A Study of Urinary Tract Infection in Post-Menopausal Women in Relation to Clinical and Microbiological Picture

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ABSTRACT

BACKGROUND
Urinary tract infection is the most common bacterial infection in post-menopausal women. Urine is a good culture medium for the growth of bacteria. This infection can lead to urinary sepsis if not diagnosed with proper clinical and bacteriological evolution. There is a need to study the various typical and atypical presentations of urinary tract infection and probe various microbiological agents causing urinary tract infection.

METHODS
This is a time bound observational hospital based prospective analytic study conducted in the Dept. of General Medicine, Down Town Hospital, Guwahati, Assam, between Jan 2017 to Dec 2017. 100 patients who showed growth on urine culture were included in the study.

RESULTS
100 urine culture positive cases of postmenopausal females aged 45 years and above were included in the study. 76 patients were found to be having complicated UTI whereas 24 patients were having uncomplicated UTI. Fever (37%) is the most common presentation of the patients in UTI, overall as well as individually in uncomplicated UTI while burning urination (30%) is the most common clinical presentation among complicated UTIs followed by pain abdomen (23%). For complicated UTI, diabetes mellitus (46.2%) is most common risk factor. Gram negative organisms are the most common uropathogens as recorded in the study.

CONCLUSIONS
Present study revealed that clinical presentation is not conclusive but plays a minor role in establishing diagnosis in UTI. Uncomplicated UTI is high among younger females in postmenopausal age group. Complicated UTI is more common among older age group. Fever and burning of micturition are the most common symptoms; combination of symptoms is more predictive of UTI. Diabetes and urogenital instrumentation are the major risk factors for complicated UTI. E. coli is still the most widely prevalent organism causing UTI in the community, and increasing rates of resistant ESBL species are found.

KEYWORDS
Urinary Tract Infection, Postmenopausal Women, Mycobacteria
Urinary tract infection (UTI) is one of the most common infectious diseases seen in the community. This infection affects all ages and both sexes. Women are usually more susceptible to this infection and has a higher prevalence compared to the men. Some of the risk factors responsible for this high prevalence are due to menopause, poor personal hygiene, pregnancy and the close anatomical relationship of the female urethra and the anus.

Urinary tract infection (UTI) is the most common bacterial infection in women in general and in postmenopausal women in particular. In the United States, every year urinary tract infections account for about 4 million ambulatory-care visits, representing about 1% of all outpatient visits. 

Urine is a good culture medium for the growth of bacteria. Factors unfavourable to their growth include a low pH (5.5 or less), a high concentration of urea and the presence of organic acids derived from a diet that includes fruits and protein. UTIs can be divided anatomically into upper and lower tract infections. By far the most common mechanism by which bacteria enters the urinary tract is by ascending from the peri urethral area. In practice the higher risk in women is mostly due to the shortness of female urethra, which is 1.5 inches compared to 8 inches in men. Bacteria from the faecal matter at the anal opening can be easily transferred to the opening of urethra. Among them postmenopausal are at higher risk. Post menopause is characterised by a significant reduction in ovary oestrogen secretion which is often associated with vaginal atrophy. Oestrogen stimulates the proliferation of lactobacillus in the vaginal epithelium, reduces the PH, and avoids vaginal colonization of Enterobacteriaceae, which are the main pathogen of the urinary tract. This describes the relationship between oestrogen and the vaginal flora and pathophysiology of urinary tract infections in elderly women. In addition, the absence of oestrogen decreases the volume of the vaginal muscles, resulting in slackness of the ligaments holding the utero pelvic floor and the bladder, resulting in the development of prolapse of the internal genitalia. And also, the walls of the urinary tract become weak and as such it reduces its ability to resist bacteria colonization, all these changes put these women at particular risk of contracting both primary and recurring UTIs.

