Impact of Socio Economic Status of the Respondents on incidence of UTI.

5.4 Educational status of the respondents

The prevalence rate of UTI based on the educational qualifications of the respondents has been presented in Table 5.4. Education seems to play a significant role in preventing the incidence of UTI as patients having an educational qualification of Master's degree and above had a very low (4.64%) incidence of UTI; while the incidence rate of UTI was very high (nearly 45.03%) among the Illiterate.

Table 5.4
The prevalence rate of UTI based on the educational qualifications of the women (n=151).

Educational Qualification	UTI Positive cases (%)
Illiterate	68 (45.03)
Primary	38 (25.17)
SSC	24 (15.89)
HSC/ Graduate	14 (9.27)
Masters and above	7 (4.64)
Total	151 (100%)

5.5 The incidence of UTI by occupational group

Table 5.5 shows the incidence of UTIs by occupational group. UTIs appear to be more prevalent among businesswomen who constituted (48.88%) of the women with UTIs, followed by Artisans/ full housewives (44.79%), Women Traders (35.25%), Students (29.16%), teachers (19.11%) and the Civil Servants students appeared to be the least UTI sufferers constituting only 11.42% (Table 5.5).

Table 5.5
Incidence by occupational groups (n=151).

Occupational groups	Total No. tested	No. positive (%)
Teachers	68	13 (19.11)
Students	24	7 (29.16)
Civil Servants	70	8 (11.42)
Businesswomen	90	44 (48.88)
Women Traders	102	36 (35.29)
Artisans/ Full Housewives	96	43 (44.79)
Total	450	151 (33.55)

5.6 Incidence of UTI in relation to use and no use of sanitary napkin

The prevalence of UTI based on the use of the type of napkin used during menstrual cycle of the participating women under the present study has been shown in Table 5.6. The use of commercial sanitary napkin has been found to play a significant role in preventing the incidence of UTI and the women's using sanitary napkins regularly had a lower (20.53%) incidence rate of UTI as compared to those not using sanitary napkin, were the incidence rate of UTI was higher (49.00%) as shown in Table 5.6.

Table 5.6
Prevalence rate of UTI based on use of sanitary napkin (n=151).

Type of User	No of UTI Positive case (%)
Always using Sanitary napkin	31 (20.53)
Occasional User	46 (30.47)
Not using Sanitary napkin but home made cloth	74 (49.00)
Total	151 (100.0)

5.7 Prevalence of UTI in relation to type of toilet used

The prevalence rate of UTI based upon type of toilet used has been depicted in Table 5.7. Results presented in the table clearly demonstrated that the prevalence rate of UTI was very high 77 (51.0%) among women not using sanitary latrine at all. On the other hand, the incidence of UTI among sanitary latrine using women was found to be lower 27 (17.88%).

Table 5.7
Prevalence of UTI based upon type of toilet used (n=151).

Type of Toilet Used	UTI Positive case (%)
Sanitary Latrine	27 (17.88)
Semi Pakka / Kancha latrine	47 (31.12)
No latrine used at all (Open space)	77 (51.00)
Total	151 (100.0)

5.8 Results of urine culture of the study population

The gold standard for detecting bacteriuria is urine culture. As shown in Table 5.8, out of 450 urine sample tested in the preset study, 151 (33.55%) yielded significant growth of single organism and 12 (2.66%) yielded mixed growth. No growth was observed in 299 (66.44%) urine samples.

Table 5.8
Results of urine culture of the study population (n=450).

Growth	Number	Percentage
Single bacterial growth	139	30.88
Mixed bacterial growth	12	2.66
Total growth	151	33.55
No growth	299	66.44
Total	450	100

5.9 Isolation and identification of pathogens from urine samples

Bacterial isolates from the urine sample were identified by staining (Microscopic) techniques and performing conventional biochemical tests like indole test, methyl red test, citrate utilization test, triple sugar iron agar and mannitol mortality tests. The various conventional bio-chemical tests were done to identify the causative organisms and their results have been presented in Table 5.9.

Table 5.9
Various conventional biochemical tests to identify organisms.

Organisms	Motility	Mannitol	Triple sugar Iron agar	Indole	Citrate	Urease	Methy red	Voges proskauer Test
Escherichia coli	+	+	++ **gas**	+	-	-	+	-
Klebsiella sp.	-	+	++ **gas**	-	+	**NT**	_	+
Pseudomonas sp	+	-	--	-	+	NT	NT	NT
Proteus sp.	+	_	-+ H2S gas	-	NT	+	+	NT
Staphylococcus saprophyticus	Biochemical tests: Coagulase positive, Catalase positive							
Staphylococcus aureus	-	Biochemical tests: Coagulase negative, Catalase positive and Novobiocin resistant						

Staining reaction, motility and growth characteristics of isolated bacterial species from urinary isolates were observed on media like blood agar, CLED agar and MacConkey's agar. The isolates were identified to belong to six (06) genera - *Escherichia, Klebsiella, Staphylococcus sp., Streptococcus sp., Proteus sp.* and *Pseudomonas sp.* based on the Bergey's Manual of Systemic Bacteriology.

Appearances of the above urinary pathogens on CLED agar media are given below and growth of all (06) genera have been shown in the Figures 8 to 13.

- *E. coli*: Yellow (lactose-fermenting) opaque colonies often with slightly deeper colored centre.
- *Klebsiella* species: Large mucoid yellow or yellow-white colonies.
- *Proteus species*: Translucent blue-grey colonies.
- *P. aeruginosa:* Green colonies with rough periphery (characteristic colour).
- *S. aureus*: Deep yellow colonies of uniform colour.
- *S. saprophyticus* and other coagulase negative staphylococci: Yellow to white colonies.

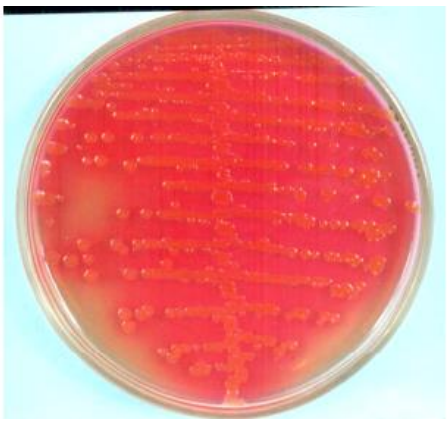


Figure 5.7
CLED medium showing Yellow (lactose-fermenting) pink semi-translucent colonies of *E. coli.*

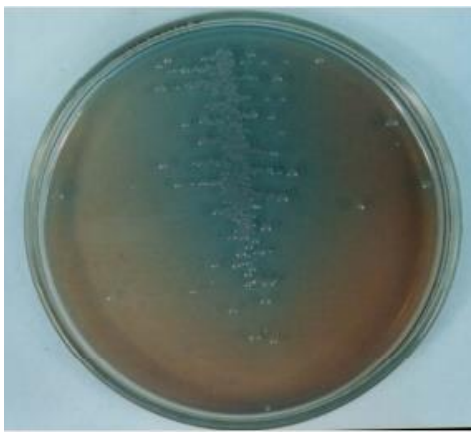


Figure 5.8
CLED medium showing blue-gray translucent colonies of *Proteus mirabilis*

Figure 5.9
CLED medium showing green colonies with rough periphery (characteristic colour) of *P. aeruginosa.*

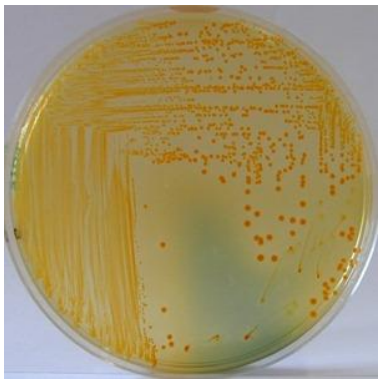


Figure 5.10
CLED medium showing deep yellow colonies of uniform growth of *S. aureus.*

Figure 5.11
CLED medium showing large mucoid yellow or yellow-whitish colonies of *Klebsiella* spp.

Figure 5.12
CLED medium showing yellow to white colonies of *S. Saprophyticus.*

The growth of some of the bacterial isolates from urinary samples on blood agar and MacConkey's agar has been shown in the Figures 14 to 18.

