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Original Research Article

Drug utilization pattern and physician adherence to treatment guidelines in inpatients with urinary tract infection

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ABSTRACT

Background: Mainstay of management in urinary tract infection (UTI) is antibiotics and it is seen in recent years that antibiotic resistance is increasing. However, very few treatment guidelines exist for UTI and often treating physicians may not adhere to these guidelines. Aims: Current study was undertaken to analyze antimicrobial prescription pattern and utilization, and check for physician adherence to treatment guidelines in UTI.
Methods: This retrospective, record-based study was carried out in a tertiary care hospital in inpatients with UTI. Tabulated data was analyzed using WHO core drug prescribing indicators and Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) index. Adherence to treatment guidelines was assessed using Indian Standard Treatment Guidelines for Urology. Data documented in SPSS software was analyzed using $\chi 2$-test and multinomial logistic regression.
Results: Among 364 patients included in study, equal incidence of UTI was seen in both sexes (male to female ratio 1.02:1). Prolonged hospital stay (>7 days) was associated with elderly age group (OR=3.09, CI95% 1.83-5.21), complicated UTI (OR=8.11, CI95% 4.62-14.24), ESBL-producing *E. coli* (OR=3.07, CI95% 1.58-5.94), non-adherence to treatment guidelines (OR=8.65, CI95% 4.19-17.84), and presence of comorbid conditions like diabetes mellitus (OR=4.89, CI95% 3.05-7.82), benign prostatic hypertrophy (OR=2.76, CI95% 1.36-5.59) and utero-vaginal prolapse (OR=8.33, CI95% 2.28-30.45). Average number of drugs prescribed per encounter was 1.59, while drugs prescribed by generic name and from essential drug list were 98.1% and 70.69% respectively. Majority of prescriptions (87.6%) adhered to standard treatment guidelines. Prescribed daily dose (PDD) and defined daily dose (DDD) were equal for most antibiotics prescribed.
Conclusions: Majority of prescriptions were adhering to treatment guidelines but the need to prescribe using generic name and from essential drug list should be emphasised upon.

Keywords: Antibiotic, ATC-DDD system, Drug utilization pattern, *Escherichia coli*, Treatment guidelines adherence, Urinary tract infection

INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections affecting humans and is one of the leading causes of both community acquired and nosocomial infections, for patients admitted to hospitals in United States.[1] It is estimated that about 150 million UTIs are reported every year worldwide.[2,3] Furthermore, it was found that 40% of all hospital acquired infections were UTIs and 10-12% of patients hospitalised in urological wards have a healthcare-associated infection.

Drug utilization is defined by the WHO as the "marketing, distribution, prescription, and use of drugs in society, with

special emphasis on the resulting medical, social, and economic consequences". Drug utilization studies help to recognize and report irrational prescribing, which adds on to patient morbidity and economic burden.[4] Among the current available methods, the Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) index developed by the World Health Organization is most important and reliable.[5] Along with this, the assessment of drug use patterns using WHO core drug use indicators is equally important to promote rational drug use.[6]

The defined daily dose (DDD) is the presumed average maintenance dose per day for a drug in its main indication for adults and is usually denoted with a specific population size denominator such as patient days or bed days. The chief disadvantage is that DDD neither reflects the recommended, nor the actual prescribed daily dose (PDD) for individual patients or specific patient populations.[7] Hence it is ideal to calculate DDD and to determine its variation from the PDD.

Though regularly updated guidelines and recommendations for UTI management exist, poor adherence to these guidelines is seen in common clinical practice. Hence the need for periodic audits to identify critical issues, sub-optimal behaviour and provide solution to problems.[8] Though a few drug utilization studies are being reported from the Indian subcontinent, there is need for constant monitoring and documenting of prescription practices from various parts of the country. Hence the current study was undertaken with the following objectives:

- To assess drug prescription pattern in inpatients of UTI using the WHO core drug prescribing indicators.
- To assess the antimicrobial utilization in UTI by the ATC/DDD system.
- To check for physician adherence to treatment guidelines using the Indian Standard Treatment Guidelines for Urology.

METHODS

This retrospective, descriptive, record-based study was conducted in a tertiary care hospital in south India from January to December 2015. The Institutional Ethics Committee clearance was obtained for the study. A waiver of consent was obtained from the same. Subjects aged ≥18 years, admitted with a provisional diagnosis of urinary tract infection and positive urine culture reports were included in the study. Pregnant women with UTI were excluded from the study. The demographic details of patients, presence of comorbid conditions predisposing to development of UTI, treatment details, duration of hospital stay and urine culture report were noted from the case records.