In spite of the fact that accurate diagnosis depends on both the presence of symptoms and a positive urine culture, in most outpatient settings this diagnosis is made without the benefit of culture. Antibiotic therapy is usually applied empirically and for this, knowledge of the common uropathogens and their susceptibility to commonly used antibiotics is needed. Treatment becomes even more challenging in the presence of risk factors such as higher age, comorbidity, and immunosuppression. Poor patient compliance and incomplete course of prescribed antibiotic therapy have resulted in the rise of resistance to many of the conventional antibiotics. Various studies done worldwide have shown changing patterns in the aetiology of UTIs. However, studies on UTI and the pattern of antibiotic resistance in India are few. The present trends of the uropathogens and their susceptibility to various antibiotics are essential to formulate guidelines for the empirical treatment of UTIs while awaiting the culture sensitivity.

Most often this infection is usually neglected but it is capable of claiming life under severe circumstances. So it is need of the hour to have a revision of the prevalence, risk factors, causative organisms and drug responsiveness of the urinary tract infections. This will be helpful in tackling the newer cases of UTIs as well as recurrent cases which are very difficult to treat and this will also serve as a guide to individuals, care givers and health planners for mobilisation of available resources accordingly and to guide the expected interventions as the management involves drug therapy and patients education.

We wanted to determine the various typical and atypical clinical presentations of patients presenting with urinary tract infection and determine the various microbiological agents causing urinary tract infections and their antibiotic susceptibility study.

### METHODS

The study was approved by the Ethics Committee of Down Town Hospital. It was an observational, hospital based prospective analytic study in the Department of General Medicine, Down Town Hospital, Guwahati, Assam, between Jan 2017 to Dec 2017. 100 Patients aged 45 years and above visiting to OPD and indoor patients in the hospital with urinary tract infection were included in the study. Patients with age less than 45 years and pre-menopausal women more than 45 years were excluded from the study. Random Sampling Technique was used.

Sample size was calculated using the formula:

\[
\text{Sample size} = \left( \frac{Z^2 \times p \times (1-p)}{d^2} \right)
\]

Where n is sample size, Z is standard normal variate corresponding to confidence level, p is expected prevalence, D is precision or margin of error corresponding to effect size. Minimum Sample size was calculated to be 245.86 with confidence level of 95% and precision of 5%. Expected prevalence was taken to be 20% as determined by reviewing previous studies. Keeping in mind the given duration of the study and concerned patient flow in this setup, the sample size is 100 subjects, with the aim to complete the study within stipulated time.

Methods of Data Collection

The sources of primary data were history and clinical examination. The source of secondary data were systematic reviews and research data. Direct observations, interviews, protocols, tests, examination of records, and collections of writing samples were used for data collection. Informed consent was obtained from all patients. A detailed history was taken after taking consent from the patient. History was taken in relation to Urinary tract infection like burning
micturition, fever, frequency, pain abdomen, hematuria. Past history of urinary tract instrumentation or catheterization, systemic disease like diabetes mellitus was also asked. A detailed examination of all systems with special emphasis on temperature, pulse rate, blood pressure, suprapubic tenderness, costovertebral angle tenderness, tenderness on deep abdominal palpation were carried out. The subjects were classified as having complicated UTI based on the criteria defined by Rubenstein and Schaeffer as shown in table 1.

**Table 1. Identification of Patients with Complicated Urinary Tract Infections**

| Known Lesion on Prior Diagnosis | Functional or Structural Urinary Tract Anomaly | Obstruction (e.g., Stone, Ureteropelvic Junction Obstruction) | Diabetes | Spinal Cord Injury | Neurological Disorders (e.g., multiple sclerosis) that Affects Bladder Function | Indwelling Catheter | Comorbidities that predispose to papillary necrosis (e.g., sickle cell disease, severe diabetes, analgesic abuse, Pseudomonas species infection) | Infection with an unusual organism (e.g., tuberculosis) | Suspected lesion based on history | Unsolved urinary tract infections – failed response to antimicrobial therapy | Bacterial persistence (recurrent urinary tract infections with the same organism) | Infection with urea-splitting organisms | Recurrent febrile urinary tract infections in childhood | Suspected lesion based on symptoms | Febrile urinary tract infections (especially >3 days) | Renal colic | Gross hematuria |
|---------------------------------|-----------------------------------------------|-----------------------------------------------------|---------|-------------------|--------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------|