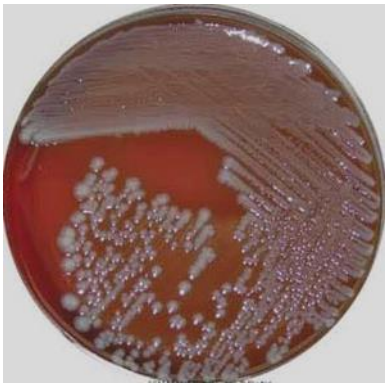


Figure 5.13
Growth of *E. Coli.* on blood agar

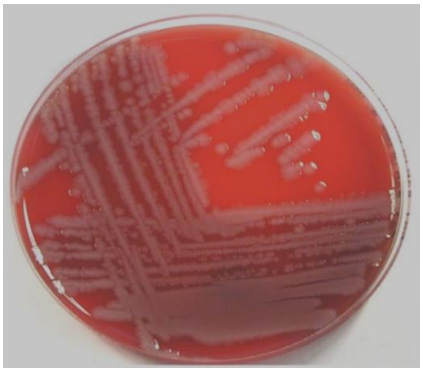


Figure 5.14
Growth of *Klebsiella* on blood agar

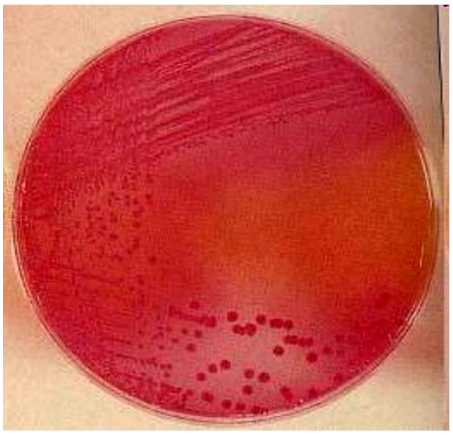


Figure 5.15
Growth of *E. coli* on MacConkey's agar.

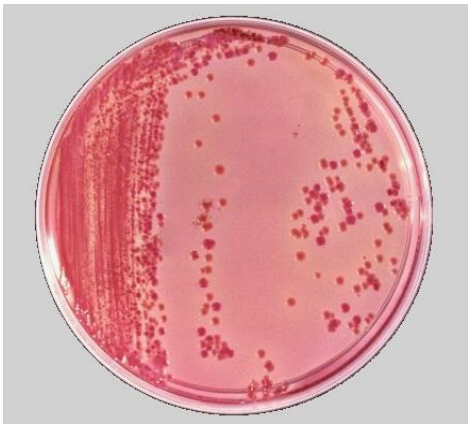


Figure 5.16
Growth of *Klebsiella* on MacConkey's agar

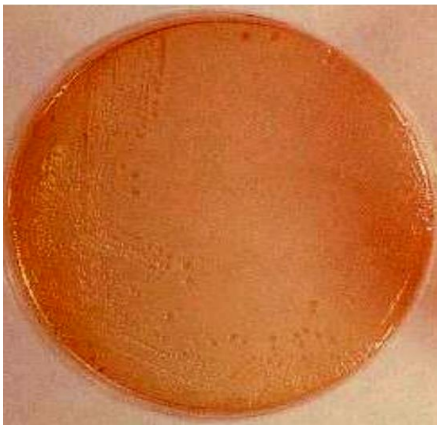


Figure 5.17
Growth of *Proteus* on MacConkey's agar

5.10 Frequency of isolation of pathogens in urine samples

The frequency of occurrence of pathogens in urine samples of the study women has been shown in Table 5.10. Of the 151 isolates obtained, Gram-negative bacteria occurred more frequently than Gram-positive bacteria, constituting 99 (65.56%) of the total isolates. Among the isolates, *E. coli* had the highest frequency of isolation with a frequency of 64 *(*42.38%), followed by *Pseudomonas aeruginosa* 19 (12.58%), *Klebsiella spp*. 8 (5.29%) and *Proteus sp* also 8(5.29%).

Gram-positive bacteria accounted for 40 (34.44 %) of the total isolates, with *Staphylococcus saprophyticus* 31 (20.52%) and *Staphylococcus aureus* 9 (5.96%). Mixed cultures of *Klebsiella spp.* and *Staphylococcus spp*. accounted for 12 (7.947%) of the total isolated as shown in Table 5.10. The distribution of the uropathogens has been shown as a pie graph (Fig. 5.18).

Table 5.10
Frequency of isolation of pathogens in urine samples of women. (n=151)

Bacteria isolated	**No. of isolates (%)**
Gram-negative bacteria	
Escherichia coli	64 (42.38)
Pseudomonas sp	19 (12.58)
Klebsiella sp.	8 (5.29)
Proteus sp.	8 (5.29)
Total Gram -ive bacteria	**99 (65.56%)**
Gram-positive bacteria	
Staphylococcus saprophyticus	31 (20.52)
Staphylococcus aureus	9 (5.96)
Total Gram + ive bacteria	**40 (26.49)**
Total Single bacterial growth (Gram + ive + Gram –ive)	**139 (30.88)**
Mixed bacterial growth of *Klebsiella and Staphylococcus spp.*	12 (7.947)
Total	**151 (100.0)**

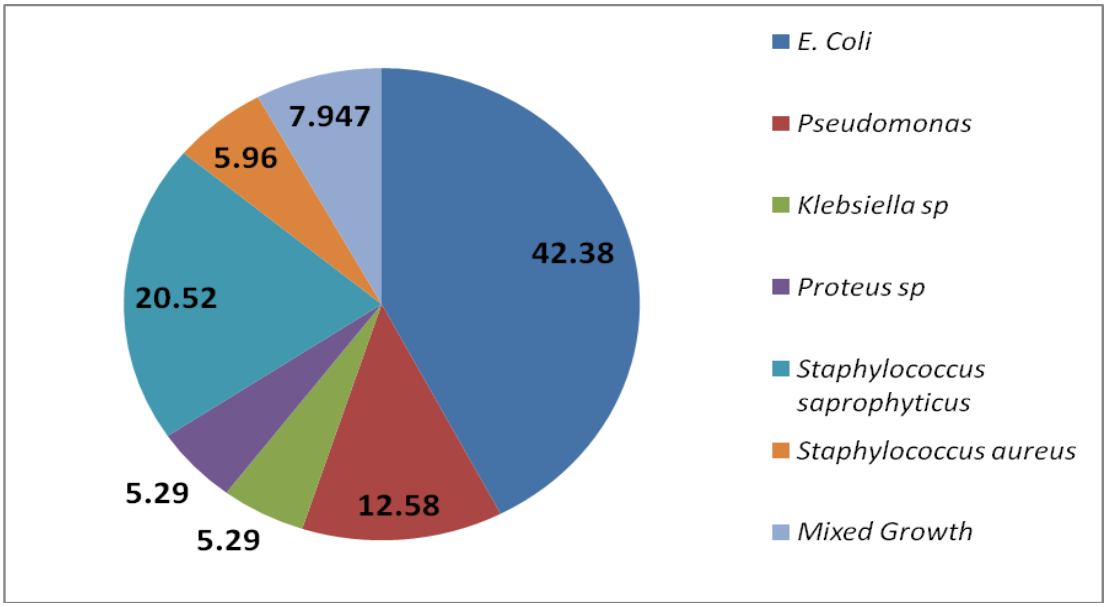


Figure 5.18
Distribution of the uropathogens of the study population.

5.11 Antibiotic susceptibility pattern of gram-negative and gram-positive bacteria isolated from urinary isolates (N=151).

Antibiotic susceptibility testing of the isolated uropathogens was performed by using the disc diffusion method described by Bauer *et al.* on Mueller Hinton Agar (Oxoid). The antibiotic susceptibility pattern of isolated uropathogens (both Gram-negative and Gram-positive bacteria) from the urine samples of the study population has been shown in Table 5.11.

Table 5.11
Antimicrobial susceptibility (S) and resistance (R) pattern of clinical bacterial strains isolated from UTI patients (N=151)

Antimicrobial agents	**Sensitivity pattern**	***E. coli* n (%)**	***Klebsiella* spp n (%)**	***Proteus* spp n (%)**	***Pseudomonas* spp n (%)**	***S. saprophyticus* spp n (%)**	***S. aureus* spp n (%)**
Cephradine	R	33.3	34.5	40	90	55	35
	S	66.7	65.5	60	10	45	65
Cefixime	R	25	78.5	30	82	45	40
	S	75	21.5	70	18	55	60
Ciprofloxacin	R	55.56	70	30	44.68	70	77.5
	S	44.44	30	70	55.32	30	22.5
Gatifloxacin	R	48	77	25	85	75.5	30
	S	52	23	75	15	24.5	70
TMP/SMZ Cotrimoxazole	R	68	60.55	52.3	78.5	72	75
	S	32	39.45	47.7	21.5	28	25

Antimicrobial agents	**Sensitivity pattern**	***E. coli* n (%)**	***Klebsiella* spp n (%)**	***Proteus* spp n (%)**	***Pseudomonas* spp n (%)**	***S. saprophyticus* spp n (%)**	***S. aureus* spp n (%)**
Nitrofurantoin	R	34	41.67	79.35	80	40	45
	S	66	58.33	20.65	20	60	55
Nalidixic Acid	R	77	77.45	55	81.12	78	75
	S	23	22.55	45	18.88	22	25
Ceftazidime	R	63	80	27.45	75.5	77	78
	S	37	20	72.55	24.5	23	22
Ceftriaxone	R	60	75.95	10.83	73.85	40	66.7
	S	40	24.05	89.17	21.15	60	33.3
Amikacin	R	16.45	8.5	7.5	23	35.7	29
	S	83.55	91.5	92.5	77	64.3	71
Gentamicin	R	22	39.87	13.55	21.28	28.6	25
	S	78	60.13	86.45	78.72	71.4	75
Azithromycin	R	85	82	78	85	34.3	22
	S	15	18	22	15	65.7	78
Imipenum	R	8.8	7.92	70	5.5	20	11
	S	91.2	92.08	30	94.5	80	89

The results showed that in general most of the urinary isolates showed higher resistance to commonly used and comparatively old drugs namely- Nalidixic acid, cotrimoxazole, nitrofurantoin, ceftazidime, ceftriaxone and Azithromycin (Table 5.11, bar graph Fig. 5.19 and Photographic Fig. 5.21 showing very higher resistance (smaller zone of inhibition) by a urinary isolates. Ciprofloxacin and gatifloxacin exhibited moderate resistance and susceptibility (Photographic Fig. 5.22 marked D and E). On the other hand, Imipenem, Gentamicin and Amikacin displayed very high sensitivity towards most of the isolated organism from urine samples (Table 5.11, bar graph Fig. 5.20 and Photographic Fig. 5.22 marked (A), (B) and (C).

