UTILIZATION OF ANTIBIOTICS IN PATIENTS WITH URINARY TRACT INFECTIONS – A STUDY

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ARTICLE INFO	ABSTRACT
	The objective of this study was to assess and analyze the prescribing pattern, rationality of antibacterial, to study medication related problems and resistance/sensitivity patterns of antibiotics in patients with urinary tract infections. The observational prospective study was conducted in 100 patients with UTI at MVJ medical college and research hospital, Bangalore, India for six months. All required patient data were collected in specially designed case report form. Prescribing patterns, medication related problems and rationality were assessed. The average number of drug per encounter was 7.02. More than 63% of prescription had more than five drugs. Brand names of drug were prescribed more than the generic names. Fluroquinolones (norfloxacin) was mostly prescribed. Female population was more. Age group of >58 years old was most prevalent. Monotherapy of antibiotic was more than combination therapy. Most of the possible drug interactions were moderate type. Norfloxacin was most frequently interacting antibiotic. No significant medication errors were identified. Rationality was assessed to be rational. The most common type of pathogen was *E.coli*. Antibacterial prescribing patterns and rationality of the medications were appropriate but, using drug brand names can increase the chance of medication related problems. Higher number of comorbidities was leading to polypharmacy which can increase possibility of drug-drug interactions therefore there is an increased requirement for close monitoring and management of these possible interactions. *E. coli*, *K. pneumoniae* and *P. aeruginosa* were more sensitive to nitrofurantoin, amikacin and norfloxacin therefore these may be the antibiotics of choice for the treatment of community-acquired UTIs.

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INTRODUCTION

Urinary Tract Infection (UTI) is an infection that affects the urinary tract which includes the kidneys (pyelonephritis), bladder (cystitis) and urethra. [1] UTIs are classified as complicated (with structural abnormalities) and uncomplicated (no structural or functional abnormalities). Symptoms of UTIs include dysuria, urgency, frequency, nocturia and suprapubic heaviness, fever, and flank pain. [2]

The main objective of this study was to understand the rationality of antibiotics being used for treatment of UTI by conducting a drug utilization study. Antibiotic resistance is becoming a threat for the public health, lives of hospitalized individual and patients with chronic conditions therefore there is a need for antibiotic guidelines to prevent such resistance also to improve the patient's therapeutic outcome.

UTI can affect both male and female of all the ages but prevalence is higher in women than men. [3] The global UTI prevalence is 0.7 %. [4] UTI is the second most common infectious presentation in community practice. Worldwide, about 150 million people are diagnosed with UTI each year. [5]

Uncomplicated UTI can be managed with short course (3 days) therapy with either trimethoprim-sulfamethoxazole or a fluoroquinolone. Complicated infections require longer treatment periods (2 weeks) usually with one of above mentioned agents. [6]

Drug utilization was defined by World Health Organization (WHO) as "marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social and economic consequences". [7]

Prescription pattern monitoring studies are drug utilization studies with the main focus on prescribing, dispensing and administering of drugs to facilitate the rational use of drugs in a population and promote appropriate use of monitored drugs and reduction of abuse or misuse of monitored drugs. According to WHO, rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." [8]

Medication related problems are defined as "an event or circumstance involving drug therapy that actually or potentially interfere with desired health outcomes". Medication related problem is the third or fourth leading cause of death in the elderly worldwide. [9]

OBJECTIVES

The primary objectives of this study were to assess and analyze the prescribing pattern of antibacterial and to study the medication related problems in patients with urinary tract infections. The secondary objectives were to study resistance and sensitivity pattern of antibiotics and to assess rationality of medications prescribed for treating patients with urinary tract infections.

METHODOLOGOY
STUDY DESIGN:
Prospective observational study

STUDY SITE:
Department of General Medicine and Obstetrics and Gynecology, MVJ Medical College and Research Hospital, Hoskote, Bangalore

STUDY POPULATION:
In-patients in General Medicine and Obstetrics and Gynecology Departments diagnosed with UTI

SAMPLE SIZE: 100 patients

STUDY PERIOD: Six months

SOURCE OF DATA:
Patient case sheets, culture sensitivity report form, case report form, informed consent form, prescriptions, standard database references (i.e. Lexicomp, Medscape, Drugs.com), standard textbook references (i.e. Pharmacotherapy: A Pathophysiologic Approach by Joseph T. Dipiro, Stockley's Drug Interactions by Ivan H. Stockley)

HUMAN ETHICAL APPROVAL:
Human ethical clearance was obtained for carrying out the research work from Ethical Committee of MVJ Medical College & Research Hospital, Hoskote, Bangalore with ethical clearance number: Central Research/MVJ MC & RH/01/2017