**Isolation and Identification of Uropathogens**

Collection of mid-stream urine: Patients were asked to clean genital region prior to micturition. In women before collection of urine labia were separated by patient or nurse and vulva cleaned twice in an anteroposterior direction with swabs soaked in clean tap water and then with a dry swab, whilst the labia held still apart. A specimen was considered positive for UTI if a single organism was cultured at a concentration of $>10^5$ colony-forming units/ml. Urine samples were sent to laboratory immediately for routine evaluation and for culture. For culture urine samples were incubated at 37°C for 24 to 48 hrs in Blood / Chocolate agar and Mac Conkeys agar plate. Organisms identified were based on colony characteristics, lactose fermentation and biochemical test. Fungal and viral etiological study, culture not done in this study due to limited recourses.

**Antibiotic Sensitivity Testing**

In the presence of any potential growth, antibiotic sensitivity testing was done by the modified Kirby-Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute guidelines. The antibiotics tested were imipenem, meropenem, ciprofloxacin, ofloxacin, norfloxacin, amikacin, gentamycin, nitrofurantoin, and cotrimoxazole (Pathotech Labs, India). Other investigations included Complete blood count, and USG abdomen for evaluating urinary tract and post-voidal residue.

**Extended Spectrum Beta Lactamase Detection**

The screening for extended spectrum beta lactamase (ESBL) was done using cefpodoxime ($\leq 17$ mm), ceftazidime ($\leq 22$ mm), aztreonam ($\leq 27$ mm), cefotaxime ($\leq 27$ mm), and ceftriaxone ($\leq 25$ mm). If the organisms showed a zone of inhibition lower than the minimum for any antibiotic disc, ESBL positivity was suspected. The phenotypic confirmation was done by testing the strain against ceftazidime (Ca) and ceftazidime/clavulanic acid. A $>5$-mm diameter of the zone of inhibition for ceftazidime/clavulanic acid in comparison to ceftazidime was considered indicative of ESBL production. Escherichia coli ATCC 25922 was used as an ESBL-negative and Klebsiella pneumoniae 700603 was used as an ESBL-positive reference strain.

**Statistical Analysis**

Descriptive statistical analysis was carried out in the present study. Results of continuous measurements are presented on Mean ± SD and results of categorical measurements - Age, gender, organisms causing UTI, their antibiotic sensitivity and resistance, symptomatology of these patients and risk factors for UTI are presented in frequency and percentage. Data is presented in charts, table formats, bar diagram, pie diagram for ease of understanding and interpretation. Microsoft office word 2007 and Microsoft office Excel 2007 was used to generate table, bar diagram and pie diagram.

**RESULTS**

100 patients who showed growth on urine culture were included in the study. Results show age wise distributions of postmenopausal patients with the mean age for the cases was 67.06 ± 13.72 years. In overall cases 76 patients were found to be having complicated UTI whereas 24 patients were having uncomplicated UTI. Most of the complicated UTIs are seen in later age group of postmenopausal period (65 to 100 years). Total 57 patient diagnosed with UTI above the age of 65 of years out of which 51 (89.4%) patients had complicated UTI and 6 (10.6%) had uncomplicated UTI, whereas patient in early age group (45-64 years) 43 patients detected with UTI out of which 25 (58.1%) patients had complicated UTIs and 18 (41.9%). patients had uncomplicated UTIs, so percentage rate of complication is more in later age groups of postmenopausal period. Fever is the most common clinical presentation of the patients in UTI, overall as well as individually in uncomplicated UTI while burning urination is the most common clinical presentation among complicated UTIs followed by pain abdomen, frequency hematuria. Diabetes (46.7%) was the most common factor associated with complicated UTI in our study. While the recent history of urogenital instrumentation (TURP, cystoscopy, stenting) for therapeutic or diagnostic purposes other than catheterization was present in 22.23% of the study subjects, catheterization alone posed a significant risk factor seen in 11.11% of them.
Figure 1. Age Distribution