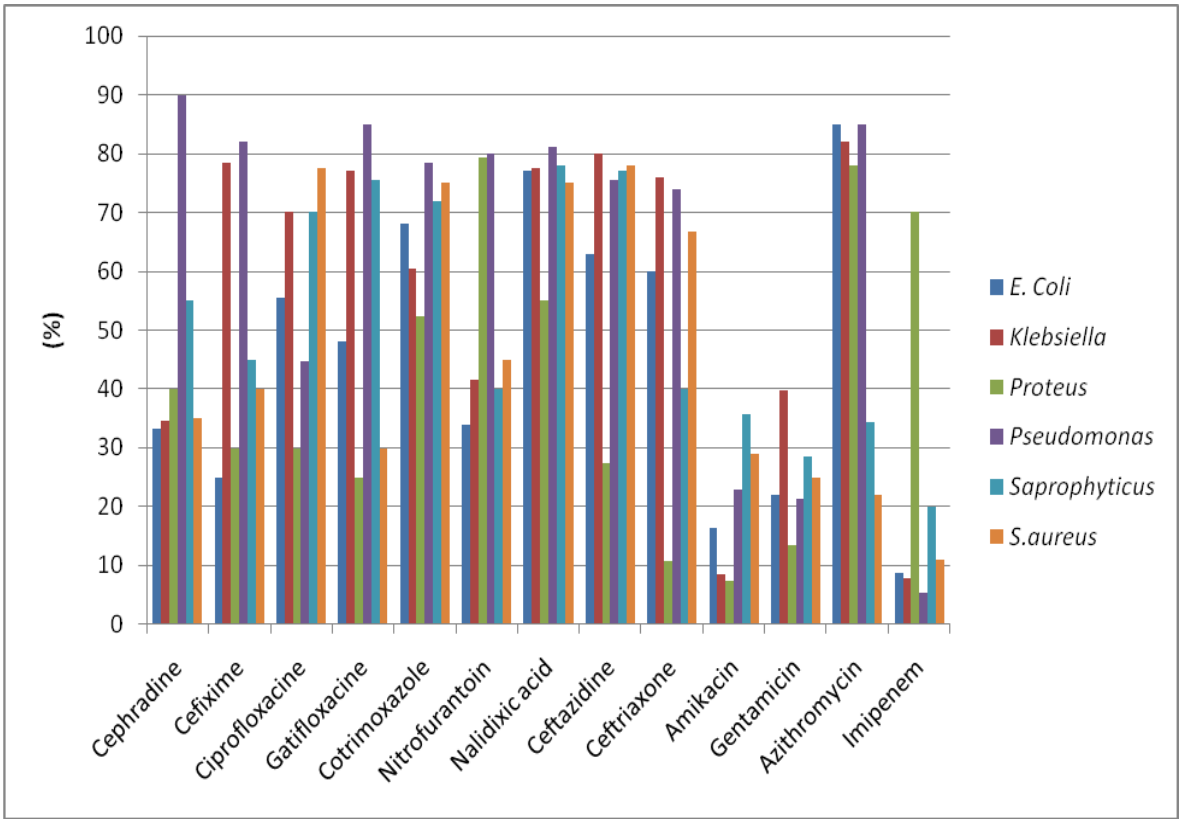


Figure 5.19
Antibiotic resistance pattern of the bacterial species isolated from urine samples.

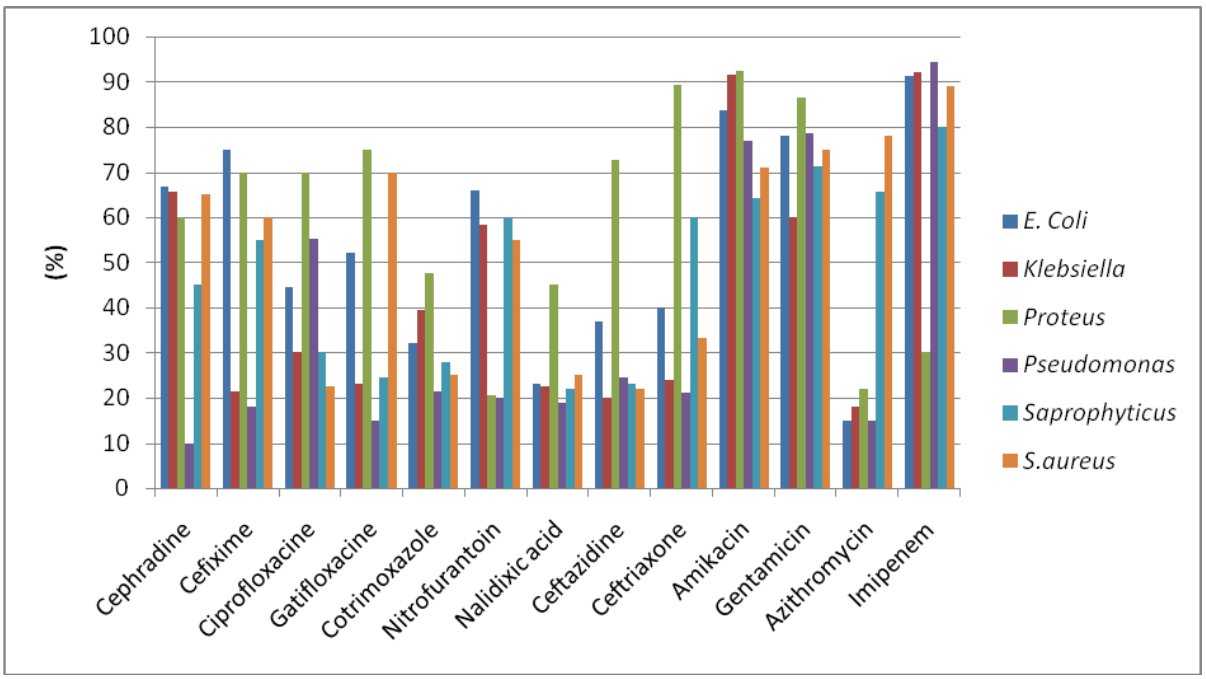


Figure 5.20
Antibiotic sensitivity pattern of the bacterial species isolated from urine samples.

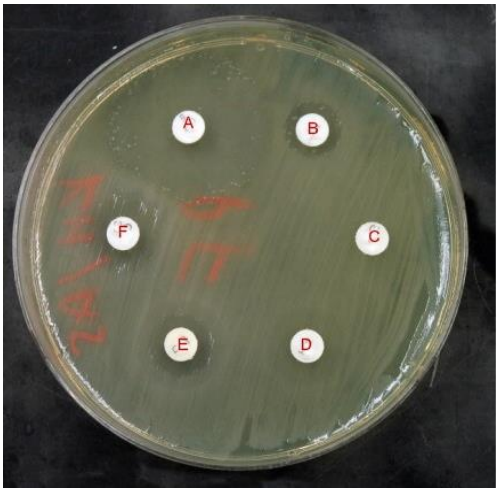


Figure 5.21
Photograph showing very higher resistance (smaller zone of inhibition) by a urinary isolate to Nalidixic acid, cotrimoxazole, nitrofurantoin, ceftazidime, ceftriaxone and Azithromycin in antibiotic susceptibility testing by disc diffusion method.

Figure 5.22
Photograph showing very high sensitivity of Imipenem (A), Gentamicin (B) and amikacin (C) as evidenced by very large zone of inhibition towards isolated uropathogen *Pseudomonas sp.* while Ciprofloxacin (D) and gatifloxacin (E) exhibited moderate resistance and moderate susceptibility (medium size zone of inhibition).

As shown in Table 5.11 above, *E. coli* showed highest resistance to Azithromycin (85%) , followed by nalidixic acid (77%), cotrimoxazole (68%), Ceftazidine (63%) and Ceftriaxone (60%). Ciprofloxacin and gatifloxacin with (55.56%) and (48%) resistance respectively were moderately resistant. On the other hand, *E coli*

showed highest sensitivity (91.2%) to Imipenum, followed by Amikacin (83.55%) and gentamicin (78%) sensitivity.

Klebsiella showed highest resistance to Azithromycin (82%), followed by Cefixime (78.5%), nalidixic acid (77.45%), gatifloxacin (77%), Ceftriaxone (75.95%), Ciprofloxacin (70%) and cotrimoxazole (60.55%). On the other hand, *Klebsiella* was found to be highly sensitive towards Imipenum (92.08%), Amikacin (91.5%) and moderately sensitive to Cephradine (65.5%).