INCLUSION CRITERIA:
• All in-patients who were diagnosed with urinary tract infections
• All in-patients over 18 years of age
• The patients diagnosed with UTIs along with/without other comorbid disease or disorders

EXCLUSION CRITERIA:
- The in-patients with urinary tract infection who are unwilling to participate in the study
- Those patients who are unable to provide the informed consent

PROCEDURE
- A Prospective – Observational Study was conducted in M.V.J Medical College and Research Hospital
- The patients who were admitted in General Medicine or Obstetrics and Gynecology in-patient wards and met the study criteria were enrolled in the study
- Informed consent from the patient or his/her legal representative was obtained
- Clinical, demographic, medication and laboratory data were collected and recorded in case report form on day one, day three and day seven
- Medication related problems such as drug-drug interactions, drug duplication, dose, route of administration, frequency, duration of therapy and dosage form were assessed from day zero to day seven by using standard references and databases
- The prescribing pattern was assessed and analyzed for parameters such as choice, dose, frequency, route of administration and dosage form, before and after culture sensitivity was done on day one and day three to check whether it's according to the hospital treatment guidelines or not
- Drug induced ADR was monitored on day three using ADR monitoring scale (WHO scale causality assessment)
- Rationality of medications used was assessed using WHO criteria
- All the data were analyzed using descriptive statistics

RESULTS

100 patients were enrolled in the study in which number of females was more than males (53% and 47%). Most of the patients were in the age group of above 58 years old (37%) which out of these 23 are males and 14 are females. The average age of the study population was 47.67. Number of patients who were admitted in the General Medicine ward was more than number of patients who were admitted in Obstetrics and Gynecology ward which are 69 patients and 31 patients respectively.

It was found that most of the patients were suffering from lower UTI i.e. cystitis (72%, in which females were more than males) and 14% were suffering from upper UTI i.e. pyelonephritis (males more than females) and in the remaining patients type of UTI was unspecified. The average age was 53.14 in cystitis population, 57.89 in pyelonephritis population and 32 in unspecified (females more than males).

In 100 cases that were collected for this study 68 cases were with comorbid conditions (UTI along with other diseases) and remaining 32 cases were without any comorbid conditions (only UTI) and the most common type of comorbidity among the 68 cases was UTI with renal calculi (10 cases, 14.74%) as shown in table 1.

Table 1: COMORBIDITY DISTRIBUTION (N=68).

CONDITIONS	NUMBER	PERCENTAGE
Renal Calculi	10	14.74%
Benign Prostatic Hyperplasia (BPH)	8	11.76%
Pelvic Inflammatory Disease	6	8.82%
Hypertension (HTN) + Diabetes Mellitus (DM)	6	8.82%
Diabetes Mellitus	4	5.88%
Hypertension	4	5.88%
Post-hysterectomy	4	5.88%
Osteoarthritis	4	5.88%
Catheterization	2	2.94%
Post-Tuberculosis + BPH	2	2.94%
Bronchitis + BPH	2	2.94%
Ischemic Heart Disease	2	2.94%
Colitis	2	2.94%
Thrombocytopenia	2	2.94%
Anemia	2	2.94%
Diarrhea	2	2.94%
Hernia	2	2.94%
Post-nephrectomy	2	2.94%
HTN+ DM + Chronic Obstructive Pulmonary Disease	2	2.94%
TOTAL	68	100%

Totally 137 antibiotics were prescribed for treatment of UTI in which number of patients who were prescribed with fluoroquinolones (66 patients, 48.18%) and cephalosporin (47 patients, 34.31%) were more than the number of patients prescribed with the other classes of antibiotics out of this, norfloxacin (35 patients, 25.54%) under the category of fluoroquinolones, cefixime (18 patients, 13.13%) under the category of cephalosporins and amikacin (11 patients, 8.03%) under the category of aminoglycosides were prescribed more compared to other antibiotics for treatment of UTI as shown in table 2.

Table 2: DISTRIBUTION OF ANTIBIOTICS USED UNDER EACH CLASS (N=137).