Figure 2. Types of UTI

Figure 3. Frequency of Risk Factors in Subjects with UTI

Figure 4. Frequency and Distribution Pattern of Pathogens Causing UTI

Table 2. Symptom Distribution of UTI among Complicated and Uncomplicated UTIs

Table: Symptom Distribution of UTI among Complicated and Uncomplicated UTIs

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Complicated UTI (n=76)</th>
<th>Uncomplicated UTI (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>%</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Fever</td>
<td>21 (27.6)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>Burning of micturition</td>
<td>25 (32.9)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Frequency</td>
<td>9 (11.8)</td>
<td>1 (4.1)</td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>21 (27.6)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3 (3.9)</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>

ESBL-positive E. coli (38%), ESBL-positive Klebsiella pneumoniae (18%), ESBL-negative E. coli (14%), Pseudomonas aeruginosa (14%), ESBL-negative Klebsiella pneumoniae (11%), and were the most prevalent microorganisms in UTI patients. The frequency and distribution of the UTI pathogens were similar in complicated and uncomplicated UTI. ESBL-positive E. coli (40.7%) was the most common causative organism in complicated cases, while ESBL-negative E. coli (41.6%) was the most common causative organism in uncomplicated cases. Gram-negative organisms were the most common organism causing UTI in the current study.

The antimicrobial potency and spectrum for nine selected antimicrobial agents of different classes against the UTI pathogens recorded in the study. Carbapenems had the least resistance (9%), followed by Cotrimoxazole (22%). Nearly three-fourths of all the isolated samples were resistant to quinolones. A high rate of resistance was recorded against quinolones (78%). While Gentamycin (40%) and Amikacin (44%) shows intermediate resistance. The antibiotic resistance pattern in complicated UTI was similar to that in overall infection with carbapenems having the least resistance (11.8%), followed by cotrimoxazole (22.0%). However, compared with complicated UTI, organisms in uncomplicated UTI showed lesser resistance toward carbapenem (9%) cotrimoxazole (20.8%) gentamycin (29.2), quinolones (66.6%). The mortality associated with complicated UTI in the present study was 11%. The mortality in patients having ESBL-positive UTI was 9% and with Pseudomomas aeruginosa it was 16%.

Figure 5. Resistance Pattern of the Uropathogens to Various Antibiotics

DISCUSSION

The present study is limited in that the data come from a population served in a tertiary health centre; therefore, this is not a population-based study. One study reported mean age for UTI as 55.47±21.51 and largest proportion of cases belonged to age group 50-79-year females. Various studies, reported mean age for UTI as 65±12 years. The present study revealed that the mean age for the cases was 67.06 ± 13.72 years.

In present study fever and burning of micturition were the commonest symptoms followed by pain in abdomen and frequency. We found that the presence of combinations of
these symptoms has a better chance to be UTI rather than the lone symptoms. No single symptom was strong predictor of diagnosis of UTI. Clinical presentation plays minor role, in diagnosing UTI, urine culture is essential to diagnose UTI. One researcher\textsuperscript{10} reported that in their study of the 235 suspected cases of UTI that were positive by microscopy (greater than 10 leucocytes per high power microscope field), only 137 (58.3\%) were positive by culture. Although the presence of white blood cells in urine signifies inflammation, based on results, they do not always indicate UTI. Therefore, the findings indicated that urine culture is essential for definitive diagnosis of UTI.