Proteus showed highest resistance to nitrofurantoin (79.35%), followed by Azithromicin (78%), while *Proteus* showed moderate resistance of 55% to Nalidixic acid and cotrimoxazole (52.3%). On the other hand, *Proteus* was found to be highly sensitive to Amikacin (92.5%), Ceftriaxone (89.17%), Gentamicin (86.45%), gatifloxacin (75%), Ceftazidine (72.55%), Cirprofloxacin a cefixime and cephradine (60%).

Pseudomonas showed highest resistance against cephradine (90%), followed by gatifloxacin (85%) and Azithromicin (85%), cefixime (82%), nalidixic acid resistance (81.12%), cotrimoxazole (78.5%), Ceftazidine (75.5%), Ceftriaxone (73.85%). *Pseudomonas* was found to be highly sensitive towards Imipenum (94.5%), gentamicin (78.72%), Amikacin (77%) and moderately sensitive to Ciprofloxacin (55.32%).

Staphylococcus saprophyticus showed highest resistance to Nalidixic acid (78%), Ceftazidine (77%), gatifloxacin (75.5%), cotrimoxazole (72%), ciprofloxacin (70%). Cephradine showed moderate resistance (55%). On the other hand, Staphylococcus *saprophyticus* was found to be highly sensitive to Imipenum (80%), followed by gentamicin (71.4%), Azithromycin (65.7%), Amikacin (64.3%). Ceftriaxone and Nirofurantoin both showed moderate sensitivity of 60%.

Staphylococcus aureus showed highest resistance to Ceftazidine (78%), followed by ciprofloxacin (77.5%), Cotrimaxazole and nalidixic acid (75%), Ceftriaxone (66.7 %). On the contrary, *Staphylococcus aureus* showed highest sensitivity towards Imipenum (89%), followed by Azithromycin (78%), gentamicin (75%), Amikacin (71%) and gatifloxacin (70%) while Cephradine showed (65%) and cefixime (60%) sensitivity which can be considered as moderate sensitivity.

Chapter Six
DISCUSSION

Against the background of paucity of reports of urinary tract infection in the Tertiary Level Hospitals in the Northern areas of Bangladesh, this study was aimed at determining the prevalence of UTI in Northern areas of Bangladesh, the effect of age on its prevalence, as well as the etiologic agents and their antibiotic susceptibility profile.

In the present study, midstream urine samples were collected from female patients having clinically suspected UTI attending the OPDs or admitted to Rajshahi Medical College Hospital, Rajshahi, SZMCH, Bogra, Rangpur Medical College, Rangpur, Dinajpur Medical College, Dinajpur, Combined Military Hospital (CMH), Bogra located in the Northern regions of Bangladesh.

Four hundred and fifty (450) mid-stream urine samples were collected from the patients following the usual laboratory protocol and processed in the laboratory. Routine urinary microscopy (RE) and urine culture was done in all cases in order to diagnose for the presence of UTI. Of the 450 patients screened for detection of UTI, 151 patients have been confirmly diagnosed to be suffering from UTI (both symptomatic and asymptomatic). Thus the prevalence rate of urinary tract infection (UTI) of the study population was 33.55%.

Among the 151 confirmly diagnosed UTI patients, asymptomatic UTI was diagnosed in 54 women whereas, significant bacteriuria i.e. symptomatic UTI in 97 patients. The prevalence of symptomatic UTI was therefore higher than asymptomatic UTI (Table 5.1, page 57, Chapter 5). This predominance might be due to the fact that greater receptivity of epithelial cells of bladder to bacteria may increase the susceptibility of UTI in symptomatic women which causes adherence of more bacteria to the epithelial cells of bladder resulting in developing symptomatic UTI (Ethel *et al.* 2006).

The distribution of asymptomatic UTI and symptomatic UTI subjects with respect to medico-demographic characteristics *i.e.* marital status (single, married, widow/divorced), pregnancy (pregnant, non pregnant), diabetes (diabetic, non-diabetic), and blood pressure (hypotension, hypertension, normal blood pressure) were observed in the current study.

As far as marital status of subjects is concerned, married women are most susceptible to UTIs due to the sexual activity (Ikaheimo *et al.*1996). Because, during sexual intercourse bacteria present in the vaginal area could be messaged into the urethra and can cause an UTI (Cornforth 2002).

In the present study, the prevalence of symptomatic and asymptomatic UTIs was also compared with respect to the marital status of subjects. Most (62.91%) of the UTI sufferers were married female where as nearly half percentage (32.45%) suffering from UTI were single females (Table 5.1, page 57, Chapter 5). This finding of ours is in good agreement with the findings of David *et al*. (2010) in Nigeria, who also reported in their study that the incidence of UTIs was higher in married women (78.51%) than in the singles (59.47%). Place India and our data

Again also incidence of UTIs with respect to marital status revealed higher prevalence of both asymptomatic UTI (70.37%) and symptomatic UTI (58.76%) in married subjects as compared to singles where the incidence rate of asymptomatic UTI was (22.22%) and symptomatic UTI was (38.14%). In contrast, the incidence rate of both asymptomatic UTI and symptomatic UTI among widow/divorced was found to be very low and was 7.41 % and 3.09 %, respectively (Table 5.1, page 57, Chapter 5).

UTI is also a common problem in pregnancy due to the increase in sex hormones and the anatomical and physiological changes during pregnancy. The pregnant women are at high risk of UTI. During pregnancy, the chemical constitution of urine is also affected and results in increased urinary substance e.g. glucose and amino acids which may facilitate bacterial growth in urine (Sheikh *et al.* 2000).

However, this seemingly benign condition may have serious consequences and, if left untreated, could lead to pyelonephritis, hypertension, preterm labor, low birth weight. Group B streptococcal infection in the newborn, septicemia and maternal death (Kristen 2004, Hazir 2007).

Approximately 20-40% of women with asymptomatic UTI develop pyelonephritis during pregnancy (Krcmery *et al.* 2001). Thus, the prevention, early detection and prompt treatment of UTIs in pregnancy have become essential components of prenatal care (Kristen, 2004). In view of this, the prevalence of symptomatic and asymptomatic UTIs among pregnant women was also studied in the present study.

In the present study, the predominance of both asymptomatic and symptomatic UTIs among pregnant women (88.89 vs. 70.10%) was noticed as compared to non-pregnant (29.63% vs. 29.90%). Thus the incidence of UTI was more than twice times higher in pregnant women than in non-pregnant women. This finding of ours agrees very well with the earlier study of Begum *et al.* (1992). She reported that incidence of bacteriuria during pregnancy is also very common in Bangladesh and 10% of pregnant women attended in antenatal clinic of Mymensingh Medical College had symptomatic urinary tract infection. The urinary tract undergoes profound physiological and anatomical changes during pregnancy facilitating the development of bacteriuria both symptomatic and asymptomatic in women (Begum 1992).

In another study in Bangladesh by Khatun *et al*. (1985) revealed that 30% of clinically healthy pregnant women had asymptomatic bacteriuria. Selimuzzaman *et al*. (2006) reported that at Rajshahi city a total of 2000 apparently healthy pregnant mothers were screened, 290 (14.5%) mothers were found to have asymptomatic bacteriuria. Symptomatic bacteriuria is an iceberg of total bacteriuria. Pregnancy is a provocation for the asymptomatic to become symptomatic (Doland 1979). About 10% 0f those with asymptomatic bacteriuria develop symptomatic bacteriuria during pregnancy (Bailey 1972).

Diabetes mellitus (DM) has long been considered to be a predisposing factor for urinary tract infection (Bonadio *et al.* 2006) and the urinary tract is the principle site of the infection in diabetics with increased risk of complications of UTI (Sahib 2008). It is evident from literature that diabetic subjects are at high risk of UTIs. For instance, in a study (Goswami *et al.* 2001), the prevalence of UTI in diabetic subjects were found to be higher when compared with non-diabetic subjects (9% vs. 0.78%).

Symptomatic and asymptomatic UTIs occur more frequently in women with diabetes mellitus than women without diabetes mellitus (Daneshgari and Moore 2006). Women with diabetes who requires pharmacological treatment have approximately twice as high risk of cystitis as non- diabetic women (Boyko *et al.* 2002) because of the changes in the immune system secondary to the high sugar concentration (Geerlings *et al.* 2002). However, gestational diabetes mellitus was not associated with increased risk of UTls (Rizk *et al.* 2001).

In the present study, the prevalence of symptomatic and asymptomatic UTIs was observed to be higher (nearly twice) in diabetic subjects (62.88% vs. 59.25%) as compared to non-diabetic subjects (37.11% vs. 40.74%) as presented in Table 5.1 (Page 57, Chapter 5). This finding of ours is comparable with the findings of Sabahat Saeed in Pakistan (2008).

Observation of the current study is that symptomatic and asymptomatic UTIs were more common in hypertensive subjects (59.79% vs. 55.55%) than subjects with normal blood pressure (37.11% vs. 42.59%) and hypotension (3.09 % vs. 1.85%).