S/N	Antibiotic (generic name)	Number	Percentage	Total %
	FLUOROQUINOLONES			
1	Norfloxacin	35	25.54%	48.9%
2	Ciprofloxacin	22	16.06%	
3	Ofloxacin	9	6.56%	
	CEPHALOSPORIN			
4	Cefixime	18	13.13%	34.3%
5	Ceftriaxone	16	11.68%	
6	Cefotaxime	7	5.12%	
7	Cefoperazone	6	4.37%	
	AMINOGLYCOSIDES			
8	Amikacin	11	8.03%	8.03%
	NITROFURANTOIN			
9	Nitrofurantoin	7	5.12%	5.12%
	MACROLIDE			
10	Azithromycin	2	1.46%	1.46%
	PENICILLIN			
11	Amoxicillin	2	1.46%	1.46%
	LINCOSAMIDE			
12	Clindamycin	2	1.46%	1.46%
	TOTAL	137	100%	100%

For treatment of UTI the number of patients who were prescribed with monotherapy of antibiotics (59%) was more than the number of patients prescribed with combination therapy of antibiotics (41%).

In monotherapy, fluoroquinolones (39 patients, 66.1%, in which norfloxacin 46.15% was prescribed most) and cephalosporins (14 patients, 23.73%, in which cefixime 28.16% was prescribed most) were prescribed more than other classes of drugs and in combination therapy the combination of injection cefotaxime (1g) and tablet cefixime (200 mg) in 6 patients as well as the combination of tablet ofloxacin (200mg) with tablet ornidazole (600 mg) in other 6 patients were prescribed more than any other combination. Monotherapy of antibiotics was found to be used more in treatment of cystitis (63.17%) than pyelonephritis (12.56%) and unspecified type of UTI (23.73%) in which norfloxacin was the most frequently used antibiotic (in 22 patients). The antibiotic combination was more in treatment of cystitis (90%) comparing with pyelonephritis (10%) which in cystitis combination of tablet ofloxacin (200mg) and tablet ornidazole (600 mg) in 6 patients as well as combination of injection cefotaxime (1g) with tablet cefixime (200 mg) in 6 other patients were used more and in pyelonephritis combination of tablet cefoperazone (1g) and tablet norfloxacin (400mg) in 2 patients as well as combination of injection ceftriaxone (1g) with tablet norfloxacin (400mg) in 2 other patients were prescribed.

Along with antibiotics used in treatment of cystitis, pyelonephritis and unspecified UTI, other drugs (407 non-antibacterial drugs) were also prescribed for different indications in which dihydrogen sodium citrate (in cystitis 51 patients and in pyelonephritis 6 patients), pantoprazole (in cystitis 45 patients and in unspecified 2 patients) and paracetamol (in cystitis 29 patients and unspecified 10 patients) were the most prescribed non-antibacterial. Out of 100 prescriptions, 131 drug-drug interactions (with antibacterial) were possible in which 88 were moderate type, 32 were minor and 10 were major as shown in table 3. From 131 possible interactions, 60 drug-drug interaction combinations were reported to the prescribers in which the most common management of interactions was to change the frequency of the drug to be administered daily (26 cases, 49.05%), followed by adjustment of dose of the interacting drugs (20 cases, 41.52%), changing the route of administration of the drug (3 cases, 5.66%) and use of an alternative drug (2 cases, 3.77%). The antibiotic found interacting in majority of the cases was norfloxacin (35.13%) and ciprofloxacin (32.44%) in which the most common pattern of major drug interactions (2 patterns) was between norfloxacin and tramadol (in 7 cases), in moderate drug interactions (11 patterns) was between amikacin and diclofenac (in 6 cases) and in minor drug interactions (3 patterns).

Table 3: DRUG INTERACTIONS – INTERVENTIONS (N=61) AND MANAGEMENT BASED ON TYPES (N=53).

Type of UTI	No. of Interaction Identified	Interventions (Reported)		Management (Result)	
		Yes	No	Considered	Not Considered
Cystitis	112	51 (10 major + 41 moderate)	61 (31 minor + 30 moderate)	45	6 (patients left the hospital against medical advice)
Pyelonephritis	19	10 (moderate)	10 (2 minor + 8 moderate)	8	2 (patients left the hospital against medical advice)
Unspecified	0	0	0	0	0
Total	131	61	71	53	8

The collected 100 prescriptions were analyzed for the medication errors as shown in table 4 in which drug duplication was observed and reported in two prescriptions but as the benefits of this combination overweighed the possible risks, the prescriber carried on with the same combination of drugs.

Table 4: MEDICATION ERRORS (N=74).

Factors	Number
Drug duplication[*]	2
Sound alike medications	0
Errors in dose	0
Errors in dosage form	0
Errors in route of administration	0
Errors in frequency	0
Errors in duration of therapy	0

*Drug duplications between flavoxate and tolterodine. Both of them belong to the same category which is anticholinergics/ antispasmodics.

The prescribing patterns of 100 prescriptions were analyzed for factors that are shown in table 5 and 6 in which it was seen that brand names were used more than generic names and 72 antibiotics were from the WHO essential antibiotics list.