The prescriptions were checked for rationality using the WHO core drug prescribing indicators, which are as follows:[9]

1. Average number of drugs prescribed per encounter was calculated by dividing total number of drug products prescribed by number of encounters surveyed.
2. Percentage of drugs prescribed by generic name was calculated by dividing number of drugs prescribed by generic name by total number of drugs prescribed, multiplied by 100.
3. Percentage of encounters with an antibiotic prescribed was calculated by dividing number of patient encounters in which an antibiotic was prescribed by total number of encounters surveyed, multiplied by 100.
4. Percentage of encounters with an injection prescribed was calculated by dividing number of patient encounters in which an injection was prescribed by total number of encounters surveyed, multiplied by 100.
5. Percentage of drugs prescribed from an essential drug list (EDL) was calculated by dividing number of products prescribed from EDL by total number of drugs prescribed, multiplied by 100.

Physician adherence to the treatment guidelines was assessed using the Indian Standard Treatment Guidelines for Urology.[10] The ATC classification for the prescribed antibiotics and DDD were noted and, PDD and DDD/1000 inhabitants/day was calculated for the current study.

Statistical analysis

The data collected was tabulated and analyzed using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, NY, USA). Statistical analysis was performed using descriptive statistics, and $\chi 2$-test was used for testing group differences, with $p \leq 0.05$ set as the level of statistical significance. Results were expressed as percentages, frequencies and mean±SD. Variables associated with a longer duration of hospital stay that showed statistically significant difference between groups were entered into the final model of the multivariate logistic regression analysis, which was used to compute odds ratio (OR) and 95% confidence intervals (95% CI) to assess the independent associations of these variables with a prolonged hospital stay.

RESULTS

Among a total of 428 patients diagnosed with UTI in the institute during the study period, 364 patients only were included in the current study, as the remaining subjects did not fulfil the inclusion criteria.

It was found that there was equal distribution gender-wise (male to female ratio was 1.02:1). Highest number of study subjects belonged to the age group of 18-30 years (26.1%), followed by 51-60 years (19.8%) (Table 1).

The commonest causative organism was *Escherichia coli* (78%), followed by extended spectrum beta-lactamase

producing *Escherichia coli* (7.9%), *Klebsiella pneumoniae* (4.8%), *Enterococcus faecalis* (4.4%), *Candida albicans* (2.6%), *Pseudomonas aeruginosa* (1.2%) and *Staphylococcus aureus* (1.1%).

Majority of them had a lower UTI (97.3%). More than half of the study subjects (54.9%) had a complicated UTI. About one-third of the patients were diabetic (37.6%), while some others had various comorbid conditions predisposing to the development of UTI It was found that majority of the prescriptions (87.6%) adhered to the treatment guidelines (Table 2).

Table 1: Age and gender distribution of study subjects (n=364).

Variable		Number	Percentage	p value*
Gender	Male	184	50.5	0.78
	Female	180	49.5	
Age groups (in years)	18-30	95	26.1	0.01
	31-40	49	13.5	
	41-50	50	13.7	
	51-60	72	19.8	
	61-70	65	17.9	
	>70	33	9.1	

*Statistical significance was considered at p≤0.05. Statistically significant p values indicated by bold.

Table 2: Disease and treatment profile in study subjects (n=364).

Variable		Number	%
UTI site	Lower urinary tract	354	97.3
	Upper urinary tract	10	2.7
Type of UTI	Uncomplicated	164	45.1
	Complicated	200	54.9
Comorbid conditions predisposing to UTI	Diabetes mellitus	137	37.6
	Benign prostatic hypertrophy	35/184	19.0
	Renal calculi	14	3.8
	Utero-vaginal prolapse with/ without cystocoele/ rectocoele	14/180	7.8
	Acute/ chronic renal injury	21	5.8
Urine culture sensitivity pattern	Sensitive	323	88.7
	Resistant	41	11.3
Duration of hospital stay	1-3 days	115	31.6
	4-7 days	158	43.4
	>7 days	91	25
Adherence to treatment guidelines	Yes	319	87.6
	No	45	12.4
Duration of treatment (mean±SD)		9.06±3.71 days	

UTI - Urinary tract infection

Table 3: Multivariate logistic regression model with longer duration of hospital stay (>7 days) as the dependent variable (n=364).