Study of age-wise incidence of UTI showed that the highest UTI sufferers (44.44%) were the most sexually active women (26-35 years age group) followed by (31.08%) of 36-45 years ;while the least sufferers of UTI (24.83%) were women of 15-25 years. A study conducted in Bangladesh by Kawser Parveen *et al.* (2011) reported high incidence of UTI in 21–25 years age group (44.61%) and show disagreement with our finding.

The reason for noticing highest incidence of UTI among the most sexually active women (26-35 years age group) in our study could be as most women of this age group were married women and they are most susceptible to UTIs due to their intense sexual activity (Ikaheimo *et al.*1996). Because, during sexual intercourse bacteria present in the vaginal area could be messaged into the urethra and can cause an UTI (Cornforth 2002).

Impact of the possible Socio Economic status of the respondents on incidence of UTI was studied under the present study. Remarkable impact of socio-economic statues on UTI incidence was noticed. The highest UTI sufferers (49%) were from poor socio-economic class while; only 6 (3.98%) UTI patients were from the rich socio-economic class. This finding shows good harmony with a study conducted in Bangladesh by Kawser Parveen *et al.* (2011) who reported 75% incidence of bacteriuria in respondents from very poor socio-economic background and only 25% were from high socio-economic background.

Education seems to play a significant role in preventing the incidence of UTI and its incidence was extremely low (4.64%) in patients having Master's degree; while very high (45.03%) among the Illiterate in the present study. This is consistent with many studies, which shows that UTI is more prevalent among young married women. This finding of ours shows good harmony with another similar study conducted in our country by Kawser Parveen *et al.* (2011). In their study, the significance of education was also evidenced by the fact that only10% of the patients suffering from bacteriuria were educated while 90% were illiterate. Begum *et al.* (2006) in their study on UTI among female workers in a selected garment industry of Dhaka city in a cross-sectional study also found that the highest (66.7%) of the UTI sufferers were married women.

The results of study of the incidence of UTI depending on the occupation of the participants of the study showed UTI to be more prevalent among businesswomen constituting (48.88%) of the women with UTIs, followed by Artisans/ full

housewives (44.79%), Women Traders (35.25%), Students (29.16%), teachers (19.11%) and the Civil servants were the least UTI sufferers (11.42%.).

Results of incidence of UTI in relation to use and no use of commercial sanitary napkin during menstrual cycle of women have been found to play a significant role in preventing the incidence of UTI. Women using sanitary napkins regularly had lower incidence rate (20.53%) of UTI as compared to those not using sanitary napkin that had higher (49.00%) incidence of UTI.

This finding of ours is similar to the observation of Ahmed and Avasarala (2009) in Karimnagar district, AP, India who reported that during the survey they found that most of the girls used a piece of cloth as pads during the menstrual period and some used it more than once due to economical reasons. The prevalence of UTI was significantly more (9.9%) in those girls using unsanitary pads during menstruation. David *et al*. (2010) in Nigeria also reported that the incidence of UTIs was 88.81% and 59.94% among women using tissue paper alone as sanitary napkin and tissue together with hygienic pads, respectively.

Results of prevalence of UTI based upon type of toilet use in our study clearly demonstrated very high prevalence of UTI (51.0%) among women not using sanitary latrine at all. On the contrary, the incidence of UTI among sanitary latrine using women was found to be lower (17.88%). However, there was no study available to be compared with our findings.

Urine culture is considered as the Gold standard for detection of UTIs. The results of urine culture of the present study showed that of the 450 urine sample analyzed, 151 (33.55%) yielded significant growth of single organism and 12 (2.66%) yielded mixed growth. No growth was observed in 299 (66.44%) urine samples. Findings of our present study are almost similar with a study done in Bangladesh by Sharmin (2005) which showed 38.5% single growth and 4% mixed growth.

In contrast to the findings of the present study, a higher rate was reported from UK (54.2% single growth and 21.6% mixed growth) [Perry *et al*., 2003]. This might be due to the fact that urine samples having pus cell > 200/cmm were included in that study. A lower bacterial isolation rate were reported from Israel (19.55% single growth and 1.66% mixed growth) [Samra *et al*., 1998], India (20% single growth and 4% mixed growth) [Lakshmi *et al*., 2004] and California (24.5% single growth and 17.5% mixed growth) [D'Souza *et al*. 2004]. Such lower isolation rate in their study were probably due to fact that all urine samples were cultured irrespective of pus cell count, while in the present study urine samples having pus cells > 5/HPF were included.

In the present study, Blood agar, CLED agar and MacConkey's agar media were used for culture studies of the urine. The presence of more than 10^5 colonies per milliliter of urine was taken as a case of UTI. The uroptahogens were identified by their growth characteristics, colony morphology, Gram staining (microscopy), motility test and various conventional bio-chemical tests. In urine culture, both Gram +ive and Gram –ive organisms were identified and belonged to six (06) genera - *Escherichia, Klebsiella, Staphylococcus sp., Streptococcus sp., Proteus sp.* and *Pseudomonas sp.* based on the Bergey's Manual of Systemic Bacteriology.

Of the 151 isolates analyzed, Gram-negative bacteria occurred more frequently than Gram-positive bacteria, constituting 99 (65.56%) of the total isolates. Among the Gram –ive organisms the significant isolate was *E. coli* which had the highest percentage of isolation 64 *(*42.38%), followed by *Pseudomonas aeruginosa* 19 (12.58%), *Klebsiella spp*. 8 (5.29%) and *Proteus sp* 8(5.29%). Gram-positive bacteria accounted for 40 (34.44 %) of the total isolates, with *Staphylococcus saprophyticus* 31 (20.52%) and *Staphylococcus aureus* 9 (5.96%). Mixed cultures of *Klebsiella spp.* and *Staphylococcus spp*. accounted for 12 (7.947%) of the total isolates.

The most common bacterial isolates from midstream urine samples of women from asymptomatic UTI and symptomatic UTI enrolled in our study were Gram – negative *Escherichia coli* (42.38%),) followed by *Pseudomonas aeruginosa*

(12.58%). Rahman *et al.* (1990) and Ahmed and Rashid (1996) in their studies in Bangladesh also reported *E. coli* as being the commonest pathogen responsible for bacteriuria which is consistent with the findings of this study. The findings of *E. coli* are also in agreement with the study done by Sharmin (2005) in Bangladesh. Another study done by Hasan *et al.* (2007) in a tertiary hospital in Indian study showed 50.7% incidence of UTI caused by *E. coli*, which was nearer to our study.

Delzell and Lefevre, (2000), Colgan *et al.,* (2006), Turpin *et al.* (2007), Hernandez *et al.,* (2007) and Hazhir (2007) have all reported *E. coli* as the dominant bacterial agent causing asymptomatic UTI.

Pseudomonas aeruginosa 19 (12.58%) was observed to be the second most common causes of UTI as per our study. Ummey Shahnaz Parvin (2009) in Bangladesh reported 12% nosocomial UTI caused by *P. aeruginosa*, nosocomia. UTI caused by *P. aeruginosa* isolated were 10.78% reported by Sharmin (2005) in Bangladesh. Anbumani and Mallika (2007) showed 11% UTI caused by *P. aeruginosa* were very close to our finding. Kenechukwu *et al* (2005) have found 1.6% isolation rate of the same organism which was not consistent with our study.

Klebsiella spp 8 (5.29%) was the third common causes of UTI in our study. Chaudhury (1998) and Sharmin (2005) from Bangladesh and Raco and Barez (1998) from Davao city in the Philippines found that *Klebsiella* spp isolation rate was nearer to 6.7%, which is closer to our finding. However, Kadri *et al* (2004) found a higher isolation rate of 32.20% and Anbumani and Mallika (2007) found isolation rate of 17.6% for *Klebsiella* spp. Findings of these two studies were not in agreement with our finding.

Our study found the incidence of UTI cases by *Proteus* species to be 8(5.29%). These were greater than the findings of 3.57% found by Sharmin in Bangladesh (2005) in case of community acquired UTI.

The findings of our study shows that *Staphylococcus saphrophyticus*, which was formerly believed to be normal commensal, was recognized as the second most common pathogen accounting overall 19.5% of bacteriuria in Tertiary community hospitals. It corresponds with the findings of Ahmed *et al.* (1999).

The dissimilarities of the rate of isolation and isolated bacterial species between the present study and previous other studies might be due the passage of time, geographical variation, difference among sexes, various personal, educational and overall socioeconomic status, , method of collection of urine samples etc., availability of medical facilities and other unknown reasons.

According to Savas *et al* (2006) the distribution of pathogens causing infections, especially antimicrobial resistant pathogens, changes with time and varies among hospitals even different locations in the same hospital. It depends on the pattern of antimicrobial usages and colonization of the organisms in the hospital environment (Lolekha *et al*, 1981). Although the spectrum of pathological bacteria isolated from urine of patients across the globe remained largely unchanged over the past few decades there have been dramatic changes in the resistance pattern and sensitivity profile in most countries (Kadri *et al*. 2004).

Therapy against UTI should be guided by antimicrobial susceptibilities as increasing numbers of urinary isolates are developing resistance to commonly use antibiotics. Increasing antimicrobial resistance of uropathogens has led to reconsideration of traditional treatment of recommendations in many areas.