Diabetes mellitus is a number of long-term effects on the genitourinary system. Diabetic nephropathy is one of the many factors that make these patients more susceptible to UTI than non-diabetics. Reduced immunity in diabetes also contributes to the increased risk for acquiring UTI. Diabetes Mellitus was found to be major risk factor (46.7\%) in present study which was followed by urogenital instrumentation in recent past. Similar results were reported\textsuperscript{9,11}

In this study catheterisation accounted for 13.2\% of complicated cases. Bladder catheterisation accounted for 145.8\% cases in one study\textsuperscript{9}. With urinary catheterisation the infection rate is about 5\% per day.\textsuperscript{12} The uropathogen profile in our study is found similar to that in other studies.\textsuperscript{9,13,14} In the present study 38\% of culture isolates were ESBL-positive E. coli. Different study\textsuperscript{16} done previously reported 43.9\% ESBL-positive E.coli cases.\textsuperscript{9,13} ESBL producers do not respond to the usually prescribed empirical therapy. Use of empirical therapy in these patients is associated with increased risk of morbidity and mortality, and cost of therapy.\textsuperscript{15} Carbapenems are the most effective in this situation but need to be administered parenterally.

Quinolones were found most resistant to the uropathogens in present study. Studies carried out in Delhi and Vellore, with support from World Health Organization during 2003-2005 suggested a very high use of fluoroquinolones in the community as compared to other antimicrobials. Resistance pattern of antibiotics in present study is found similar to that in other studies.\textsuperscript{16-18} although, quinolones were considered as one of the drugs of choice for the treatment of UTI, the increasing resistance rate necessitates a change in the empirical treatment against UTI.

In present study there was highest sensitivity to carbapenems followed by Cotrimoxazole and aminoglycosides. Nearly more than one third of uropathogens showed resistance to Gentamycin and Amikacin. Due to less frequent use of cotrimoxazole during last 2 decades is pattern showing less resistance among common pathogens causing UTIs. Resistance to carbapenems though found in only few cases, raises concern for treatment of complicated and drug resistant cases. Some strains of Gram-negative organisms have developed resistance to carbapenems by various mechanisms such as by producing beta lactamases which destroy the antibiotics, by blocking the entry of these antibiotics, or by efflux pumps which actively pump out these antibiotics.\textsuperscript{19}

Clinical presentation is not conclusive but plays a minor role in establishing diagnosis of UTI. Uncomplicated UTI is high among younger females in postmenopausal age group. Complicated UTI is more common among older age group. Fever and burning micturition are the most common symptoms, combination of symptoms is more predictive of UTI. Diabetes and urogenital instrumentation are the major risk factors for complicated UTI. E. coli is still the most widely prevalent organism causing UTI in the community, and increasing rate of resistant ESBL species are found. Due to less frequent use of cotrimoxazole during last 2 decades pattern shows less resistance among common pathogens causing UTIs. Resistance pattern is increasing due to uncontrolled abuse of available antibiotics. There is need for change in empirical therapy to prevent increasing resistance and development of complications. Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics.

Antibiotic resistance crisis is global, reflecting the worldwide overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge. Antibiotic-resistant infections place a substantial health and economic burden on the Indian health care system and population. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed. Hospital based studies showed higher and varied spectrum of resistance in different regions, while there are limited number of community-based studies at country level. There exist lacunae in the structure and functioning of public health care delivery system with regard to quantification of the problem and various determining factors related to antimicrobial resistance. There is an urgent need to develop and strengthen antimicrobial policy, standard treatment guidelines and national plan for containment of antimicrobial resistance in India. There should be more focus on research related to public health aspects of antimicrobial resistance at community and hospital level. Information, education, communication activities with monitoring and evaluation of the existing health care delivery system for both health care providers and consumers to improve drug use, should be undertaken simultaneously.

CONCLUSIONS

Presently there is no national program for prevention of drug resistance and there is inadequacy of quality assured laboratories, insufficient data analysis and dissemination, absence of national guidelines on antimicrobial usage, no control on sale of these drugs for public consumption. Implementation and follow up of intervention research should be strengthened by health care planners, managers and practitioners to identify the most appropriate strategies to improve drug use and prevent the emergence of drug resistance.
REFERENCES