Independent variables		B	Wald	p value*	Odds ratio	95% CI	% variance (Nagelkerke pseudo R^2)
Age >65 years		1.13	17.91	<0.001	3.09	1.83-5.21	0.067
Gender (males)		-0.03	0.02	0.89	0.97	0.62-1.5	<0.001
Comorbid conditions	Diabetes mellitus	1.59	43.7	<0.001	4.89	3.05-7.82	0.17
	Benign prostatic hypertrophy	1.02	7.95	0.005	2.76	1.36-5.59	0.03
	Renal calculi	-0.59	0.78	0.38	0.56	0.15-2.04	0.003
	Utero-vaginal prolapse with/without cystocoele	2.12	10.26	0.001	8.33	2.28-30.45	0.049
	Acute/chronic renal injury	1.53	10.2	0.001	4.6	1.8-11.72	0.042
Complicated UTI		2.09	53.17	<0.001	8.11	4.62-14.24	0.237
Upper UTI		-0.12	0.03	0.87	0.89	0.23-3.51	<0.001
ESBL-producing *E. coli* in urine culture		1.12	11.02	0.001	3.07	1.58-5.94	0.042
Non-adherence to treatment guidelines		2.16	34.1	<0.001	8.65	4.19-17.84	0.148

*Statistical significance was considered at $p \leq 0.05$. Statistically significant p values indicated by bold. UTI-Urinary tract infection.

Table 4: The WHO core prescribing indicators assessed for drug prescriptions (n=364).

Prescribing indicators assessed	Total drugs/ encounters	Average/ percentage	Standard derived or ideal
Average number of drugs per encounter	580	1.59	1.6-1.8
Percentage of drugs prescribed by generic name	569	98.1	100
Percentage of encounters with antibiotics	580	100	20-26.8
Percentage of encounters with injections	209	36.03	13.4-24.1
Percentage of drugs from essential drug list	410	70.69	100

Table 5: Antibiotic consumption in the study population (n=364).

Antibiotic used	Dose and route of administration	ATC code	DDD (mg)	PDD (mg)	DDD/ 1000 inhabitants/ day
Fluoroquinolones					
Norfloxacin	Oral	J01MA06	800	800	2.22
Ciprofloxacin	Oral	J01MA02	1000	1000	3.83
Ofloxacin	Oral	J01MA01	400	400	4.78
Levofloxacin	Oral	J01MA12	500	1000	1.73
Cephalosporins					
Ceftriaxone	Parenteral	J01DD04	2000	2000	1.05
Cefoperazone+Sulbactam	Pareneteral	J01DD62	4000	4500	17.78
Cefepime	Parenteral	J01DE01	2000	2000	0.05
Cefotaxime	Parenteral	J01DD01	4000	400	0.01
Cefixime	Oral	J01DD08	400	400	0.34
Penicillins					
Piperacillin+Tazobactam	Parenteral	J01CR05	14000	13500	0.22
Amoxicillin clavulanate	Parenteral	J01CR02	3000	2305	0.03
Ampicillin	Oral	J01CA01	2000	1000	0.11
Cloxacillin	Oral	J01CF02	2000	2000	0.04
Carbapenems					
Imipenem	Parenteral	J01DH51	2000	1875	0.9
Meropenem	Parenteral	J01DH02	2000	1500	0.04
Co-trimoxazole	Oral	J01EE01	4 UD	4 UD	-
Tetracycline					
Doxycycline	Oral	J01AA02	100	200	2.18
Aminoglycoside					
Amikacin	Parenteral	J01GB06	1000	875	2.57
Nitrofuran derivative					
Nitrofurantoin	Oral	J01XE01	200	200	7.26
Oxazolidinone					
Linezolid	Oral	J01XX08	1000	1200	0.45
Triazole derivative					
Fluconazole	Oral	J02AC01	200	235	1.24
Macrolide					
Azithromycin	Oral	J01FA10	300	500	0.55

The different antibiotics that were used in the treatment of UTI are depicted in Figure 1. The commonest prescribed were fluoroquinolones (77.4%), nitrofurantoin (32.7%) and cephalosporins (29.4%).

The association of variables with a prolonged hospital stay suggested that elderly age group (OR=3.09, CI 95% 1.83-5.21), complicated UTI (OR=8.11, CI 95% 4.62-14.24), ESBL-producing *E. coli* in urine culture (OR=3.07, CI 95% 1.58-5.94), non-adherence to treatment guidelines (OR=8.65, CI 95% 4.19-17.84), and presence of comorbid conditions like diabetes mellitus (OR=4.89, CI 95% 3.05-7.82), benign prostatic hypertrophy (OR=2.76, CI 95% 1.36-5.59), utero-vaginal prolapse (OR=8.33, CI 95%

2.28-30.45) and acute/chronic renal injury (OR=4.6, CI 95% 1.8-11.72) had a positive association (Table 3).