In the present study of ours conducted in several tertiary level hospitals in the northern region of Bangladesh, the antibiogram of the isolated uropathogens revealed that *E. coli* the major pathogen causing UTI showed highest resistance to Azithromycin (85%), followed by Nalidixic acid (77%), cotrimoxazole (68%), Ceftazidine (63%) and Ceftriaxone (60%). Ciprofloxacin and gatifloxacin with (55.56%) and (48%) resistance respectively were moderately resistant (Table 5.11, page 70 of Chapter 5). On the other hand, *E coli* showed highest sensitivity

(91.2%) to Imipenum, followed by Amikacin (83.55%) and Gentamicin (78%) sensitivity (Table 5.11, page 70 of Chapter 5).

Our finding of *E. coli* showed high resistance to Nalidixic acid (77%) and cotrimoxazole (68%), is a little bit higher than that reported by Chaudhury (1998) in Bangladesh who found *E. coli* were resistant to Cotrimoxazole (72.22%) and Nalidixic acid (58.89%) and shows good agreement with our finding. Likewise, Umme Shanaz Parvin (2009) in her study in Mymemsingh Bangladesh also reported that *E. coli* was less sensitive to the commonly prescribed drugs like Ampicillin (21.2%), Tetracycline (21.2%), Nalidixic acid (12.1%) and Cotrimoxazole (18.2%). In a study in Netherlands, the level of resistance towards Cotrimoxazole was 92.8% that was higher than our study.

In our study, *E. coli* was 55.56% resistant to Ciprofloxacin and gatifloxacin (48%) i.e. were moderately resistant (Table 5.11, page 70 of Chapter 5). Sabita Rezwana Rahman *et al.* (2014) in their study in Shanti Town Dhaka have noticed that the *E. coli* isolates were resistant 68% to Ciprofloxacin and 70% to levofloxacin which is consistent to our findings. In our country the increased rate of resistance towards Ciprofloxacin as shown other researchers as well as noticed in our study, were probably due to carelessness, misuse, erratic and improper use of this drug for a long period.

As per findings of our study, *E coli* exhibited highest sensitivity (91.2%) towards Imipenum, followed by Amikacin (83.55%) and Gentamicin (78%) sensitivity (Table 5.11, page 70 of Chapter 5) which is in good agreement with the same findings by Sharmin (2005) in Bangladesh. Sabita Rezwana Rahman *et al.* (2014) in their study on UTI in women in Shanti Town Dhaka reported high sensitivity of *E. Coli*. to imipenem (80%), meropenem (85%) and Amikacin (88%). Also our results agree very well with the study conducted by Mejbah Uddin Ahmed *et. al.* (2011) in Enam Medical College Hospital, Savar, Dhaka who reported best activity against *E. Coli* (>90% susceptible) was attained with Imipenum and Gentamicin.

In our study *P. aeruginosa* isolates from urine sample from study subjects showed highest resistance towards cephradine (90%), followed by gatifloxacin (85%), Azithromicin (85%), cefixime (82%), nalidixic acid resistance (81.12%), cotrimoxazole (78.5%), Ceftazidime (75.5%), Ceftriaxone (73.85%). Study done in India found *Pseudomonas* 72.2% resistant to Ceftazidime which is very similar to our observed resistance (75.5%) of *Pseudomonas* towards Ceftazidime (Hasan *et al* 2007). Chaudhury (1998) from Bangladesh reported in his study 83.33% resistance towards Ceftriaxone.

As per our study, *Pseudomonas* was found to be highly sensitive towards Imipenum (94.5%), gentamicin (78.72%), Amikacin (77%) and moderately sensitive to Ciprofloxacin (55.32%). Ummey Shahnaz Parvin (2009) in her study in Mymemsingh also reported no resistance towards Imipenem and Amikacin which was consistent to our study. Similar results were reported by investigators from other countries (Jones *et al*, 1999). However, in a study in India (Hasan *et al* 2007) reported 89.7% resistance of *Pseudomonas* to Gentamicin , 54.6% to Amikacin, and 70.1% to Ciprofloxacin which was not consistent with our study .

Our study found *Klebsiella* showing highest resistance to Azithromycin (82%), followed by Cefixime (78.5%), nalidixic acid (77.45%), gatifloxacin (77%), Ceftriaxone (75.95%), Ciprofloxacin (70%) and cotrimoxazole (60.55%). Ummey Shahnaz Parvin (2009) in her study in Mymemsingh showed *Klebsiella* spp also reported were solely resistant to Cotrimoxazole, Nalidixic acid, Ciprofloxacin , Azithromycin and agrees very well with our findings. Again, Ummey Shahnaz Parvin (2009) in her study reported *Klebsiella* spp were highly sensitive 100% to Imipenem and Gentamicin. In our study similarly, *Klebsiella* was found to be highly sensitive towards Imipenum (92.08%), Amikacin (91.5%). Farzana Rahman *et al.* (2009) in their study in Dhaka City reported *Klebsiella* spp. also showed high sensitivity to Amikacin (91.5%) and Imipenem (92.08%) which is in harmony with our findings.

In our study *Proteus* species showed highest resistance to nitrofurantoin (79.35%), followed by Azithromicin (78%). Ummey Shahnaz Parvin (2009) in her study in

Mymemsingh also reported *Proteus species* were highly resistant towards Nitrofurantoin which shows good agreement with our finding but she noticed *Proteus* showing no resistance towards Azithromicin, which is not consistent with our finding and is contradictory. Study done in India showed almost similar results observed by us where *Proteus* was 100% resistant towards Nitrofurantoin (Hasan *et al*, 2007). Kenechukwu *et al* (2005) also reported in another study that *Proteus* was 70% resistant to Nitrofurantoin shows good harmony with our study findings.

In our study *Proteus* showed moderate resistance of 55% to Nalidixic acid and cotrimoxazole (52.3%). But Ummey Shahnaz Parvin (2009) in her study in Mymemsingh reported *Proteus species* were 100% resistant towards, Nalidixic and Cotrimoxazole which is almost the twice higher resistance observed by us and does not agree very well with our findings.

As per our study, *Proteus* was found to be highly sensitive to Amikacin (92.5%), Ceftriaxone (89.17%), Gentamicin (86.45%), gatifloxacin (75%), Ceftazidine (72.55%), Imipenum (70%), Cirprofloxacin, Cefixime and Cephradine (60%). Ummey Shahnaz Parvin (2009) in her study showed *Proteus* to be highly sensitive towards Imipenem, Ceftazidime, Ceftriaxone, while in Sharmin's (2005) study showed 25% resistance towards Ceftazidime, 50% to Ceftriaxone, 25% to Nitrofurantoin and to Imipenem no resistance at all which show good agreement with our study.

The antibiogram of isolated *S. saprophyticus* in our study showed *Staphylococcus saprophyticus* was found to be highly sensitive to Imipenum (80%), followed by gentamicin (71.4%), Azithromycin (65.7%), Amikacin (64.3%). Ceftriaxone and Nitrofurantoin both showed moderate sensitivity of 60%. In a study conducted in Sir Salimullah Medical College & Mitford Hospital, Dhaka by Sanya Tahmina and Shikha Paul (2011) reported that the antibiogram of isolated *S. saprophyticus* from female UTI patients showed that all strains of *S. saprophyticus* (100%) were sensitive to Imipenem. High sensitivity was also observed to gentamicin (86.20%) and ceftriaxone (72.41%), which is consistent with our finding.

Ummey Shahnaz Parvin (2009) in her study in Mymemsingh also reported *Staph. saprophyticus* was 100% sensitive to Imipenem and a good sensitivity of 60% towards Ceftriaxone and Azithromycin, which is also consistent with our finding.

Isolated *S. saprophyticus* in our study showed highest resistance to Nalidixic acid (78%), Ceftazidime (77%), gatifloxacin (75.5%), cotrimoxazole (72%), ciprofloxacin (70%). Cephradine showed moderate resistance (55%). Sanya Tahmina and Shikha Paul (2011) in Dhaka reported *S. saprophyticus* isolates from uropathogens to be resistant to Amoxycillin (75.86%), Nalidixic acid (65.52%), Cotrimoxazole (58.62%), Tetracycline (55.17%) and Nitrofurantoin (51.72%) and resistance rate (31.04%) to ciprofloxacin which are comparable to our study and show good agreement with most of our findings.

Ciprofloxacin is the most frequently prescribed fluoroquinolone for UTIs because of its availability in oral and intravenous formulations. It is well absorbed from oral doses and is rapidly excreted from the body under normal conditions (Shao *et al.* 2003, Kahlmeter 2003). But in our study *S. saprophyticus* isolates from the Northern region of Bangladesh showed very high resistance (70%) against Ciprofloxacin and only sensitive against (30%) isolates. Akhtaruzzaman (2002) in his study reported high resistance rates to ciprofloxacin against *S saprophyticus*, which shows good agreement with our finding.