Table 5: PRESCRIBING PATTERNS DISTRIBUTION (N=100).

| Factors	Number	Percentage
Brand names	649	91.66%
Generic names	59	8.33%
TOTAL	708	100%
PARENTERAL DOSAGE FORM		
Intravenous	170	86.74%
Intramuscular	18	9.18%
Subcutaneous	8	4.08%
TOTAL	196	100%
Essential antibiotics used	72	52.56%
Nonessential antibiotics used	65	47.44%
TOTAL	137	100%
Polypharmacy average		Patients are prescribed an average of 7.22 drugs per prescription. 63% of the prescriptions were seen to have more than 5 drug prescribed.

Table 6: PRESCRIPTION AND UTILIZATION PATTERN OF ANTIBIOTICS (N=100).

Question pattern	Response pattern	Frequency	(%)
Pattern of antibiotics prescription	Single antibiotic	59	59%
	Multiple antibiotics	41	41%
Information about the directions* for antibiotic use	Complete direction	94	94%
	Incomplete direction	6	6%
Clinical test for prescribing antibiotics	With test	92	92%
	Without test	8	8%
Completion of full antibiotic course	Yes	92	92%
	No	8	8%
Patient's compliance	Disease recovery	88	88%
	Incompliance	12	12%

*Dose, frequency, rout of administration, duration, diet.

Rationality of the prescribed antibiotics were assessed and found to be rational by comparing with the guidelines (i.e. hospital antibiotics policy of OBG and GM departments, standard textbooks and online databases) for the factors like dose, dosage form, frequency, duration of therapy, route of administration and therapy indications for the prescribed drug.

The urine analysis and culture sensitivity test has been done for 92 patients who were enrolled in the study in which the most common type of pathogen found was *Escherichia coli* (in 66 patients) which was more in males (35 patients) than females followed by *Klebsiella pneumonia* (in 16 patients) and *Psueodomonas aeruginosa* (in 6 patients) that were more in females than males. The frequency of all the type of pathogens were more in cystitis comparing with pyelonephritis, which were: *Escherichia coli* (61.76%), *Klebsiella pneumonia* (23.52%), *Psueodomonas aeruginosa* (8.83%) and *Staphylococcous aureus* (5.89%). *E. coli* was causative pathogen in 66 cases where it was mostly resistant to the ampicillin, amoxicillin, cefotaxim and ceftriaxone antibiotics and *K. pneumonia* was resistant to ampicillin, cloxacillin, norfloxacin and ofloxacin antibiotics as demonstrated in figure 1 and *E. coli* was sensitive to the cotrimoxazole, norfloxacin, nitrofurantoin as well as amikacin antibiotics and *K. pneumonia*, was sensitive to cefotaxim, cotrimoxazole, nitrofurantoin and amikacin as shown in figure 2.

Figure 1: ANTIMICROBIALS RESISTANCE PATTERN (N=92)
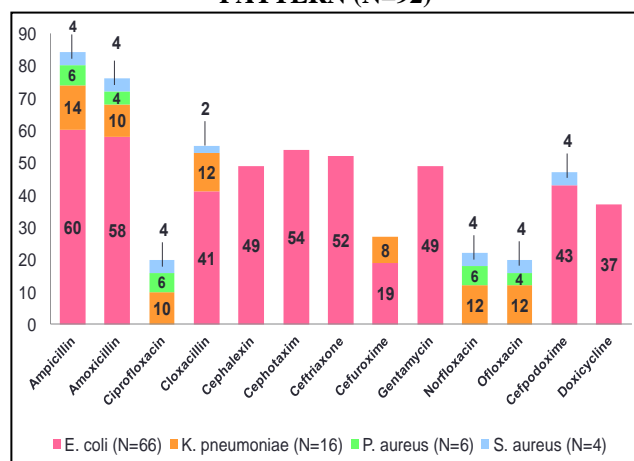
Figure 2: ANTIMICROBIALS SENSITIVITY PATTERN (N=92)
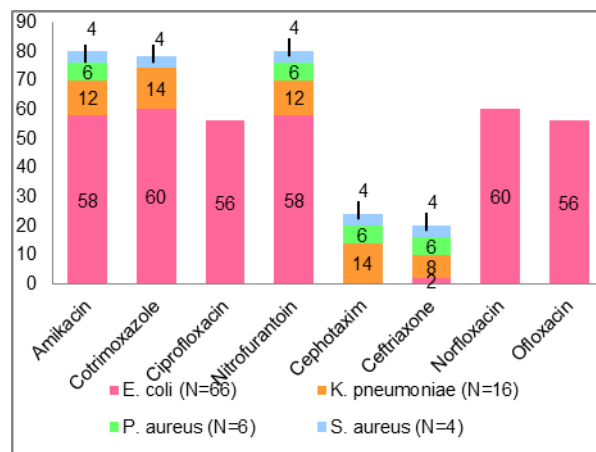
DISCUSSION