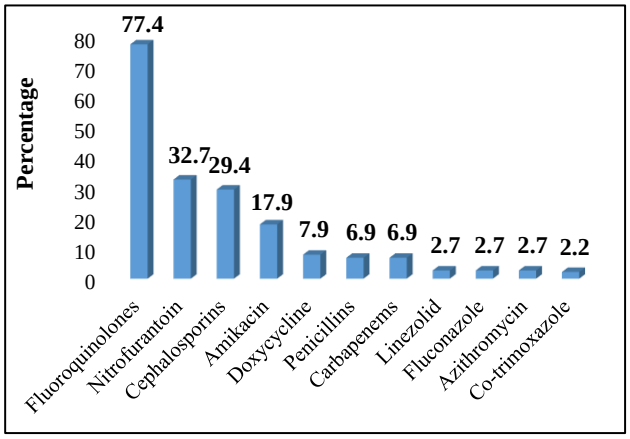

Figure 1: Antibiotics used for treatment of urinary tract infection (n=364).

The rationality of prescriptions was checked using WHO core drug prescribing indicators and the results are depicted in Table 4.

Table 5 illustrates the ATC classification, DDD, PDD and DDD/1000 inhabitants/day of the prescribed antibiotics. It was found that PDD was equal to the DDD for most antibiotics prescribed like fluoroquinolones, cephalosporins, nitrofurantoin and co-trimoxazole. A few antibiotics like doxycycline, linezolid, fluconazole and azithromycin had a PDD higher than the DDD, while yet others like penicillins, carbapenems and amikacin had a PDD lower than the DDD.

DISCUSSION

In the current study it was seen that UTIs were almost equally distributed in both genders whereas in some other studies a higher incidence was seen in women, while yet other studies reported more incidence in men.[11-15] The highest incidence was seen in the age group of 18-30 years, which is similar to that was reported, while other studies reported more incidence in a higher age group.[3,11,16] The commonest causative organism was found to be *Escherichia coli* which is in concordance with other reports.[2,16-18] ESBL producing *E. coli* was the next common pathogen, however the incidence was less as compared to other studies.[2,19] Incidence of various associated risk factors for developing UTI found in the study like diabetes mellitus and renal calculi was comparable with that reported.[20]

Development of standard treatment guidelines for therapy of common infections of public health importance and adhering to these guidelines becomes very important in preventing development of antibiotic resistance.[21] The Indian Standard Treatment Guidelines for Urology has listed the antibiotics that can be used for treatment of UTI and the recommended treatment duration. Majority of the prescriptions in the current study were found to be adhering to the above-mentioned guidelines. This finding is comparable to that found in a study, and is much higher than those reported elsewhere.[22-24] Commonest prescribed drugs were cephalosporins, nitrofurantoin and fluoroquinolones, which are all recommended antibiotics for treatment of UTI and findings are in accordance with other similar studies.[8,16,25]

Various factors like elderly age group, complicated UTI, UTI associated with risk factors, non-adherence to treatment guidelines and ESBL-producing *E. coli* in urine culture, were found to be associated with a prolongation of hospital stay in UTI infected patients. This is akin to the findings reported by other studies done in different settings.[26,27] As per the WHO core drug prescribing indicators, average number of drugs per encounter and those prescribed by generic name were close to the ideal values mentioned. As the main management of UTI is entirely comprised of antibiotics, it cannot be compared with the ideal values set by WHO. Percentage of encounters with injections was higher, while drugs prescribed from essential drug list were lower than the ideal values of WHO prescribing indicators. These findings are higher than those reported by other studies.[25,28]

The antibiotic consumption was calculated using DDD/1000 inhabitants/day and was compared with PDD. In ideal situations, the PDD should be equal to the standard DDD. In the present study, it was found that most of the prescribed antibiotics had a PDD equal to that of the recommended DDD. A few of the antibiotics like doxycycline and azithromycin had a PDD more than that of the suggested DDD, while others like Penicillins and carbapenems had a PDD lower than the commended DDD. In antibiotic treatment regimens, it is common to see a variation between the DDD and PDD as therapy depends on multiple factors like severity of disease, presence of comorbid conditions that complicate the clinical scenario and national treatment guidelines. These findings of the current study are comparable to results of other previous studies.[29,30]

The study describes the prescribing patterns and physician adherence to treatment guidelines in a single setting and the results cannot be generalised. Moreover, the focus of the study was on inpatients, in whom usually the infection is more severe than those treated on an outpatient basis. A comparison between the two groups would have been ideal. However, the study does enhance the existing literature by providing valuable information on the current trends in management of UTIs.

CONCLUSION

In conclusion, periodic audits and surveys are very essential to determine prescription errors in order to prevent development of antibiotic resistance to a certain extent. The need to adhere to standard treatment guidelines

and prescribe from the essential drug list, using generic names has to be impressed upon treating physicians.

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