The increasing resistance pattern of different antibiotics to *S. Saprophyticus* in this study in comparison to previous ones should make us conscious that time is not far away when we have also worry about antibiotic resistance of *S. Saprophyticus.*

As per our study, *Staphylococcus aureus* showed highest resistance to Ceftazidime (78%), followed by ciprofloxacin (77.5%), Cotrimaxazole and nalidixic acid (75%), Ceftriaxone (66.7 %). Ummey Shahnaz Parvin (2009) in her study reported *Staphylococcus aureus* isolates were highly resistant towards Cotrimoxazole Cefaclor, Ceftriaxone, and moderately high (more than 50% resistance) towards Ciprofloxacin, Ceftazidime and are in agreement with our findings.

We observed that *Staphylococcus aureus* showed highest sensitivity towards Imipenum (89%), followed by Azithromycin (78%), gentamicin (75%), Amikacin (71%) and gatifloxacin (70%) while Cephradine showed (65%) and cefixime (60%) sensitivity which can be considered as moderate sensitivity. Ummey Shahnaz Parvin (2009) in her study reported highest sensitivity of Imipenum towards *Staphylococcus aureus* which is consistent with our finding but she reported that Azithromicin and Gentamicin exhibited more than 50% resistance towards *Staphylococcus aureus* whereas we found Azithromicin and Gentamicin to be highly sensitive 78% and 75%, respectively to *Staphylococcus aureus* which disagrees with our finding.

The improper and indiscriminate use and easy availability of antibiotics in our country culminate the patients suffering from drug resistant UTI. As the patients were hospitalized, each of them was taking antibiotics. So, preceding antibiotics may be acted as the common risk factors of maximum drug resistance for the patients. Our studies reflected that the prior and ongoing use of antibiotics correlates with the UTI, most probably due to the use of multiple antibiotics or prolonged use of single antibiotic previously.

The empirical use of commonly used antibiotics has led the drug resistant phenomenon. Cotrimoxazole being a commonly used drug to treat UTI once, the use of it has been reduced by many folds due to its resistance pattern. Cotrimoxazole was found to be ineffective for UTI in the present study as all the uropathogens showed high degree of resistance to it. The very high rate of Ciprofloxacin resistance among both Gram negative and Gram positive organisms observed in our study can possibly be attributed to Ciprofloxacin being a commonly prescribed drug in our tertiary care hospital and thus warrants special precaution. Majority of the UTI patients in our country receive Cephalosoprins, Aminoglycosides, Fluoroquinolone or a combination of these drugs as empirical therapy or as definitive treatment.

In the present study all the isolates were 100% sensitive to imipenem. This high level of sensitivity to imipenem could be due to its restricted and limited use in the

clinical practice. The drug has only recently been introduced in Bangladesh and is very expensive which has further restricted its widespread use.

The emerging trends of drug resistance to almost all the commonly used antibiotics to treat both the UTI provoked the scientists and physicians to switch over to newer antibiotics to overcome the problem.

The overall antibiotic susceptibility testing of the major isolated uropathogen *E. coli.* and other uropathogens of the present study indicated that most uropathogens exhibited very higher level of resistance to the commonly used antibiotics such as Azithromycin, Nalidixic acid and Cotrimoxazole. These drugs have limited value for the treatment of UTI and should no longer be used. Moreover, from the findings of the study it can be concluded that the major pathogen *E. Coli* causing UTI in the Northern regions of Bangladesh and other gram negative (as well as gram positive) isolates were more highly sensitive to Imipenum, Amikacin and Gentamicin as compared to the other antibiotics tested. Therefore these should be the drugs of choice for the treatment of complicated UTI caused by gram negative isolates in our region i.e. in the Northern region of Bangladesh.

Under the present study, very alarming level of antibiotic resistance has been observed were Ciprofloxacin and even newer floroquinones like Gatifloxacin, the broad spectrum antibiotics and major anti-pseudomonad weapons are becoming moderately sensitive to bacteria causing UTI. Ciprofloxacin, Gatifloxacin, Cephradine and cefixime (Except *Klebsiella* and *Pseudomonas* showing > 79 and 90% resistance, respectively) exhibited moderate to less moderate sensitivity in many cases under the study.

The once blockbuster antibiotics like Cephradine, and cefixime also has exhibited moderate resistance and reduced susceptibility to the isolated uropathogens. These findings are clearly alarming as our country could be running out of effective antibiotics if this trend continues. As most of the uropathogens from the study areas are showing resistance to routinely used antimicrobials in UTI, especially

fluoroquinolones, no guidelines for empirical treatment of UTIs can be given. It is imperative to rationalize the use of fluoroquinolones in order to prevent the dissemination of resistant strains in the population.

For treatment of UTI caused by Gram-positive isolates *S. saprophyticus* and *S. aureus* the antibiotics - Imipenem, Azithromycin, Gentamicin and Amikacin to which they are found to be highly sensitive, should be the drug of choice in the Northern areas of Bangladesh.

Cephradine and cefixime with moderate sensitivity can be considered as second line therapy, however only after performing a culture and sensitivity (CS) test of urine specimens. On the other hand, Gram-positive isolates showed highest resistance towards Nalidixic acid, Ceftazidine, ciprofloxacin, gatifloxacin, cotrimoxazole, and Ceftriaxone and these antibiotics should no longer be prescribed for treating UTI caused by Gram-positive isolates in our region.

Under the aforesaid stated, prevailing and changing antibiotic resistance pattern noticed among uropathogens in the present study in the northern region of Bangladesh, for the physicians to prescribe the drugs cautiously for the betterment of the patient's treatment of each and every UTI patients need to be individualized, It is recommended that, antibiotics should be prescribed after performing a routine microscopy and culture/ sensitivity of urine in order to inhibit acquisition and spread of drug resistance by the bacteria.

Antimicrobial sensitivity testing is needed for selection of antibiotics for treatment of UTI patient's. Routine monitoring of drug resistance pattern will help to identify the resistance trends regionally. This will help in the empirical treatment of UTI to the clinicians and also for the preparation of antibiotic policy of the individual institute. This will avoid the indiscriminate use of antibiotics and prevent the further development of antimicrobial resistance. It is also urged that antimicrobial policy should be adopted at both the tertiary level hospital and the National level supervised by monitoring cell for taking necessary steps to minimize the drug resistance.

Chapter Seven
CONCLUSION AND RECOMMENDATIONS

The present study is one of the very few studies ever undertaken on Tertiary Care Hospitals in the Northern Areas of Bangladesh to resolve the prevalence of urinary tract infection in pregnancy and to study the common organisms involved in urinary tract infection and their antibiotic susceptibility pattern, which will act as an evidence for the future research. The changing scenario of uropathogen resistance against different classes of antibiotics and the new aspects of the treatment regimen is the extract of this study.

The present prospective study has furnished in details about common uropathogens and their drug resistance pattern. In the Northern areas of Bangladesh, *E. coli* is still the leading cause of UTI as observed in most of earlier studies conducted in the country and in view of its increasing resistance pattern to various antibiotics; it is going to be an alarming health hazard.

Most of the other urinary pathogens also show almost the same picture as evidenced from the findings of the present study. Hence the larger amount of antibiotic consumption and its irrational and indiscriminate use may result in losing even the last weapon to fight against UTI. Most probably in near future if this process is not stopped, UTI will once cause mortality along with extreme morbidity.

Antibiotic susceptibility testing of the major isolated uropathogen *E. coli.* and other uropathogens of the present study revealed that in general most uropathogens showed very higher resistance to commonly used drugs - Azithromycin, Nalidixic acid and Cotrimoxazole and these drugs have limited value for the treatment of UTI and should no longer be used although the are still being prescribed.

Moreover, this study concludes that *E. Coli* the major pathogen and other gram negative (as well as gram positive) isolates were highly sensitive to Imipenum, Amikacin and Gentamicin as compared to other antibiotics tested and therefore these may be the drugs of choice for the treatment of complicated UTI caused by gram negative isolates in our region *i.e.* in the Northern region of Bangladesh.

This study has revealed the alarming level of resistance and even Ciprofloxacin and relatively newer Gatifloxacin, broad spectrum antibiotics and the major anti-pseudomonad weapons are becoming moderately sensitive to bacteria causing UTI. Ciprofloxacin, Gatifloxacin, Cephradine and cefixime (Except *Klebsiella* and *Pseudomonas* showing > 79 and 90% resistance, respectively) exhibited moderate to less moderate sensitivity in many cases under the study. The once blockbuster antibiotics such as Cephradine, and cefixime exhibited moderate resistance and reduced susceptibility. These findings are clearly alarming as our country could be running out of effective antibiotics if this trend continues.

Since most of the uropathogens are showing resistance to routinely used antimicrobials in UTI, especially fluoroquinolones, no guidelines for empirical treatment of UTIs can be given. It is imperative to rationalize the use of fluoroquinolones in order to prevent the dissemination of resistant strains in the population.

For treatment of UTI caused by Gram-positive isolates *S. saprophyticus* and *S. aureus* the antibiotics - Imipenem, Azithromycin, Gentamicin and Amikacin to, which they are found to be highly sensitive, should be the drug of choice in the Northern areas of Bangladesh. Cephradine and cefixime with moderate sensitivity can be considered as second line therapy, however after culture and sensitivity (CS) of urine specimens. On the other hand, Gram-positive isolates showed highest resistance towards Nalidixic acid, Ceftazidine, ciprofloxacin, gatifloxacin, cotrimoxazole, and Ceftriaxone and these antibiotics should no longer be prescribed for treating UTI in our region.