The number of females who were diagnosed with UTI (53%) was more than males (47%) and the most common age group was 58 years old and above (37%). This result was similar to the studies done by following: Mohammed Akram et al females (66.66%) and males (43.44%) [10]; Sunil S Gidamudi et al female (55.6%) and male (44.4%) and the most common age group was patients in 40-60 years age group (40.7%).[11] In this study most of the patients were with comorbid conditions in which the most common comorbid conditions were diabetes mellitus (17.64%), hypertension (17.64%), renal calculi (14.74%), and benign prostatic hyperplasia (11.76%). In a study by Sunil S Gidamudi et al the similar results was found that comorbidity was more (90.74%) in which the most common comorbid conditions were diabetes mellitus (32.65%), hypertension (26.53%) and renal/ureteric calculi (12.25%). [11]

The prescription pattern for 100 patients were reviewed in this study where totally 137 antibiotics were prescribed in which quinolones [fluoroquinolones] (48.18%) were mostly prescribed. Syed Zahed pasha et al carried out a similar study with the same result i.e. quinolones (36.55%) [12] and Cenk Aypak et al also conducted a study with almost similar results i.e. prescribed fluoroquinolones (77.9%). [13]

In this study majority of patients were prescribed with monotherapy of antimicrobials (59%). In the study that was done by Sah Om P et al the results stated that commonly used type of therapy for patients was monotherapy of antimicrobials (62.9%). [14]

Combination of antibiotics (two or more) was prescribed in 41% of prescriptions. Among the prescribed antibiotics, 94% had complete direction for the use of antibiotics, 92% patients completed full course of antibiotics, 92% prescriptions had clinical test for using antibiotics and patient's disease recovery 88%. Mohitosh Biswas et al conducted a study that had similar results i.e. two or more antibiotics were prescribed in 25.44% of prescriptions, prescriptions with complete direction for antibiotics use (57%), 64.22% patients completed full course of antibiotics, prescriptions with no clinical test for using antibiotics (83%) and the percentage of patient's disease recovery was 61.78%. [15]

The most common pathogen was *E. coli* (71.74%) followed by *K. pneumoniae* (17.39%), *P. aeruginosa* (6.53%) and *S. aureus* (4.34%). In a study by Mohammed Akram et al similar results [10] were found that *E. coli* (61%), *K. pneumoniae* (22%), *P. aeruginosa* (4.0%), *S. aureus* (7.0%) and same results in a study by Sah Om P et al [14] that is *E. coli* (64.4%), *Klebsiella* species (13.3%), *Pseudomonas* species (3.8%). *E. coli* was resistant to ampicillin (90.90%), amoxicillin (87.87%), cefotaxim (81.81%) and (78.78%). *K. pneumoniae* was resistant to ampicillin (87.5%) but *E. coli* was sensitive to norfloxacin (90.90%), amikacin (87.87%) and nitrofurantoin (87.87%), amoxicillin (6.06%) and ceftriaxone (3.03%). Sunil S Gidamudi et al have done a research with almost similar results i.e. *E. coli* was resistant to ampicillin (86.96%) and ceftriaxone (82.61%) but sensitive to amikacin (91.3%) and ceftriaxone (13.04%). [11]

CONCLUSION

Prescribing pattern of antibacterials and rationality of the medications used for treating patients with UTIs was appropriate and according to the standard guidelines but using brand names for prescribing drugs can increase the chance of medication related problems. Higher number of comorbidities was leading to polypharmacy which is a precursor for increasing possibility of drug-drug interactions, in return there is an increased requirement for close monitoring and management of these possible interactions. E. coli, K. pneumoniae and P. aeruginosa were more sensitive to nitrofurantoin, amikacin and norfloxacin therefore these may be the antibiotics of choice for the treatment of community-acquired UTIs. Antibiotic resistance is becoming a threat for the public health, lives of hospitalized individual and patients with chronic conditions therefore there is a need for antibiotic guidelines to prevent such resistance.

ACKNOWLEDGEMENT

ABBREVIATIONS

ADR   : Adverse Drug Reaction
BPH   : Benign Prostatic Hypertrophy
DM   : Diabetes Mellitus
GM   : General Medicine
HTN   : Hypertension
OBG   : Obstetrics and Gynecology
UTI   : Urinary Tract Infection
WHO   : World Health Organization

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