Under the above stated prevailing and changing antibiotic resistance pattern noticed among uropathogens under the present study in the northern region of Bangladesh, for the physicians to prescribe the drugs cautiously for the betterment of the patient's treatment of each and every UTI patients need to be individualized, as far as possible.

It is recommended that, antibiotics should be used after doing a routine microscopy and culture/ sensitivity of urine in order to inhibit acquisition and spread of drug resistance by the bacteria. The antimicrobial sensitivity testing is needed for selection of antibiotics for treatment. Routine monitoring of drug resistance pattern will help to identify the resistance trends regionally. This will help in the empirical treatment of UTI to the clinicians and also for the preparation of antibiotic policy of the individual institute. This will avoid the indiscriminate use of antibiotics and prevent the further development of antimicrobial resistance.

It is also urged that antimicrobial policy should be adopted at both the tertiary level hospital and the National level supervised by monitoring cell for taking necessary steps to minimize the drug resistance.

The prevalence rate of 33.55% UTI observed among women of childbearing in the Northern region of Bangladesh is much higher than earlier studies conducted elsewhere in the country and is an alarming health hazard. The predisposing factors for very high prevalence of UTI among women of the study area as revealed from the present study appeared to be due to illiteracy, ignorance about UTI and its consequence and not practicing health and hygiene factors properly.

Prompt steps, therefore, should be taken by the Government of Bangladesh and others NGOs working in Bangladesh through use of mass media (Electronic and print media) to make the inhabitants aware about UTI, about the ultimate the consequences of UTI (ESRD) and the effects recurrent UTI's and provide knowledge how to prevent UTI through properly practicing health and hygiene factors.

Significant impact of socio-economic statues on UTI incidence was noticed and the highest UTI sufferers were from poor socio-economic class; whereas very few cases were from the rich socio-economic class. Therefore, efforts should be made by the Government and others NGOs working in Bangladesh to take necessary steps to improve the Socio-economic condition and education level of the inhabitants especially, the rural women who are the most sufferers of UTI.

Also, use of commercial sanitary napkin has been found to play a significant role in preventing incidence of UTI. But its use is still extremely low among the subjects of the study possibly due to the high prices of sanitary napkins, which is not affordable by them.

In this regard, the government of Bangladesh can play a role buy providing sanitary napkins for women at subsidized rate and may request the healthcare companies and Pharmaceutical Companies in the country to make a less profit so that price of sanitary napkins are cut to a low level and is affordable even by the poor rural women. At the same time, illiterate rural women need to be informed about the health benefits of using sanitary napkins during their menstrual cycle and motivated to use them.

If the above recommended steps are taken, it is believed that high incidence of UTI among women of childbearing age noticed in the Northern region of Bangladesh can be minimized.

Finally, in spite of maximum sincerity and dedication invested to carry out the present study; it is never free of limitations as the sample size was not large enough. Again, due to lack of proper logistic support, the genetic analysis of resistant bacteria that could help us finding the actual cause behind the emerging drug resistance could not be performed by us.

Chapter Eight
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Chapter Nine
APPENDICES

APPENDIX I

Data collection sheet / Questionnaire

1. Name: **Date:**

2. Father / Husband's Name:

3. Age: **Sex:** Female

4. Mailing Address:

5. Present Address:

6. Contact No:

7. Father / Husband's Profession:

8. Self Profession (If applicable):

9. Father / Husband's monthly Income:

□ Upto 5000 Tk □ 5001 to 12000 Tk

□ 12001 to 20000 □ Above 20000 Tk

10. Self Income (If applicable): □ Upto 5000 Tk □ 5001 to 12000 Tk

□ 12001 to 20000 □ Above 20000 Tk

11. Type of latrine Used:

- ❑ Sanitary Latrine □ Semi-pacca
- ❑ Kacha □ No Latrine Used

12. Dwelling House:

- ❑ Pacca □ Semi-Pacca
- ❑ Kancha □ Hut □ Slum

13. Educational level:

□ Illiterate □ Primary □ SSC □ HSC / Graduate □ Masters and Above

14. Previous Drug History:

□ Under Treatment of antibiotic? If yes, name of the drug
□ Completed Drug recently? If yes, name of drug

□ Under no treatment
□ Any other (specify)

Please answer questions

1. Please circle the symptoms experiencing. (& explain if space)

question: Ans: Yes or No

(Women between 15-45 yrs of age :)

- urgency to urinate
- incontinence during day and/or night
- frequent urination
- painful or difficult urination
- discomfort above the pubic bone
- blood in the urine
- foul smelling urine
- nausea and/or vomiting
- fever
- chills
- pain in the back or side below the ribs
- small amount of urine while voiding despite feeling of urgency

Frequency: How many times an hour does the patient urinate? _____

Dysuria: (Burning or pain on urination)

Hematuria: (Blood in urine)

Urgency: (sudden need to urinate)

Nocturia: (awakening during sleep to urinate)

How many times during sleep?_____

Incontinence: (loss of control)

Back pain: if yes, right side, left side or both?_____

Fever: if yes, highest temp_____ for how many days? ___

2. How long (days) has the patient had these symptoms?_____

3. Had the patient had a previous urinary tract infection (UTI)? Yes No

If yes, more than 2 per year? Yes No

Please list medication taken for past UTI:_____

_____

4. Have you ever had an infection of the kidney? Yes No

5. Has the patient taken any medication for current symptoms? Yes No

List all prescription, over the counter medication, or herbs that you have taken in the last 2 days:_____

_____

_____

Urinalysis results: Color:_____ Turbidity:_____ pH:_____ Sp. Gr.:_____

Labstix results: _____

Reviewed by (nurse):_____

TO BE COMPLETED BY PHYSICIAN/NURSE PRACTITIONER:

Notes:_____

Microscopy results: _____

Tests ordered: U/A with micro C&S CBC w/diff w/o diff _____

RX/Plan: _____

_____

_____

Physician/Nurse Practitioner Signature

Appendix-II

RESEARCH INFORMED CONSENT FORM

RAJSHAHI/BOGRA/DINAJPUR/…… MEDICAL COLLEGE & HOSPITAL/Clinics

TITLE OF THE RESEARCH PROJECT: PREVALENCE OF URINARY TRACT INFECTON AND ANTIBIOTIC SUSCEPTIBILITY AMONG WOMEN IN CHILD BEARING AGE IN NORTHERN AREA OF BANGLADESH

M.PHIL SUPERVISOR'S NAME: PROFESSOR DR. PARVEZ HASSAN
B.Sc. (Hons), M Sc. and PhD (Biochemistry)
Institute of Biological Sciences, University of Rajshahi

INVESTIGATOR: ROZINA AKTAR ZAHAN (MBBS)

PURPOSE OF RESEARCH:

I have been explained about the reason for doing the study and selecting me as a subject of the study. This study is for the better understanding of the role of hygiene and other factors preventing Urinary Tract Infections in child bearing age of women and also finding out the antibiotics susceptibility during treatment.

RISK AND DISCOMFORTS:

I understand that I may experience some pain or discomfort during my examination or during my treatment. This is mainly the result of my condition and the procedure of the study is not expected to exaggerate these feeling which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will have no direct benefits to me other than potential benefit of treatment.

ALTERNATIVES:

Even if you decline the participation in the study, you will get the routine line of management.

CONFIDENTIALITY:

I understand medical information produced by this study will become part of my hospital record and will be subject to the confidentiality and privacy regulations of the said hospital.

If the data are used for publication in the medical literature for teaching purposes, no names will be used, and other identifiers, such as photographs and audio or videotapes, will be used only with my special written permission. I understand I may see the photographs and videotapes and hear the audio tapes before giving this permission. For this purpose every effort will be made by publishing person to contact me in the address furnished by me through postal communication. If no response is received within a reasonable time, all the identities will be removed from the photographs and case report before being submitted for publication.

REQUEST FOR MORE INFORMATION:

I understand that, I may ask more questions about the study at any time. Researcher is available to answer my questions or concern in this research period. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or my withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that researcher may terminate my participation in the study at any time after I have been explained the reasons for doing so and has been helped to arrange for my continued care by my own physician, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study. If such injury were reported promptly, then medical treatment would be available to me, but no further compensation would be provided. I understand that my agreement to participate in the study I am not waiving any of my legal rights.

I have explained to _____

(Patient/Guardian Name)

The purpose of research, procedures required the possible risk and benefits to the best of my ability.

Investigator **Date:** / /

I have been explained clearly about the reason for doing this study, reason for selecting me as a subject in the study. I also have been explained about the risks, benefits and confidentiality of the study. Alternative procedures that might be used in the treatment of my disease also explained to me. I am willing to attend any follow up requested to me at a future date. Freedom is given to me for the participation in the study or discontinues participation at any time without prejudice.

All the above explained in detail to me clearly in my own language. I am giving consent voluntarily for inclusion of me in the study as a subject.

Participant/Guardian